Clinical Studies at the MDA/ALS Center of Hope

Studies Starting Up Soon

Use of fNIR optical imaging to detect hemodynamic changes in the frontal lobes of people with ALS

The overall goal of this project is to determine if there are hemodynamic changes detected by Functional Near Infrared (fNIR) Spectroscopy that differ in ALS and control subjects and whether these changes correlate with cognitive changes assessed with neuropsychological tests in ALS. While the traditional teaching has been that cognition remains intact in ALS, recent evidence suggests behavioral and memory deficits from frontal lobe brain involvement in a sizable number of people with ALS. fNIR is a safe, non-invasive and portable optical neuroimaging technology that can be used to monitor hemodynamic changes that occur in the brain, i.e., blood oxygenation and blood volume, during select cognitive tasks. The system is composed of three modules: a flexible headpiece (sensor pad), which holds light sources and detectors; a control box for hardware management; and a computer that captures data. The safe, portable and cost-effective nature of fNIR suggests that this technology is an ideal candidate for monitoring cognitive activity with concomitant hemodynamic changes not only in the laboratory but also in the clinic.

In our studies we will examine if there are any differences in the hemodynamic changes during thinking tasks in individuals with ALS compared to controls as well as comparing ALS patients with and without cognitive changes on formal neuropsychology tests. If corresponding changes can be identified, this will set the foundation for longitudinal studies to determine if fNIR can provide a biomarker to be followed during clinical studies as well as whether it can help identify and track ALS subjects at risk for cognitive involvement at an earlier stage of illness than traditional neuropsychological assessments.
iBrain: Single channel EEG based system to detect intent and allow communication in ALS

The objective of this project is to examine whether a single channel of electroencephalogram (EEG) data recorded by NeuroVigil's iBrain™ device can be analyzed to identify brain waves that will serve as neurological biomarkers of human intent. This would allow us to use these biomarkers to enable a wide range of ALS patients to communicate throughout all stages of disease progression. Preliminary results from NeuroVigil's signal analysis of data collected on Professor Steven Hawking revealed high-frequency/low spectral power signals when he attempted to move. Distinct signals were demonstrated and appeared specific to attempted or imagined movements. We plan to validate these preliminary findings in a larger group of ALS subjects. If successful, these signals indicating the subjects' intent could be used to link brain activity with a library of words and convert them into speech, thus providing people living with ALS communication tools more dependent on the brain than on the body. We will be partnering with NeuroVigil to perform these studies.

Dexpramipexole: Phase 3

Recently the first of two planned Phase 3 trials of the drug called KNS-760704 (dexpramipexole) completed enrollment at the Center of Hope (see below).

While the precise mechanism of action of KNS-760704 is currently unknown, it appears to increase the level of functioning of mitochondria in cells, which in turn helps to protect nerve cells that are stressed or at risk of dying. The results of the Phase 2 safety and tolerability study of KNS-760704 in ALS demonstrated that KNS-760704 was safe and well-tolerated for up to nine months. The study results also showed trends suggesting the potential for improved outcomes in function and survival. The results of this Phase 3 trial will be available at the end of 2012 and used to decide whether a second Phase 3 study will be initiated. The MDA/ALS Center of Hope will be participating in this trial if it moves forward.

Ongoing Studies, Still Enrolling

Trial of High fat/High Calorie Diet versus Optimal Nutrition in Amyotrophic Lateral Sclerosis

This study is a phase II double-blind placebo-controlled clinical trial designed to study the safety, tolerability and feasibility of a high fat/high calorie diet versus high calorie diet, versus normal diet. Secondary outcome measures include lipid levels, weight, body mass, body composition and preliminary effects on disease progression. 60 subjects who are already receiving percutaneous nutrition will be randomized to each treatment arm and followed for five months. Energy needs for each subject will be calculated based on measured energy expenditure using indirect calorimetry and basal metabolic rate (BMR). The control diet will
be treated with optimal calorie replacement while both intervention arms will be provided a high calorie diet 1.25 times their calculated energy needs. Primary outcome measures will be adverse events and compliance rates.

We will also test biomarkers of body composition, and lipid metabolism before and during diet intervention. Serum levels of total cholesterol, HDL, non-HDL cholesterol, calculated LDL, triglycerides, and oxidized cholesterol will be measured at enrollment in a fasting state and postprandial. This study is still enrolling.

**EEG-Based Brain-Computer Interface**

By using EEG (brain wave) signals from the scalp to create a signal, the Brain-Computer Interface (BCI) allows people to make selections from the computer screen. The study is intended to evaluate both the complexity of the system and the degree to which each participant will be able to communicate. Trials will consist of asking the subject to follow a series of simple instructions and to complete certain tasks while using the BCI. We are also working to simplify the system as a prelude to home based use.

**Tissue Donation**

In a disease like ALS in which the cause is unknown, no animal models of ALS can substitute for understanding how it affects humans. We are currently collecting blood, urine, CSF and autopsy materials from people with ALS and other motor neuron diseases to look for clues in the human tissue. All samples are tied to de-identified clinical information in a database to help maximize the usefulness of this precious resource. This includes demographic information; environmental exposures; and medical history. This will increase availability of human tissue for research with pertinent corresponding clinical information.

**Substrate Utilization**

This study investigates the utilization of sugar, fat and protein by using a metabolic cart to measure the calories an individual needs and whether these calories are coming from sugar, fat or protein. Our goal is to understand shifts in substrate utilization through the progression of ALS, helping patients attain a healthier lifestyle and quality of life. This study will also clarify the influence of improved nutrition via PEG tube feeding.

**GI Dysmotility**

Studies have shown delayed gastric emptying may be associated with ALS, possibly due to involvement of the autonomic nervous system. This may be the cause of the abdominal discomfort and constipation common in ALS. This study examines the small bowel transit time in people with ALS and controls in an effort to gain further insight into the extent and severity of GI dysmotility in ALS. Companion studies are also underway in autopsied material that examine the pathology underlying the delay in GI motility.
Barriers to PEG tube placement
Offering Percutaneous Endoscopic Gastrostomy (PEG) tube placement is considered standard of care at a certain point in the management of ALS. This study will explore the reasons why individuals with ALS might delay a PEG tube placement following the recommendation of the health care provider. A questionnaire will be administered pre and post watching a video of an individual living with a PEG.

Ongoing Studies, Fully Enrolled

Ceftriaxone
This study is designed to examine whether chronic intravenous treatment with ceftriaxone prolongs survival with ALS. Ceftriaxone may increase the level of a transport protein that decreases glutamate levels near nerves. Researchers think that increased levels of glutamate may be related to motor neuron death. The study is fully enrolled. Results will be available in mid 2013.

Dexpramiprexole
Recently we have completed enrollment for the first of two planned Phase 3 trials of the drug called KNS-760704 (dexpramiprexole) at the Center of Hope. This trial will be completed towards the end of 2012 and if the agent remains promising we will be participating in the second Phase 3 trial (see above).

Validation of ALS Biomarkers
The purpose of this study is to learn more about the underlying cause of ALS, as well as find unique biological markers which could be used to diagnose ALS and monitor disease progression. We will do this by collecting and comparing blood samples from healthy subjects, and both blood and cerebrospinal fluid (CSF) samples from people with not only classical ALS, but other forms of neurodegenerative diseases.

Development of a Pennsylvania State-wide ALS Registry
We are working to develop an ALS Registry for Pennsylvania to facilitate future investigations into the environmental and genetic determinants of ALS as well as provide a database of ALS subjects that would be useful for clinical and basic research. In this regard we have designed a database that is presently being improved based on our initial testing.
Recently Completed Studies

Cytokinetics

This study demonstrated that the experimental drug called CK-2017357 was safe and well tolerated when administered over 14 days. This drug may improve muscle strength and fatigue in ALS. It improved muscle function in SOD1(G93A) mice the animal model of ALS. The major side effect was dizziness and it is likely that there will be a follow-up Phase II study.

Geographic Clustering and Risk Factors in the Development of ALS

The primary objective of this research was to investigate toxic/heavy metal exposure and the development of ALS across Pennsylvania using a case control design. We examined the life-long occupational exposures and hobbies related to metal exposure as well as residential history and proximity to superfund sites and their relationship to increased risk of ALS. This work was a collaboration of researchers across Pennsylvania. We have submitted two publications from this work that suggest there is a potential association of increased ambient air concentration of hazardous air pollutants, especially pesticides and solvents, among place of residence and risk of ALS. In addition occupations involving metal and pesticide exposure may be at greater risk of ALS. We plan to pursue this research with our collaborators.

TIV (Tracheostomy with invasive ventilation) for Patients with ALS in Japan and the U.S.A.:

A Comparative Study

Over the past 20 years, it has become increasingly recognized that the choice of tracheostomy with invasive ventilation among ALS patients varies tremendously between countries, between regions in the same country, and even among colleagues at the same institutions. The most striking disparities are perhaps those between the United States and Japan in rate of patients on TIV. A collaboration of Japanese and American investigators proposes to conduct surveys in both countries of patients, caregivers and neurologists. The study goal is to develop a more comprehensive understanding of decision-making and perceived advantages and disadvantages of TIV in the view of the various stakeholders, and implications for improved clinical care.

Optimizing Non-invasive Ventilation

The purpose of this study is to test if feedback based on device data cards improves the use of non-invasive positive pressure ventilation (NIPPV) in individuals with ALS. NIPPV is a breathing machine that helps to push air into your lungs through a mask. NIPPV has been shown to provide effective noninvasive breathing support (i.e. helps to maintain breathing without a tube in the throat), to extend life, and to improve quality of life (QOL) in ALS. The data card records critical information about the use of the noninvasive ventilator including how much it is being used (acceptance) and whether there is mask leakage or differences in the amount of air movement. However, to date data card monitoring has not been incorporated into routine ALS clinic practice. Therefore we want to investigate whether data card monitoring and communication of these results to clinicians and patient families promotes “optimal use” of NIPPV including better acceptance and adherence.
New and Ongoing Initiatives

Assistive Technology
Through specific grants and donations, we have developed a library of equipment that is available for demonstration, education and trial. Individuals with ALS will have the opportunity to try some assistive technology including access to computers and communication devices. We will also provide information on purchasing devices that can help you with environmental control and access. Most recently we have added iPads with software to allow communication.

Education
We have been active in education of health professionals in the community caring for people with ALS as well as in clinic education. We are initiating several new educational programs. These will include educational videos about feeding tubes as well as ventilators, educational seminars which will be in the form of webinars, conference programs, and DVDs, and written materials. We encourage you to let us know what you would like to hear about.

Neuropsychiatric Examination
While the traditional teaching has been that cognition (thinking and memory) in ALS remains intact, recent evidence suggests behavioral and memory deficits from frontal lobe brain involvement occur in a sizable number of people living with ALS. As a result of these changes, people living with ALS may have more difficulty with compliance and decision making. Therefore we are now integrating neuropsychiatric testing at clinic visits in order to identify any problems as early in the disease as possible. In this way we can initiate compensatory strategies and encourage decision making when people are still capable.