2016 – 2017
YEAR IN REVIEW

THE LATEST IN RESEARCH IN
FAMILIAL DYSAUTONOMIA

NYU Dysautonomia
A MESSAGE FROM OUR DIRECTOR

Our clinical research program at the Dysautonomia Center is dedicated to treating familial dysautonomia (FD). Having directed the Center for the last 10-years, I’ve seen how research can drive advances that shape our approach to treating FD.

A decade ago, we had a lot to learn. We’ve taken the lead in FD research and transformed much of our thinking about the disease. This progress was made possible thanks to a dedicated talented team of researchers at the Center and the partnership between the Foundation and FD families.

Every person on our team is committed to making the lives of people living with FD better and bringing new treatments to the clinic. We focus our research efforts on understanding the neurological underpinnings of FD so that we can rethink our medical approach and make rational decisions on how to prevent complications and lessen suffering.

As always, we want you to see the Center as a resource for your health. A major advantage of having the research program closely linked with our FD clinic is that important discoveries can quickly be translated into practice.

We have an active translational research program for FD. We have treatment trials aimed at reducing the burden of symptoms. There are also on-going treatment trials to modify the genetic defect of FD. We are studying the gut microbiome to help pave the way to develop better treatments for the gastrointestinal problems. We are working on ways to overcome imbalance and improve walking. We are using cognitive behavioral therapy as a way to help patients manage stressful situations. We encourage you to read about our trials in this booklet and consider participating.

The research progress we can make is only possible thanks to the patients and families that give up their time to participate in studies. We still have a lot to do for the future. Now more than ever, we are in a race to make a difference. Each time a family with FD gives up their time to help research, they bring us a step closer to understanding FD and developing a new treatment. When you give up your time to take part in research, you are also helping the FD community throughout the world.

Here is a highlight of our research achievements within the last year. You will also find a list of our current research trials.

Horacio Kaufmann, MD, FAAN
Felicia B. Axelrod Professor for Dysautonomia Research
Director of the Dysautonomia Center
A NEW ARTICLE MARKS RESEARCH PROGRESS

Familial dysautonomia is rarer than most rare diseases, but this little known genetic disorder has become a gateway for research that could lead to new treatments for a range of inherited diseases. FD has no cure and is hard to diagnose. The disorder was first described in the medical literature in 1949, by New York City pediatricians that were intrigued by the bizarre but similar symptoms of 5 children they had encountered. Although doctors may learn briefly about FD in medical school, very few have actually encountered a patient. This means that even today, for most new patients, diagnosis can be a long struggle.

A new paper in Progress in Neurobiology focuses on FD, as an example of how the challenges of a rare disease can be overcome through partnership and perseverance in the pursuit of better medical care.

Origins

Our genetic code is inherited and stretches back through time. FD is caused by a mutation in the IKBKAP gene. Researchers have dated the mutation back to the 1500s, and its origins are deeply rooted in European history.
After centuries of Crusades and forced expulsions across Europe, the Jewish population was diminished to very small numbers. In 1785, Catherine the Great restricted the Jews to live within boundaries – in an area known as the Pale of Settlement. Within these tight geographical constraints, the population grew exponentially with subsequent generations. This meant recessive genetic mutations – that pose no problem to the carrier, could flourish within the Ashkenazi Jewish population. It is what is known as bottleneck in population genetics.

Conditions within the Pale were not the best, with large numbers emigrating. Today cases of FD throughout the world closely map emigration patterns of Jews from Europe before the 1900s. The genetic mutation has been traced back to a “founding” person in the Pale of Settlement at the period of rapid population growth.

Once the mutation was discovered in 2001, it allowed carrier testing, which means today, fewer children are born with the disease.

**Progress**

More recently, researchers have been unraveling why patients that inherit two copies of the *IKBKAP* mutation lack the ability to control most of the body’s automatic functions. Problems with swallowing, breathing, tear production, control of the organs, and bone growth and walking all emerge. By carefully examining their neurological function, it became clear that the sensory information coming from the body to the brain is absent.

Finding why these bodily functions go wrong has had a major impact on how patients are treated. Partnership between academic researchers, federal granting agencies, and patient advocacy groups has made it possible for us to develop a pipeline for drug development and translational clinical trials. Taking things to the clinic requires vigorous scientific testing to see if a treatment is both safe and effective.

The new article in *Progress in Neurobiology* summarizes our present understanding of the biological underpinnings of the disease. The article is the latest and most comprehensive review on everything that is known about FD. It describes the history, clinical features and genetic cause. Basic scientists, clinical researchers and affected families have partnered together to change the lives of patients living with this rare genetic disease.
Familial dysautonomia (FD) is a rare neurological disorder caused by a splice mutation in the IKBKAP gene. The mutation arose in the 1500s within the small Jewish founder population in Eastern Europe and became prevalent during the period of rapid population expansion within the Pale of Settlement. The carrier rate is 1:32 in Jews descending from this region. The mutation results in a tissue-specific deficiency in IKAP, a protein involved in the development and survival of neurons. Patients homozygous for the mutations are born with multiple lesions affecting mostly sensory (afferent) fibers, which leads to widespread organ dysfunction and increased mortality. Neurodegenerative features of the disease include progressive optic atrophy and worsening gait ataxia. Here we review the progress made in the last decade to better understand the genotype and phenotype. We also discuss the challenges of conducting controlled clinical trials in this rare medically fragile population. Meanwhile, the search for better treatments as well as a neuroprotective agent is ongoing.
NEW FINDINGS SHOW REMARKABLE INBORN ADAPTABILITY OF THE BRAIN TO PROTECT ITSELF AGAINST LOW BLOOD PRESSURE

The human brain weighs less than 2% of our total body weight, yet consumes 20% of the body’s energy. The brain is fueled by oxygen and glucose rich blood, which flows through a network of tiny arteries supplying each brain cell. These blood vessels are constantly working to regulate flow and keep it stable. They act as the brain’s own defense line, making sure it can protect itself against systemic blood pressure changes. Each time we stand up, they dilate to re-route more blood to reach areas with higher metabolic demands.

In patients with familial dysautonomia (FD), blood pressure swings wildly from low to high based on gravity and emotions. Patients lack the ability to coordinate the autonomic nervous system, so they cannot control the pressure of blood reaching the brain. After just moments of standing, blood pressure can plummet to extraordinarily low values; at which any healthy person would lose consciousness and faint.

But quite remarkably, patients with FD seldom faint. To investigate why, the NYU Dysautonomia team set out to measure how the brain responds to hypotension. Using a small ultrasound probe they were able to monitor blood flow in the brains of patients with FD and healthy volunteers while sitting and standing. The measurements showed that despite very low blood pressure at the level of the brain when standing, the pattern of blood flow changes in patients was not different to controls. Patients were still able to keep their blood flow constant and ensure that the brain was receiving oxygenated blood to remain conscious in the face of hypotension.

Despite being born with a catastrophic lesion that prevents the control of blood pressure, these patients have extraordinary abilities to protect the brain. "The tiny arteries that regulate blood flow in
the brain work remarkably well” explained Dr. Lucy Kaufmann, “this probably explains why patients rarely faint when the blood pressure is low and they have a low incidence of hemorrhagic stroke despite their blood pressure surging to high levels.”

This finding teaches us a lot about the intrinsic ability of the cerebral vessels to quickly respond to ensure the brain is receiving enough blood to remain upright and conscious. Because patients have the ability to compensate for hypotension, when they do faint, it should raise suspicions. “We need to rule out whether something that else may be going on like dehydration, bleeding, anemia, or hypoxia due to a lung infection” added Dr. Kaufmann. Patients with FD are born with an inherent skill to regulate the brain’s circulatory system and adapt to support consciousness. This is something they do better than you and I.

THE PAPER:


Familial dysautonomia is an inherited autonomic disorder with afferent baroreflex failure. We questioned why despite low blood pressure standing, surprisingly few familial dysautonomia patients complain of symptomatic hypotension or have syncope. Using transcranial Doppler ultrasonography of the middle cerebral artery, we measured flow velocity (mean, peak systolic, and diastolic), area under the curve, pulsatility index, and height of the dicrotic notch in 25 patients with familial dysautonomia and 15 controls. In patients, changing from sitting to a standing position, decreased BP from 124 ± 4/64 ± 3 to 82 ± 3/37 ± 2 mmHg (p < 0.0001, for both). Despite low BP, all patients denied orthostatic symptoms. Middle cerebral artery velocity fell minimally, and the magnitude of the reductions were similar to those observed in healthy controls, in whom BP upright did not fall. While standing, patients had a greater fall in cerebrovascular resistance (p < 0.0001), an increase in pulsatility (p < 0.0001), and a deepening of the dicrotic notch (p = 0.0010), findings all consistent with low cerebrovascular resistance. No significant changes occurred in controls. Patients born with baroreflex deafferentation retain the ability to buffer wide fluctuations in BP and auto-regulate cerebral blood flow. This explains how they can tolerate extremely low BPs standing that would otherwise induce syncope.
BREAKTHROUGH FOR THE ACUTE TREATMENT OF CRISIS IN PATIENTS WITH FD

Life is very unpredictable at times, but imagine how it must feel like to have no control over your body’s response to stress. This is part of everyday life for patients with familial dysautonomia (FD).

Without warning, their blood pressure surges, their heart races at more than 100 beats a minute, and they quickly become overwhelmed with nausea and cannot stop retching or vomiting. These episodes – which families often call a crisis – can be terrifying for patients. Uncontrollable crisis episodes frequently land patients in the hospital, sometimes for days on end.

While carbidopa has shown to be effective for the treatment of recurrent frequent crises, it has to be taken each day. Patients that do not have frequent episodes may not want to take a preventative medication every day. This leaves them with limited options at the times that they do have a crisis.

Until now...

Three years ago, one of our patients had undergone spine surgery and immediately thereafter he began suffering a severe autonomic crisis. None of the usual measures were working and he was transferred to the intensive care unit. His father, an experienced anesthesiologist, suggested that we try a new compound, dexmedetomidine (Precedex). What an excellent idea that turned out to be. Soon after, his blood pressure became under control, his heart rate slowed and his symptoms began to ease.

In 2015, the NYU Dysautonomia Center started collaborating with the Pharmacy Department to evaluate the effectiveness of dexmedetomidine in a bigger group of patients with FD. Each time patients were admitted to NYU for uncontrollable crisis and dexmedetomidine was administered, we methodically monitored their progress. In almost all people, the adrenergic crisis symptoms were under control within one hour and had completely resolved by the time the medication was weaned off. This means we now have a way to safely and effectively stop acute adrenergic crisis induced due to emotions or illness. It enables us to treat the underlying cause, while making the patients comfortable.
Dexmedetomidine acts within the brain and spinal cord on α2 receptors. Its mechanism of action is somewhat similar to clonidine, but the drug is far superior and much more specific. Dexmedetomidine needs to be infused constantly because it acts for only a very short period of time. This is a great advantage, as it allows us to tightly regulate the dose at the touch of a button, allowing the effect of the drug can be stopped quickly. Importantly, it does not suppress the drive to breath, so it appears to be a safer alternative.

What is next?

At the moment, dexmedetomidine can only be given IV while in the intensive care unit. But this may change. We are planning a clinical trial using this compound intranasally. Stay tuned.

THE PAPER:

Dexmedetomidine for refractory adrenergic crisis in familial dysautonomia.

Objective: Adrenergic crises are a cardinal feature of familial dysautonomia (FD). Traditionally, adrenergic crises have been treated with the sympatholytic agent clonidine or with benzodiazepines, which can cause excessive sedation and respiratory depression. Dexmedetomidine is a centrally-acting α2-adrenergic agonist with greater selectivity and shorter half-life than clonidine. We evaluated the preliminary effectiveness and safety of intravenous dexmedetomidine in the treatment of refractory adrenergic crisis in patients with FD.

Methods: Retrospective chart review of patients with genetically confirmed FD who received intravenous dexmedetomidine for refractory adrenergic crises. The primary outcome was preliminary effectiveness of dexmedetomidine defined as change in blood pressure (BP) and heart rate (HR) 1 h after the initiation of dexmedetomidine. Secondary outcomes included incidence of adverse events related to dexmedetomidine, hospital and intensive care unit (ICU) length of stay, and hemodynamic parameters 12 h after dexmedetomidine cessation.

Results: Nine patients over 14 admissions were included in the final analysis. At 1 h after the initiation of dexmedetomidine, systolic BP decreased from 160 ± 7 to 122 ± 7 mmHg (p = 0.0005), diastolic BP decreased from 103 ± 6 to 65 ± 8 (p = 0.0003), and HR decreased from 112 ± 4 to 100 ± 5 bpm (p = 0.0047). The median total adverse events during dexmedetomidine infusion was 1 per admission. Median hospital length of stay was 9 days [interquartile range (IQR) 3-11 days] and median ICU length of stay was 7 days (IQR 3-11 days).

Conclusions: Intravenous dexmedetomidine is safe in patients with FD and appears to be effective to treat refractory adrenergic crisis. Dexmedetomidine may be considered in FD patients who do not respond to conventional clonidine and benzodiazepine pharmacotherapy.
FINDING THE HIDDEN TEARS IN FD

In 1949, when pediatricians Conrad Riley and Richard Day first encountered 5 children unable to cry with tears, they knew they’d stumbled upon something quite unique. The syndrome they went onto report in the medical literature later became known as familial dysautonomia – the disease without tears.

Fast forward 68-years later and this no longer appears to be the case.

Human tears are produced in the lacrimal glands and secreted through ducts onto the surface of the eye. They contain oils and lubricants and flow continuously in response to chemical and irritant stimuli to keep the cornea clean and moist. These are known as reflex tears, and are released when the eye is exposed to wind, foreign bodies or irritating gases. Psychogenic crying – in response to emotional stress – appear to be unique to man and key to social bonding. Usually, infants begin shedding overflow tears within the first weeks of life. The parents Riley and Day encountered never saw their children weep in pain, sorrow or anger.

The lack of tears in patients with FD takes its toll on the eye. Without the liquid film on the surface, the corneas become injured by dust and debris, heal poorly, and become clouded by scars resulting in defects in the visual fields. Around 30% of patients with FD will lose their sight after repeated corneal abrasions.

When Dr. Horacio Kaufmann joined forces with Dr. Carlos Mendoza 5-years ago, they set out on a mission to better understand the eye problems facing patients with FD. Tear production was one of the areas vastly understudied.

Using a substance known as pilocarpine, they were able to show that the tear apparatus itself was intact. With pilocarpine drops, the tears could be drawn out of the lacrimal glands and released on to the surface of the eye. This meant that rather than a disease without tears, FD was a disease with hidden tears.
Now the team had to understand why patients with FD cannot cry.

Reflex tears are produced when the sensory receptors in the surface of the eye are excited. Using a special pen-like device, known as an esthesiometer, with nylon-tipped filaments they were able to measure the sensitivity of the cornea in patients with FD. What they showed was remarkable. Some patients had more sensitive corneas, were able to produce more basal tears, and had a thicker liquid film on the surface of the cornea.

“"It all makes sense," explained Dr. Kaufmann “the lacrimal glands are there and we can make them shed tears with drugs that we can deliver as eye drops”. Secretagogues – like pilocarpine – hold promise for the treatment for dry eye in FD.

What is still not apparent is why patients with FD don’t cry with emotions. The connections from the central nervous system that innervate the lacrimal system may not be fully developed.

THE PAPER:

Familial dysautonomia: a disease with hidden tears.
Mendoza-Santiesteban CE, Palma JA, Norcliffe-Kaufmann L, Kaufmann H

Defective lacrimation is a cardinal feature of familial dysautonomia (FD). The reason for the alacrima in FD is unclear. We examined the relationship between corneal sensory thresholds and basal tear production. We then conducted a single-blind placebo-controlled clinical trial to test whether topical administration of the M3 muscarinic agonist pilocarpine (4%) could stimulate tear production. Sixteen patients completed the protocol [11 women, 5 men, 32 eyes; mean age (+standard deviation) 27 ± 8 years]. The results show that patients with FD have functional lacrimal glands, which can be stimulated with topical cholinergic agonists, and that afferent pathways from the cornea regulate, at least in part, basal tear production.
A BREAKTHROUGH IN THE RACE TO SAVE VISION FOR PATIENTS WITH FD

Our ability to see depends on dozens of tiny ganglion cells in our retina that encode our visual world. These cells send electrical signals through the optic nerve to the brain where they are interpreted.

For patients with familial dysautonomia (FD) – a rare Jewish genetic disease, their world progressively darkens overtime as they lose visual acuity. They become unable to distinguish colors or their intensity as well as differences between light and shade. Instead of being sharp and well defined, objects become murky and impossible to perceive at a distance, especially at night.

The optic nerve transmits electrical signals from photoreceptors in the retina to the brain. This enables us to interpret visual images.

Peering into the eyes of patients with FD, Dr. Carlos Mendoza – a specialist in nerve cells in the eye – noticed something quite odd. Their optic nerves were pale and appeared to be dying. Using a technique known as optical coherence tomography (OCT) he was able to measure the thickness of the specific layers in the retina, and showed how they thin overtime. “We knew there was a problem,” explained Dr. Mendoza, “but which cells were dying and why they were dying was not clear”.

Before Adam* lost his fight against FD he made clear to his parents that he wanted to donate his body to help others with the disease. His decision provided scientists with the possibility of understanding why patients with FD lose their site.
FD is caused by a single mutation in just one base pair along the strand of DNA that encodes for a protein known as IKAP. This “typo” in the genetic code has catastrophic consequences. Dr. Mendoza suspected that the loss of vision was due to mitochondrial dysfunction. Previous findings had also suggested that there was a problem with the mitochondria.

Mitochondria are tiny bodies that live within a cell and are responsible for generating energy. These energy-generating machines are essential to the health of each cell. The average cell has several hundred mitochondria, which are shuttled around the cell to balance its energy needs. Dr. Mendoza had seen many patients with optic neuropathies due to mitochondrial dysfunction. To him the eye in FD looked strikingly similar.

Progress in the battle to save sight

In collaboration with Tufts University, the team at the Center was able to study the eyes from patients with FD with microscopic detail. Not only did they confirm that the ganglion cells in the retina were dying overtime, they also showed a distinct problem with the mitochondria. These tiny energy-making machines were degenerating, leaving the cells of the retina starved of energy. The cells that the patients were losing were the ones with the highest energy demands – the ones that needed their mitochondria the most.

These findings are very important. By rescuing the mitochondria and boosting their health we have a new target to help save vision. "This is an incredible discovery," explained Dr. Kaufmann – Director of the Center “it gives us new opportunities of drugs we can try. Each day we come to work thinking of ways we can help stop patients going blind. This is a real step forward in that mission."

THE PAPER:

Pathological confirmation of optic neuropathy in familial dysautonoma
Mendoza-Santiago et al., Palma JA, Hedges TR 3rd, Laver NV, Farhat N, Norcliffe-Kaufmann L, Kaufmann H.

Clinical data suggest that optic neuropathy and retinal ganglion cell loss are the main cause of visual decline in patients with familial dysautonoma, but this has not previously been confirmed by pathological analyses. We studied retinas and optic nerves in 6 eyes from 3 affected patients obtained at autopsy. Analyses included routine neurohistology and immunohistochemistry for neurofilaments, cytochrome c oxidase (COX), and melanopsin-containing ganglion cells. We observed profound axon loss in the temporal portions of optic nerves with relative preservation in the nasal portions; this correlated with clinical and optical coherence tomography findings in 1 patient. Retinal ganglion cell layers were markedly reduced in the central retina, whereas melanopsin-containing ganglion cells were relatively spared. COX staining was reduced in the temporal portions of the optic nerve indicating reduced mitochondrial density. Axonal swelling with degenerating lysosomes and mitochondria were observed by electron microscopy. These findings support the concept that there is a specific optic neuropathy and retinopathy in patients with familial dysautonoma similar to that seen in other optic neuropathies with mitochondrial dysfunction. This raises the possibility that defective expression of the IkB kinase complex-associated protein (IKAP) resulting from mutations in IKAP affects mitochondrial function in the metabolism-dependent retinal parvocellular ganglion cells in this condition.
Abstracts are brief summaries of scientific work. They provide an important opportunity for our research team to present their work on FD to the scientific community at International Meetings. Each abstract submitted to a meeting is peer reviewed, and only accepted if the review panel deems them scientifically sound. Abstracts are published in conference proceedings and indexed online, which means that they can be read by other clinicians and scientists.

Abstracts are an important part of the progress in any research project. When presented at a meeting, other scientists have the opportunity to review the work. The feedback they provide offers an important chance to find ways to enhance the work.

We believe strongly that our research in FD should be presented to the scientific community. Not only does this benefit our researchers, but it also allows others to stay up to date with the latest research findings in FD.

Award winning work

In the last year, the Center’s work in FD has been recognized at several international clinical meetings. PhD medical student Jelle de Jong rotated at the Center as part of the clinical observership program. In November 2016, he was awarded the Don Summers Memorial MSA Travel Award for his work on blood pressure control in patients with FD at the Annual American Autonomic Society Congress. At that same meeting, Dr. Alberto Palma won the Society’s top poster prize award for the work on stimulating tears in FD.

Scientific presentations describing our work in FD were presented at the American Autonomic Society (San Diego, November 2016), the Rare Metabolic Disorders Conference (London, United Kingdom, December 2016), the European Federation of Autonomic Societies (Innsbruck, Austria, February 2017) and at the American Academy of Neurology Meeting (Boston, April 2017).

To achieve our goals to extend and improve the quality of life for patients living with FD, we know it is important to educate the clinical research community on the progress that we are making. Our research team was very productive in the last year and they are continuing to work hard. We are fortunate to be supported in our mission by the Dysautonomia Foundation.
Background: Patients with familial dysautonomia (FD) have asthma-like exacerbations with coughing, wheezing, and hypoxia. While many are treated empirically with bronchodilators, it is still unknown whether airway obstruction in these patients is pharmacologically reversible by modifying autonomic tone.

Methods: We conducted a two-center, randomized, placebo-controlled, double blind, crossover study to assess the safety and efficacy of albuterol (a direct acting sympathomimetic) vs. ipratropium bromide (a parasympatholytic muscarinic blocker). Albuterol (0.083%, 2.5 mg/3ml), ipratropium bromide (0.02%, 500mcg/2.5 ml) and placebo (0.9% sodium chloride 3 ml) were administered by nebulization in random order over 15 minutes in the seated position. Airway responses were assessed with spirometry and impulse oscillometry pre- and 30 minutes post-dose. Continuous blood pressure, RR-intervals and cardiac impedance were measured non-invasively (TaskForce Monitor, CNSystems, Graz, Austria). Raw data tracings were analyzed blindly.

Results: Fifteen patients were enrolled. All had a documented history of aspiration into the airway and acute episodes of coughing and wheezing. Beta-adrenergic activation with albuterol significantly increased forced vital capacity (p=0.041) and forced expiratory volume within 1 second (p=0.002). In line with this, impulse oscillometry at 5Hz was significantly lower post-albuterol (p=0.006), suggesting a reduction in total airway resistance. Blockade of muscarinic acetylcholine receptors with ipratropium had less bronchodilatory effects. Both treatments were well tolerated and had no effects on blood pressure, heart rate or derived cardiac output.

Conclusions: In patients with FD, beta-adrenergic stimulation more effectively reversed airway obstruction than muscarinic blockade. Both treatments were well tolerated and had no measureable systemic effects.

This work was funded by the Dysautonomia Foundation, Inc.
Dexmedetomidine: A novel approach to treating refractory adrenergic crisis in familial dysautonomia

Presented at the American Autonomic Society Annual Meeting (November 2016, San Diego, USA)


Background: Stress-induced adrenergic hypertensive crises are a cardinal feature of familial dysautonomia (FD). Classically, this is treated with clonidine and benzodiazepines, which cause excessive sedation and can lead to respiratory arrest. Dexmedetomidine is a recently introduced compound, 8 times more specific for central alpha-2 adrenergic receptors than clonidine, resulting in less sedation. Advantages over clonidine are also that dexmedetomidine can be administered intravenously (IV), and its half-life is shorter (12 h vs. 2 h), which allows an easy titration.

Methods: Retrospective chart review of IV dexmedetomidine use to treat refractory hypertensive crisis in patients with FD.

Results: IV dexmedetomidine was used 15 times in 9 patients (mean age: 26 years; 44% men) with acute adrenergic crisis. Crisis triggers included respiratory infection (n=8), emotional stress (n=3), surgery (n=1), bacteremia (n=1), gastroenteritis (n=1) and bleeding gastric ulcer (n=1). Before treatment, all patients had signs of adrenergic activation including skin flushing, nausea/retching, vomiting, diaphoresis, and agitation. Blood pressure (BP) was 161±6/102±6 mmHg and heart rate (HR) was 113±4 bpm. IV dexmedetomidine was administered at an average rate of 0.51±0.13 mcg/kg/hr. One hour post-infusion, BP decreased to 116±5/58±6 mmHg (p<0.0001) and HR to 97±5 bpm (p=0.002). Drowsiness occurred in one patient, although he was easily arousable. There were no episodes of rebound hypertension or respiratory depression. In one case, rapid titration at a high dose resulted in paradoxical hypertension, which subsided immediately upon dexmedetomidine discontinuation.

Conclusions: IV dexmedetomidine is an effective, well-tolerated approach for managing adrenergic crises in patients with FD. In contrast to other commonly used medications, dexmedetomidine does not induce excessive sedation or respiratory depression. In a small percentage of patients, rapid IV dosing may result in paradoxical hypertension due to its direct action on peripheral postsynaptic alpha2-adrenergic receptors.

This work was funded by the Dysautonomia Foundation, Inc.
Familial dysautonomia (FD) is frequently referred to as a disease with no tears, but the underlying reason for this alacrima is unknown. Normally, nerves in the cornea stimulate the production of tears from lacrimal glands in the eye. Whether the absent/reduced tears in FD is due to denervation or an abnormality in the lacrimal glands themselves is unclear. To clarify this, we used pilocarpine (4%, a parasympathetic M3 receptor agonist), which can be applied topically to the eye to stimulate the tear secretion directly in the lacrimal glands, bypassing the nerve pathways.

We assessed corneal sensitivity using a Cochet-Bonnet esthesiometer. Tear volume was estimated with the Schirmer’s test (a scaled paper strip placed in the lower eyelid and the length of moisture measured after 5 minutes). Schirmer’s test was performed four times: (1) at baseline, (2) 30-minutes after instillation of normal saline (placebo, 2 drops), (3) 30-minutes, and (4) 3-hours after pilocarpine instillation (2 drops).

Basal tear secretion was 6.3mm (±2.6 SD), and 6.9mm 30 min after placebo (±3.0 SD, p<0.395). Thirty minutes after the instillation of pilocarpine, tear volume more than doubled to 19.6mm (±8.3 SD, p<0.001); and the increased tear production persisted at 3 hours (12.6mm±5.1 SD, p<0.001). There was a significant positive correlation between corneal sensitivity and tear secretion at baseline ($R^2=0.74$).

Our results indicate that patients with FD have functional lacrimal glands, which can be stimulated with an M3 agonist to produce tears. Basal tear secretion was directly related to corneal sensitivity. The findings suggest for the first time that tear production in patients with FD can be restored pharmacologically.

This work was funded by the Dysautonomia Foundation, Inc.
NEW STUDY OPENS FOR PATIENTS WITH FD

Tackling rare diseases requires a well-planned strategy. The Center is kick-starting a new clinical project as part of an international coordinated effort to bringing together physicians, researchers and families with FD. The study will help us understand which treatments lead to real improvements for patients.

The FD Natural History Study is designed to collect clinical information from patients with FD overtime and observe the course of their disease. Well-organized natural history studies are very important for rare disease research.

The Center has a long history of caring for patients with FD. Dr. Felicia Axelrod began the first electronic database for patients with FD in 2002. That source of information has led to a number of important discoveries about the disease. It is still used on a daily basis to answer pressing medical questions. But it needs an overhaul.

The new natural history study will build on this existing knowledge and continue to follow patients with FD by collecting their clinical information. The project will unite specialists in FD care from around the globe to capture information from all patients with FD regardless of where they live in a standardized way. All information is made anonymous and details that can identify the patient themselves are removed.

"It's really simple”—explained Dr. Norcliffe-Kaufmann, Principal Investigator for the project —“When patients come to an FD clinic, they grant permission for us to take information from their clinical records. We collect this information to follow the function of each patient’s lungs, heart, kidneys, eyes, gut, sleep patterns, and bone formation. The natural history study will enable us to display this
information in real time. By putting together the data set from all patients with FD, we can evaluate which treatments we use in the clinic actually improve survival and quality of life at different stages of the disease.”

The FD Natural History Study will partner with Dr. Susan Slaughenhaupt at MGH and the team will work with PTC Therapeutics. Patients are asked to give us a small sample of blood for the David Brenner Bio-Repository. This will be used to look at the FD genome and how the protein is expressed, which will ultimately help in the quest to find potential genetic treatments.

However, in order for any therapy to succeed, we must first know what the benchmarks for success will be and how best to measure any improvement, explained Dr. Kaufmann.

This is easier than it sounds. The search for “biomarkers” is a hot topic in research right now and the chase is on. The Dysautonomia Foundation and The Michael J Fox Foundation support the Center’s Eye Lab, dedicated to following neurodegenerative changes in the retina. Patients in the FD Natural History Study will have their retina scans stored in the database archives, so that they can be retrieved and compared year-to-year, Dr. Carlos Mendoza, an investigator in the project explained, “These patients have a progressive optic neuropathy. It is this death of cells in the retina that robs them of their ability to see.” The Center’s goal is to stop patients with FD from going blind. Each year patients have their retina closely scrutinized as part of their clinical care. As Dr. Mendoza explained “I see the retina as a window to follow cell loss and as a target for therapy. The eye gives us great insight into the effectiveness of any drug designed to alter the course of the disease”.

Dr. Alberto Palma will lead the quest to better understand sleep in FD and look at the impact of therapies like CPAP or BiPAP. As he explained, “Sleep is an important issue for patients with FD and we have an urgent need to understand this better. Following patients overtime and carefully documenting their sleep patterns should help us treat sleep disordered breathing to improve the quality of life in FD and avoid related problems”.

The worldwide FD Natural History Study is an important project at the Center. Sharing your clinical information when you have a disease as rare as FD will help you and it will help others, because it will lay the foundations for other scientific projects and help bring new therapies to the clinic. The FD Natural History Study is an important way to unite people, and to speed up progress in medical care.

Patients who participate in the project will not need to undergo any additional tests at their annual visits. The donation for blood for the bio-repository is optional. All data is anonymous. For more details on the study, please contact the Center at: 212-263-7225.
CURRENT CLINICAL TRIALS IN FD

** NEW **
THE NATURAL HISTORY OF FAMILIAL DYSAUTONOMIA
IRB#: S16-01774
ELIGIBILITY: Patients with FD of any age
PURPOSE: To use the clinical information collected during routine medical visits to define the clinical features of FD and how they evolve overtime. The goal of the project is to find biological signals that we can use to track the features of FD to use in clinical trials to test new drug treatments. The study will also measure IKAP protein levels to see how well they correlate with symptoms of FD.
SPONSOR: Dysautonomia Foundation, Inc.

** NEW **
DRONABINOL FOR THE TREATMENT OF NAUSEA AND VOMITING IN FAMILIAL DYSAUTONOMIA
IRB#: S14-01577
ELIGIBILITY: Children above the age of 18 are eligible to participate in this trial
PURPOSE: To assess the safety, tolerability and efficacy of dronabinol for the treatment of nausea in patients with FD. Patients with familial dysautonomia suffer recurrent attacks of uncontrollable nausea and vomiting that can last several hours or days and are severely disabling. The ultimate goal of this study is to demonstrate that dronabinol is a safe, well-tolerated drug that blocks the peripheral formation of dopamine and thus prevents dopamine-induced nausea and vomiting attacks in patients with FD.
SPONSOR: Dysautonomia Foundation, Inc.

** NEW **
AN OPEN-LABEL PILOT TRIAL OF COGNITIVE BEHAVIORAL THERAPY IN FAMILIAL DYSAUTONOMIA
IRB#: S16-01823
ELIGIBILITY: Patients with FD over the age of 18.
PURPOSE: To evaluate the effect of cognitive behavioral therapy in the severity of anxiety and depression in adults with familial dysautonomia. To ascertain the levels of self-esteem in adults with familial dysautonomia at baseline and after the last session of cognitive behavioral therapy.
SPONSOR: Dysautonomia Foundation, Inc.

ENROLLING
CARBIDOPA IN FAMILIAL DYSAUTONOMIA
IRB#: S13-00065
ELIGIBILITY: Patients with FD over the age of 10.
PURPOSE: Researchers at our Center showed that, a drug called carbidopa might dampen the production of norepinephrine during hypertensive crisis in FD, and therefore decrease high BP surges. The goal of this study is to use carbidopa and evaluate the effect in blood pressure peaks and variability, norepinephrine levels and crisis in FD. The drug is currently used to treat other conditions and it is safe. Amendments to the protocol now allow for local monitoring and tele-medicine visits
SPONSOR: Food & Drug Administration Office of Orphan Product Development
A STUDY OF GUT FLORA IN FAMILIAL DYSAUTONOMIA (MIBIOM)
IRB#: s16-00718
ELIGIBILITY: Patients with FD age 4 and older and their family members
PURPOSE: Maintaining a healthy weight is a problem for a number of patients with FD. The aim of this study is to better understand the microorganisms that live in the gut of patients with FD and whether these play an important role in digestive function. In this project, we want to understand if differences in the microorganisms in the gut of patients with FD affect the energy derived from food. We will compare differences between tube and oral fed subjects to better understand the differences and also we will compare it with healthy controls. Better understanding of the microbiome in FD might help also to understand whether fungal overgrowth in the GI tract of FD patients is associated with persistent diarrhea in the absence of known pathogens.
SPONSOR: Dysautonomia Foundation, Inc.

ENROLLING
PROPRIOCETION AND SENSORIMOTOR CONTROL IN HEREDITARY SENSORY AND AUTONOMIC NEUROPATHY
IRB#: s16-00530:
ELIGIBILITY: Patients with FD 16-40 years old.
PURPOSE: The purpose of this study is to understand disturbances in proprioception (how well we sense the positions of our limbs without seeing them) in patients with FD. Our ultimate goal is the help patients with FD walk better. We want to find new and better ways to enhance signals from the skin to help guide the movement of the limbs.
SPONSOR: National Health and Medical Research Council of Australia

ENROLLING
RESEARCH AND TREATMENT IN FAMILIAL DYSAUTONOMIA (HSAN III)
IRB#: R07-938
ELIGIBILITY: Patients with FD of any age.
PURPOSE: Our goal to bring the best clinical care to patients with FD with focus on quality of life. We strive to provide the treatments that are safe and effective, through evidence based-medicine. Research on FD is constantly on going at the Center. We focus on understanding the mechanisms that cause the symptoms of FD and implementing clinical interventions that improve this condition. The medical information collected during each comprehensive evaluation is also used follow the clinical evolution of FD and define treatments have the best outcomes. Information from the FD evaluation is used to understanding cardiovascular, renal, respiratory and neurological function.
SPONSOR: Dysautonomia Foundation, Inc.

ENROLLING
PHOSPHATIDYLSERINE (PS) IN FAMILIAL DYSAUTONOMIA – DOSE TITRATION STUDY
IRB #: 11-02100
ELIGIBILITY: Patients with FD age 12 years and older
PURPOSE: We propose to conduct a safety, tolerability and early proof of concept efficacy study of phosphatidylserine in patients with FD. Phosphatidylserine is a dietary supplement. We aim to evaluate the potential of Phosphatidylserine to correct the genetic abnormality and restore IKAP protein levels in FD patients. Researchers have shown that Phosphatidylserine can increase IKAP in cell lines derived from patients with FD and in a
mouse model of FD.
Sponsor: Dysautonomia Foundation Inc. and Country Life LLC (which donated PS for the clinical trials).

**ENROLLING**

**PHOSPHATIDYLSTERINE (PS) IN FAMILIAL DYSAUTONOMIA – LONG-TERM STUDY**

IRB #: 11-02100
ELIGIBILITY: Patients with FD of any age
PURPOSE: In this study we will follow, on a yearly basis, patients with FD of all ages who opt to take phosphatidylserine. In this study, we will evaluate the long-term safety of phosphatidylserine in patients with FD and hope to determine whether phosphatidylserine has any impact on the clinical evolution of the disorder.
SPONSOR: Dysautonomia Foundation Inc.

**OPEN**

**KINETIN IN FAMILIAL DYSAUTONOMIA**

IRB #: 09-0762
ELIGIBILITY: Patients above the age of 15 years are eligible to participate in this trial
PURPOSE: During the first part of the trial we will evaluate the safety and tolerability of kinetin, a nutritional supplement that corrects the splicing defect, in patients with familial Dysautonomia. In the second part of this trial we will evaluate if kinetin enhances the ability of neuronal tissue to correctly splice *IKAP* mRNA.
SPONSOR: Dysautonomia Foundation, Inc.

**OPEN**

**THE EYE IN FAMILIAL DYSAUTONOMIA**

IRB#: S12-03577
ELIGIBILITY: People with familial dysautonomia of any age.
PURPOSE: Understand the features of the eye in familial dysautonomia patients and how the eye change overtime. We have a state of the art laboratory to conduct research into the eye. In recent years, this work has lead to a clearer understanding of the cause of visual loss in patients with familial dysautonomia. We have shown that patients with FD have a progressive loss of nerves in the retina, and it is this particular pattern of nerve fiber loss that causes the decline in visual acuity overtime. Our main goal is to develop strategies to preserve and enhance vision.
SPONSOR: Dysautonomia Foundation, Inc.

**ENROLLING**

**UNDERSTANDING THE MUSCLE IN FAMILIAL DYSAUTONOMIA**

IRB#: S14-01192
ELIGIBILITY: People with familial dysautonomia of any age.
Purpose: Patients with FD frequently develop muscle atrophy. Moreover, the incidence of rhabdomyolysis (episodes of muscle destruction) is increased in people with FD. To investigate this we aim to examine muscle function in patients with FD and other hereditary sensory neuropathies by studying muscle samples. Small pieces of muscle are obtained during programmed surgery (scoliosis, hip replacement, etc) and studied.
SPONSOR: Dysautonomia Foundation, Inc.

**OPEN**

**RENEAL INJURY MARKERS IN FAMILIAL DYSAUTONOMIA**
IRB#: 13-00279
ELIGIBILITY: People with familial dysautonomia of any age.
PURPOSE: Our ultimate goal is to be able to detect the early onset and stop the progression of chronic kidney disease in patients with familial dysautonomia. The first purpose of this pilot project is to identify early, non-invasive biomarkers of renal injury. The second purpose of this project is to establish a panel of renal injury biomarkers to monitor the progression of renal disease. This study is being carried out in collaboration with Dr. Howard Tractman (Professor of Pediatric Nephrology at NYU Langone Medical Center).
SPONSOR: Dysautonomia Foundation, Inc.

OPEN
BRAINSTEM REFLEXES IN FAMILIAL DYSAUTONOMIA
IRB#: R07-938
ELIGIBILITY: People with familial dysautonomia of any age.
PURPOSE: To understand if dysphagia and dysarthria in FD are due to a reduction in number and/or excitability of afferent trigeminal nerve fibers. In order to achieve this, we are studying brainstem reflexes in familial dysautonomia using electrophysiological techniques.
SPONSOR: Dysautonomia Foundation, Inc.

RECENTLY COMPLETED CLINICAL RESEARCH STUDIES IN FAMILIAL DYSAUTONOMIA:

THE EFFECTS OF BRONCHODILATOR THERAPY ON RESPIRATORY AND AUTONOMIC FUNCTION IN PATIENTS WITH FAMILIAL DYSAUTONOMIA
IRB#: S13-00004
ELIGIBILITY: Patients with FD age of 12 and older
PURPOSE: Assess the effects of ipratropium and albuterol, which are commonly used in FD patients, on respiratory and autonomic function in patients with FD
SPONSOR: Dysautonomia Foundation, Inc.

THE USE OF CARBIDOPA IN FAMILIAL DYSAUTONOMIA
IRB#: R09-0011
ELIGIBILITY: Patients with FD age of 12 and older
PURPOSE: The study objective was to determine if carbidopa reduces the spillover of dopamine into the circulation and decreases the frequency of nausea in FD patients
SPONSOR: Dysautonomia Foundation, Inc.
DYSAUTONOMIA CENTER

STAFF

Horacio Kaufmann, MD
Director

Lucy Norcliffe-Kaufmann, PhD
Associate Director

Jose-Alberto Palma, MD, PhD
Assistant Director

Christy Spalink, ACNP
Nurse Practitioner

Erin Barnes, FNP
Nurse Practitioner

Jose Martinez, MS
Clinical Trials Manager

Lee-Ann Lugg, BS
Administrative Assistant

Angelo Porciuncula, PhD
Post-doctoral Fellow

Isabel Vanegas, MS
Visual Scientist

Miguel Perez
Data Manager

Valerie Iktina, BS
Project Assistant

Joy Wang, BS
Project Assistant

COLLABORATORS

Susan Slaughenhaupt, PhD
Frances Lefcort, PhD
Howard Trachtmann, MD
Joseph Levy, MD

Carlos Mendoza, MD
Vaughan Macefield, PhD
Mikhail Kazachkov, MD
Shay Bess, MD

FUNDING SUPPORT

Dysautonomia Foundation, Inc.
Food and Drug Administration
MSA Coalition

National Institutes of Health
Michael J Fox Foundation