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Pathways to a Cure

The CAA Newsletter

MESSAGE FROM THE DIRECTOR

As always, we are proud to be at the forefront of Cerebral Amyloid Angiopathy research. What continues to be the crux of our work is understanding how CAA leads to brain injury. In this issue, we would like to share two cutting edge approaches that are helping us achieve that goal.

The first approach uses an incredibly powerful magnet to look at properties of the brain that we have never been able to observe before. This 7T (Tesla) magnet captures MRI images in exquisite detail. The highly sensitive scan allows us to analyze how the blood vessels in the brain respond to simple, everyday things like your own heartbeat, as well as more complex measures such as how slightly increased CO2 levels and slightly lowered blood pressure affects the vessels in the brain. This advanced 7T MRI shows promise not only to explain how amyloid affects the brain without causing bleeding but also how altering blood vessel properties may allow amyloid to build up and worsen the severity of the disease.

The second approach utilizes one of the most precious resources we have in CAA research, the donated brains of those who have passed. Brain donation can be one of the toughest topics to raise with patients and their families, but for many can be the ultimate contribution to advance research in a meaningful way. As you will see in this issue, Dr. Van Veluw has used this brain tissue to link what we see on an MRI to what is truly happening in the brains of those with CAA during their lifetimes.

All we have learned about CAA has come from the generous gifts of patients participating in research and brain donation. Those who decide to participate or donate continue to significantly transform the field of CAA research. We can never express just how grateful we are to everyone who allows us to make strides in fighting this challenging disease. We hope you enjoy the spring edition of our newsletter. Thank you for your inspiring interest and dedication to our studies.

Sincerely,
Steve Greenberg, MD, PhD

The Physiologic 7 Tesla MRI: A New Way to Look at CAA

The JPK Stroke Research Center has been using high quality brain imaging in the investigation of CAA for about two decades and continues to seek out the most cutting-edge imaging tools to collect pictures of the brains of patients with CAA. Brain imaging obtained on high-definition MRI machines can show the shape and composition of blood vessels as well as showing the effects of CAA including large hemorrhages, microbleeds, shrinkage of the brain and tiny strokes. Other forms of imaging used by our Center include Positron Emission Tomography (PET) scans, that can help diagnose CAA by showing the amount of amyloid in the brain. Being able to visualize molecular changes caused by CAA is a powerful tool in understanding how the disease acts on the brain and its vessels.

Our research group developed a functional MRI (fMRI) method that enables researchers to assess the ability of blood vessels to dilate (expand) and constrict (narrow). Functional MRIs help us understand changes in the structure of blood vessels in the brain and how they react to physiological changes in the body.

Over the past year, we have started to use ultra-high field strength MRI techniques to get an even closer look at the changes in the physiological response of blood vessels in CAA. MRI scanner (Continued on page 2)

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The Physiologic 7 Tesla MRI

(Continued from page 1) strength is measured in Tesla which is the strength of the magnetic field generated by the scanner. Regular scanners used at most hospitals and medical offices have a strength of 1.5 or 3 Tesla (1.5T or 3T). The cutting-edge scanner that the MGH CAA research team is now using is a strength of 7 Tesla (7T). The 7T scanner produces images of the brain and its vessels that are much more detailed and clearer than the images a 1.5T or 3T MRI machine can collect.

The 7T MRI has been proven useful in CAA patients across the world, however the 7T machines are rarely available in regular doctor's offices or hospitals, and insurance companies do not yet cover the cost. Participants who have this scan as part of our CAA research can have this scan free of charge, and thus far we have successfully performed these 7T MRIs on 25 participants, with promising data.

Research participants taking part in our 7T MRI complete two unique tasks - the first of these is the "C02 gas challenge." The C02 gas challenge involves inhaling a low dose of carbon dioxide (CO2) through a small mouth piece. C02 is flavorless and odorless but dilates the blood vessels in a safe and controlled manner allowing researchers to record the reactions of the brain vessels for a period of time during the MRI scan. Thus far, images collected from our 7T participants have shown excellent response to C02 inhalation and using this technique enables researchers to create maps of the brain to understand how vessels react in different areas.

The second task that occurs as part of the 7T MRI is the "thigh cuff" task. In this task, we use blood pressure cuffs similar to those used by doctors at primary care offices – however, instead of being placed at the upper arm, the cuff is worn around the participant's thigh. By inflating and deflating the thigh cuff while the participant is undergoing a 7T MRI, we are able to obtain mild changes in blood pressure and view the way that the brain vessels respond to these changes or "pulsations."

The 7T project, as MGH CAA physician-researcher Dr. Gurol has said, may be "the biggest innovation in CAA research over the past 5 years." Standard-resolution imaging (such as 1.5T and 3T MRIs) has enabled us to better understand different brain "lesions" (abnormalities) in CAA, and PET scans have helped us learn about CAA at a molecular level. The new, cutting edge 7T MRI scans are enabling us to analyze the brain with far more detail and accuracy, helping us connect what we have learned about molecular brain changes and structural brain changes in patients with CAA. Each of the different methods and activities used in our research studies is like a different puzzle piece in our investigation of CAA: linking them to one another helps us better understand how CAA starts and how blood vessel functions lead to the symptoms we see in patients with CAA. We are excited to continue our diligent investigations in CAA and are grateful to our many 7T research participants for helping us in this cause.

Meet the Clinical Research Coordinators: Nana Frimpong and Vanessa Gonzalez

Nana Frimpong joined the J. Philip Kistler Stroke Research Center in July of 2016. Nana holds a bachelor's degree in Behavioral Neuroscience. Nana joined JPK as a coordinator for the Biorepository for Neurological Injury and in September of 2018, took over as lead coordinator for Dr. Greenberg's study examining people who have probable CAA and hemorrhagic stroke. In his new role, Nana enjoys meeting study participants and helping them contribute to medical advancements through research. If interested in learning more about this study, contact Nana at nfrimpong@mgh.harvard.edu!

Vanessa Gonzalez joined the J. Phillip Kistler Stroke Research Center in December of 2018. Vanessa holds a bachelor's degree in Biology. At JPK, Vanessa coordinates Dr. Anand Viswanathan's study examining the progression of "microbleed-only" CAA subjects and mild cognitive impairment in subjects with probable CAA. In her role, Vanessa enjoys getting to know the study participants and their families, and helping them through MRI, PET scans and memory cognitive testing. If interested in learning more about this study contact Vanessa at vagonzalez@mgh.harvard.edu.

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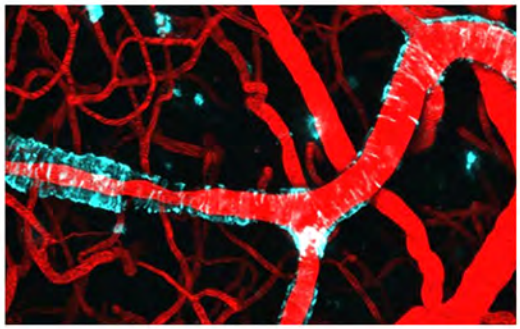
RESEARCH FELLOW SPOTLIGHT: SUSANNE VAN VELUW

My name is Susanne van Veluw and I grew up in the Netherlands. Already at an early age I became fascinated with the human brain and was curious to figure out why some people develop brain diseases and others don't. I studied Neuroscience and received my PhD a few years later, on the topic 'cerebral small vessel disease'. Using a novel state-of-the-art MRI scanner that uses a strong magnetic field to create beautifully detailed images of the brain, I was able to find microscopic strokes in the brains of patients that had problems with the small vessels in their brains. This discovery has helped us to understand the impact that even the smallest lesions – that we usually don't see – have on brain function. After my thesis defense, I was incredibly lucky to be able to continue my research in small vessel disease within the stroke research center at the MGH, under the wonderful leadership of my mentor Dr. Steven Greenberg.

Research Projects

As a post-doctoral research fellow in Dr. Greenberg's group, my main research focus is trying to understand what happens to the small vessels of the brain in patients with cerebral amyloid angiopathy before a bleed or an infarct occurs. To do that, we scan the brains of patients who were diagnosed with CAA during life, passed away from the consequences of this disease, and decided to donate their brain to our ongoing research projects. I feel incredibly humbled to be able to work with these brains – the organ that defines who we are – and realize that trusting someone else with your (or your loved one's) brain is such a valuable gift. After we receive a brain donation, the brain is scanned in one of our MRI scanners. These scans are several hours per session. Doing this, we obtain several images at very high resolution that allows us to look at different types of minuscule pathologies in great detail. Afterwards, we examine the same brains under microscope which enables us to interpret what we see on the MRI scans. This is very important, because with this information we can do a better job at interpreting findings on MRI scans made in the clinical setting and will eventually help neurologists to make more informed clinical decisions for their patients.

One important limitation of investigating MRI scans and brain tissue after someone has passed away is that it does not tell us about what happened before a patient got sick. That is why, in my research, I also started to use experimental mouse models that mimic important aspects of CAA, such as accumulation of amyloid in the walls of small vessels. In the lab, we can image the brains of these mice while they are awake and perform a task at a resolution that we cannot achieve in humans. For example: we can image individual small vessels in the outer parts of the brains of these mice and see how they react to a certain stimulus. Importantly, because we have carefully mapped and controlled the course of the disease in these mice, we can perform our experiments at an age when they are developing the pathology but don't show the symptoms yet. This allows us to understand what goes wrong early on with the goal of finding targets to prevent amyloid accumulation and ultimately CAA altogether.



An image from the brain of a living mouse with a moderate degree of cerebral amyloid angiopathy (CAA). The blood vessels are labeled in red, and amyloid β depositions in blue.

➔ Interested in our brain donation program? Please contact our coordinator, Nana Frimpong at NFRIMPONG@mgh.harvard.edu or 617-643-2782.

J. Philip Kistler MGH Stroke Research Center
175 Cambridge Street, Suite 300
Boston, MA 02114

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Please send your comments, questions and suggestions to: pathwaystoacure@partners.org

For more information on our CAA research and for FAQs, please visit: www.angiopathy.org

Looking to support CAA Research? Many patients and families have lent their time and heartfelt dedication to finding a cure for CAA by helping raise funds for our clinical research program. The CAA Research Team at MGH encourages your interest in hosting a charity event or fundraising among friends, family and colleagues, and appreciate the efforts many of you have already made to this end!

If you would like to learn more about how to support CAA research at MGH, please visit this link: https://giving.massgeneral.org/crowdfunding-community-fundraising/

Individual donations can also be mailed to:

MGH Development Office c/o Shawn Fitzgibbons
125 Nashua Street, Suite 540 Boston, MA 02114
*Please make checks payable to *Mass General Hospital, memo: #1200-028184*

This past fall, some of our Neurology Residents ran the Boston Athletic Association's half marathon to raise money for CAA research. With the help of generous donors, they raised thousands of dollars for CAA research at MGH!

Pictured are Drs. Sergi Martinez-Ramirez, Jacqueline Schulman, Meabh O'Hare, Mariel Kozberg.