Deater Foundation, Inc.

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Deater Foundation Newsletter 2015

A Foundation dedicated to finding the cause and cure of HSAN1

Hereditary sensory neuropathy type 1A (HSAN1) is a condition characterized by nerve abnormalities in the legs and feet (peripheral neuropathy). Many people with this condition experience prickling or tingling sensations (paresthesias), numbness, and a reduced ability to feel pain and sense hot and cold. Some affected individuals do not lose sensation, but instead feel shooting pains in their legs and feet. As the disorder progresses, the sensory abnormalities can affect the hands, arms, shoulders, joints, and abdomen. Affected individuals may also experience muscle wasting and weakness as they get older. Weakness in the ankle muscles can make walking difficult. As the condition progresses, some people with hereditary sensory neuropathy type IA require wheelchair assistance.

Individuals with hereditary sensory neuropathy type 1A typically get open sores (ulcers) on their feet or hands or infections of the soft tissue of the fingertips (whitlows) that are slow to heal. Because affected individuals cannot feel the pain of these sores, they may not seek immediate treatment. Without treatment, the ulcers can become infected and may require amputation of the surrounding area or limb.

Some people with hereditary sensory neuropathy type 1A develop hearing loss caused by abnormalities of the inner ear (sensorineural hearing loss). Hearing loss typically develops in middle to late adulthood.

The signs and symptoms of hereditary sensory neuropathy type 1A can begin anytime between adolescence and late adulthood. While the features of this condition tend to worsen over time, affected individuals have a normal life expectancy if signs and symptoms are properly treated.

Mutations in the *SPTLC1* gene cause hereditary sensory neuropathy type IA. The *SPTLC1* gene provides instructions for making one part (subunit) of an enzyme called serine palmitoyltransferase (SPT). The SPT enzyme is involved in making certain fats called sphingolipids. Sphingolipids are important components of cell membranes and play a role in many cell functions.

SPTLC1 gene mutations reduce the amount of functional SPTLC1 subunit that is produced, which results in an SPT enzyme with altered activity. This altered enzyme makes molecules called deoxysphingoid bases, which it does not normally produce. Because of this new function, the SPT enzyme's production of sphingolipid is reduced. Overall, there does not seem to be a decrease in sphingolipid production

because the body is able to compensate for the SPT enzyme's reduced production. When accumulated, deoxysphingoid bases are toxic to neurons. The gradual destruction of nerve cells caused by the buildup of these toxic molecules results in loss of sensation and muscle weakness in people with HSANI. Although the SPT enzyme does not produce a normal amount of sphingolipids, the body is able to compensate, and there does not seem to be an overall reduction of these fats in the body.

This condition is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder.

Hereditary sensory neuropathy type 1A is a rare condition; its prevalence is estimated to be 1 to 2 per 100,000 individuals. In most cases, an affected person has one parent with the condition.

National Institutes of Health: http://ghr.nlm.nih.gov/condition/hereditary-sensory-neuropathy-type-ia

Progress report on the L-serine HSAN1 Trial
by Florian Eichler, M.D.

There are 18 subjects currently enrolled in the two-year, double-blind, placebo-controlled trial studying the efficacy of L-serine in patients with HSAN1. This is lower than our original recruitment aim of 20. However, at the last meeting of the Data Safety Monitoring Board (DSMB) it was discussed that if two additional subjects could not be identified, then enrollment should be closed. Of the 18 subjects enrolled, all have completed their 48-week visit.

The study was initially randomized to placebo versus study drug, and both the participants and the investigators were blinded as to who was on placebo and who was on the study drug. At week 48 all participants were switched over to L-serine, regardless of their randomization from the previous year. The investigators are blinded until the end of the study, so they currently cannot assess whether L-serine is more effective than placebo.

To date no adverse events have been deemed related to the study drug. To ensure data integrity and compliance with the study protocol, for which we receive our funding, we have regular DSMB meetings scheduled. During the last DSMB meeting the investigators also discussed an open label extension until the DSMB meeting following the last study visit. We are in the process of discussing this with the Massachusetts General Hospital Institutional Review Board as well as with the Food and Drug Administration, who provided funding. In an open label extension, at the conclusion of a randomized, placebo-controlled trial, all participants are invited to take the active study drug, regardless of whether they were on the active study drug or placebo. Researchers continue to gather information from participants during the open-label phase. If a drug is shown to be ineffective or unsafe, the open-label extension is closed.

We also had the Partners Human Research Quality Improvement Program complete an internal audit on our trial, and have been in close contact with their team to ensure Good Clinical Practice compliance. All of these oversight programs insure the integrity of the study.

New Research

In the laboratory, new research continues to provide new insights into HSAN1 and related neuropathies. In addition to amino acids, lipid (fat) content in the diet may influence HSAN1 symptoms and disease progression. In HSAN1 mice, high fat diets seemed to cause an earlier onset of symptoms. This may help explain why some people have symptoms earlier, or show faster progression. Controlling lipid/fat intake may help manage HSAN1 symptoms.

The amino acid L-serine seems to play a beneficial role in HSAN1, and may also improve neuropathic symptoms in other diseases such as Diabetic Neuropathy. Diabetic mice display neuropathy similar to HSAN1, and L-serine in these mice showed positive results in terms of symptoms and nerve pathology.

Lastly, we discovered that cultures of sensory neurons from HSAN1 mice respond differently to injury. HSAN1-associated mutations seem to cause excessive growth and branching of sensory neurons. This may represent a poor response to neuronal damage, which in culture can be corrected with L-serine. These results warrant a closer investigation of nerve damage in the earlier stages of HSAN1.

6 Months Left!

a personal perspective on the L-serine Supplementation Study by Jon Ellsworth

When I was asked to put together a quick article on my experience with the trial, I wasn't really sure what to say. But I will give it a shot anyway. For the past 18 months, I have made numerous trips to Boston to participate in the two-year trial with the Serine supplement. I have become quite familiar with the process to get to and from the airport and the hospital on each end. The folks that are coordinating all of the Study do a great job getting all of our travel and visits scheduled out.

Since I have lived in Florida for the last eight years, going to Boston in November 2013 was a bit interesting. I had not experienced winter in seven years, and there were even some snow flurries to welcome my first visit. I don't own a winter coat, so I am always the crazy looking person in the airport that isn't dressed for the occasion.

The study itself is actually quite simple. I get to take this Serine supplement three times a day, that doesn't really taste so great, but all in all a little bit of bad taste for the potential to stop or reverse any effects of HSAN1 are well worth it. I have not been a big fan of nerve conduction testing or skin biopsies, but it's a very small price to pay for the doctors to get some quality research information. I have said from the start, that at 40 years old I am not participating in this study to necessarily help me but more to help future generations to come including possibly my children.

Research is quite expensive and I am very happy that the doctors in Boston are willing to do what they can to help generate funds and look for grants in order to continue research. The only way to ever figure this whole thing out is to continue research. I'm glad that the company I work for,

Enterprise Holdings, has been willing to donate money each year for the last 9 or 10 years. In the grand scheme of things what they donate isn't much, but every little bit helps.

Finally, I just want to thank all of the people who help with funding; the doctors that are doing research - especially Drs. Brown and Eichler; the study coordinators Diane, Elise and Kailey; those who give of their time and resources to assist and operate the Deater Foundation; and finally to my wife and kids whose support is vital to my participation.

Foundation Donation

The Deater Foundation is grateful to Jon Ellsworth and Enterprise Holdings, the largest car rental service provider in the world (Enterprise, Alamo, and National). Because of Jon's efforts through his employer, Enterprise Rent-A-Car, and the generosity of the Enterprise Holdings Foundation, a donation of **$5,000.00** was received this year. The **$5,000.00** given this year is an increase of $500.00 over the record amount donated last year! **Enterprise has provided the Deater Foundation with over $22,000.00 in the 9 years that the organization has supported our cause.**

The Enterprise Holdings Foundation gives back and strengthens through charitable support the thousands of communities where our employees and their customers work and live.

Our giving flows from the belief that we owe our success to the communities we serve, and we must support their good causes in return.

Many companies have a fund or a foundation set up for philanthropic purposes. We encourage you to check with your Human Resources Department to see if your company offers a grant or gift matching program to benefit non-profit organizations.

NATURAL HISTORY AND BIOMARKERS IN HEREDITARY SENSORY NEUROPATHY TYPE 1

Fridman, V., Oaklander, A.L., David, W.S., Johnson, E.A., Pan, J., Brown, R.H., and Eichler, F.S. (2015), Muscle Nerve, 51: 489-495. doi; 10.1002/mus24336

Last year we reported on an article about to be published. The manuscript was accepted in July, 2, 2014, first published online in February this year, and is included in the April 2015 issue of the journal, "Muscle and Nerve".

This study used “a questionnaire created by HSAN1 patients plus a follow-up survey created by our group”. Eric Newcomer and Tami Newcomer Murphy devised and distributed the original survey. The researchers also analyzed results of nerve conduction, autonomic function testing, and skin biopsies. The purpose of the study was “to characterize the natural history and disease progression of HSAN1 and to assess the utility of various outcome parameters to identify the best biomarkers for future clinical trials.” The conclusion was that the “results confirm sensory loss as the initial symptom of HSAN1 and suggest that skin biopsy may be the most promising biomarker for future clinical trials.”

At the end of the article is this statement, “The authors thank the families for their participation and the **Deater Foundation** for support.” Thanks to all who contributed to help document this important natural history.

Helpful Products

by Chris Deater Christensen

Removable Hand Grip
Great for places you need to grip with fingertips or just hard to open doors. You can fit your whole hand through- some of us can fit both hands. It makes pulling so much easier. Attaches and detaches easily so you can use it lots of places. So far I have found it to be handy on the dryer and dishwasher. Available at medical supply stores and Walmart.

Shower Dispenser
This $20.00 item changed my life. This shower dispenser is indispensible! It is available at Bed, Bath, and Beyond. It comes in a two or three size dispenser style, sticks to your shower wall, and has many labels so you know what you filled them with! Mine say, “soap”, “shampoo”, and “conditioner”. No more juggling bottles and lids. Just fill the dispensers, push the button, and you are ready to go.
No muss. No fuss.

If you have other helpful products to share, send the information to deaterfoundation@yahoo.com

Deater Family Reunion July 25, 2015 at 12 Noon

Deater Foundation Meeting at 10:30 AM

This gathering of the decendents of Alvin and Ellen Wilson Deater Will be held at the Butler property near Noxen, Pennsylvania and will be preceded by a Deater Foundation meeting open to all.

Everyone is invited and welcome to attend!

An early Deater Family Gathering

The Deater Foundation

The Deater family has been involved in research on Hereditary Sensory and Autonomic Neuropathy Type 1 for eight decades in two centuries. Doctors have dedicated countless hours to research; those affected have endured years of pain and debility. Through it all, hope has lighted the way. Hope burned brightly when the gene was identified. The steady flame flared again when new discoveries turned old assumptions on their head. In recent years research techniques and technology morphed at lightning speed, fanning the flame.

Hope continues to burn in the hearts of those affected and those who care about them and about future generations. Hope burns in the passion of the researchers. Research is more technical and more expensive than ever. Your contributions make a tremendous difference in the ability to maintain hope for treatment and ultimately a cure of this debilitating disease. Please contribute to this important work. 100% of your contribution goes to research. Thank you for your years of support through encouragement, prayer, and donations of money. Our small gifts, gathered together, can make a mighty difference. Each of our small candles of hope can illuminate the path to a cure.
Hope is the physician of each misery- Irish proverb

Deater Foundation Inc. Treasurer's Report:

Balance as of 6/1/14	$32,601.66

Income:		Expense:	
Contributions 6/1/14-12/31/14	5,890.00	Oct 2014 Mass Gen Donation	-5,000.00
Interest 6/1/14-12/31/14	5.89	Oct 2014 U Mass Donation	-15,000.00
Contributions 1/1/15-5/31/15	10,040.00	Network for Good Service/ PayPal Charges	-2.97
Interest 1/1/15-5/31/15	1.84		

Balance as of 5/31/15	$28,536.42

Update on the Genetic Research at the University of Massachusetts
By Robert H. Brown, Jr., D.Phil., M.D.

The UMass Team has made progress in three activities in the laboratory. First, we have continued work on our program to find ways to turn off the gene that makes the mutant HSAN protein (serine palmitoyltransferase or SPT). This has involved developing a set of reagents that can interact with the working template of the gene, which is a string of RNA molecules copied from the DNA in the gene itself. Guided by Dr. Anastasia Khvorova and aided by a graduate student, Havisha Karnam, we have made starting tools - short strings of DNA molecules (known as oligonucleotides, or just "oligos") that bind to the target RNA from the SPT gene. We have generated two types of the oligos and are very encouraged because they both successfully turn off the SPT gene in cells in a Petri dish.

In our second, parallel effort, we have also been studying the degree to which these oligos permeate the target sites in the nervous system (the dorsal root ganglia and spinal cord). We have addressed this in mice, using infusions into the spinal fluid. One of the oligos shows excellent penetration into the target tissues. This provides considerable encouragement that we should be able to take oligo's that silence SPT in a Petri dish, infuse them into the spinal fluid, and attain good silencing of the SPT gene in the nervous system tissues in the mouse.

In our third line of studies, we have continued the efforts to generate new mouse models of HSAN. This has involved making in the mouse SPT gene the same mutations that cause HSAN in people. If all goes well, the resulting mice will have one normal copy of the gene and one mutated copy, which is exactly the balance of genes present in individuals with HSAN. In the transgenic model now in hand, there are two copies of the normal SPT gene and extra copies of an extra gene (the "transgene") with the mutated SPT. This transgenic mouse will continue to be extremely informative in many studies. However, as we move toward testing gene silencing in mice, the improved mouse with one normal and one mutant gene will be very advantageous.

In efforts outside the laboratory, we have been working jointly with Dr. Eichler and the Massachusetts General Hospital team to continue the clinical trial and pursue other issues related to clinical evaluation of HSAN (such as developing biomarkers).

It cannot be over-emphasized that all of us in the HSAN research program are very fortunate to work closely with the Deater Foundation in these investigations. We look forward to another productive year in the laboratory and the clinic. We welcome the chance to help plan another outstanding workshop on HSAN. With the current rate of progress, we anticipate that the next HSAN conference will be timely and exciting, and another milestone on the path to finding a treatment.

----------The Deater Foundation is committed to supporting a fourth international conference to further the understanding of HSAN1----------

In Memoriam: Larry Michael Deater

Larry Michael Deater died February 19, 2015 at his home in Kittery Point, Maine following a brief bout with cancer. The son of Harvey Deater and Charlotte Thompson, he was 59 years old. He graduated from University of New Hampshire with a BA and MA in Education. Larry worked in the hospitality industry for many years. He managed several restaurants in Portsmouth, NH, and owned the managed several restaurants in Portsmouth, New Hampshire, and Privateer restaurant in York Beach. Larry was active in local politics.

Larry was also a gifted teacher of life skills to teenagers with special needs, history to middle-schoolers and at Hesser College, and physicians about HSAN1. All of his adult life Larry coped with HSAN1 with dignity and grace. He fiercely maintained his independence, positive outlook, and sense of humor while participating in numerous research trials, and served on the Deater Foundation board to find a cause and cure for HSAN1. His final selfless act was to offer his body for research. His wife, Rory Robb, requested contributions to the Deater Foundation in his memory.

At Larry's service Dr. Brown said, "Larry had an extraordinary and indelible impact and influence on a small army of physicians and scientists. The combination of Larry's tireless efforts, his warm and engaging people skills and always infectiously positive good nature has had a hugely positive impact on the science of neuropathy and on the work and careers of a host of people. Larry will always be right there at our sides on the team, and none of us will rest until the job is done."

DFI

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