WINTER 2015
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Pathways to a Cure

The CAA Newsletter

MESSAGE FROM THE DIRECTOR

Happy fall, from all of us at the MGH Stroke Research Center and best wishes for a joyful and healthy 2016! We will mark the New Year with the usual celebrations, plus one that is unique to us: the 20th anniversary of the Boston Criteria for the diagnosis of CAA. This represents a major milestone in CAA research, as you'll read more about in our main article.

As scientists, we tend not to look backward very often, but as you'll read, CAA research has a storied history. Looking back once in a while gives us the opportunity to see what we have learned, and helps guide today's research efforts. A critical advancement over the past century has been the ability to diagnose CAA during life, as opposed to through autopsy. Additionally, we have learned the importance of blood pressure management when living with CAA, that blood thinners should be used cautiously and that steroid treatment may reduce symptoms for that subgroup of patients with the inflammatory variant of CAA.

Looking to the future, we are hopeful that increasingly specialized technologies like PET scans and higher strength MRIs can be paired with existing techniques like lumbar punctures and biopsy to reveal new insights into how the disease affects the blood vessels over time. While we don't yet know if the recently tested antibody treatment (Ponezumab) will be effective, we are confident that we will learn much from the results and can use that information to guide the design of future therapies.

In this edition of *Pathways to a Cure,* we will take you back 110 years in time, when researchers initially began to investigate the mechanisms behind memory loss and bleeding strokes. We hope you enjoy this edition, and as always, thank you for your continued interest in our newsletter!

Sincerely,
Steve Greenberg, MD, PhD

History of CAA

At the turn of the 20th century, scientists identified amyloid protein in the brain while looking at slides of brain tissue under a microscope. These tissue samples came from patients who had suffered from dementia, allowing them to quickly connect the presence of amyloid plaques in the brain to the existence of cognitive impairments and similar symptoms in their patients. Still, scientific understanding of what amyloid truly did was new, and therefore very minimal. The importance of the amyloid protein's location in the brain was not considered early on, which we now know is a key difference between Alzheimer's disease (amyloid deposits on top of brain tissue) and Cerebral Amyloid Angiopathy (amyloid deposits within the brain's blood vessels).

Research on the significance and implications of amyloid was slow-moving in the beginning of the 20th century. This finally began to change when, in the mid-1950's, amyloid was described in a number of scientific papers published on Alzheimer's Disease (AD). In these papers, vascular amyloid (amyloid found in the vessel walls, as opposed to found on top of the brain tissue) was described as an "innocent bystander" in the disease, assumed to play no significant role in the development or manifestation of the symptoms of AD. Although the protein was beginning to be investigated by scientists and physician researchers, its presence in the brain

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— History of CAA

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and what that meant for a patient remained unknown even near 50 years after its initial discovery.

Dissatisfied with that explanation, Dr. Stefanos Pantelakis, a curious Greek doctor working in Geneva, set out to investigate vascular amyloid to see what he could learn about it. Over time, he began to classify vascular amyloid in terms of location and severity, and inspired others to follow suit.

A second key development in the discovery of CAA came in 1972 with the invention of the CT scanner. Finally, doctors were able to use imaging to study the brain and to diagnose bleeding strokes. The brains of patients who had undergone CT scans during life were examined post-mortem, and it was through the study of the physical brain tissue itself that doctors were ultimately able to connect extensive vascular amyloid to the brain bleeds patients had suffered during life. The first major study to verify this connection was published by a team at the Mayo Clinic shortly thereafter.

Flash forward two decades, to Boston in the mid-1990's. Dr. Greenberg and his team at MGH noticed a pattern in the locations of the bleeds within the brains, and recognized how multiple bleeds restricted to the outer regions of the brain (the lobes) correlated with a high likelihood of finding amyloid within the vessels in post-mortem examinations. Therefore, if an individual suffered from two or more brain bleeds in the lobes, it was probable that he/she had CAA. A landmark paper published in 1996 by Dr. Greenberg et al was the first to describe this diagnostic tool used in the classification of CAA. It has since come to be known around the world as the "Boston Criteria," and is widely used in the diagnosis of CAA today.

As Dr. Greenberg and his team worked to validate the Boston Criteria, another way to image the brain was quickly advancing: MRI scans. Due to the high-quality images an MRI provides, doctors were able to see things that were invisible on a CT scan. They identified that many of the people with large lobar brain bleeds also had tiny spots of blood (that were only seen on MRI) in that same region, and the term "microbleeds" was coined. Dr. Greenberg and his team used this new finding to further elaborate on their initial criteria. These microbleeds were integrated into the Boston Criteria in a 2001 paper, and allowed for detection of CAA earlier than ever (before a large bleeding stroke or cognitive decline.)

What began as a slow-moving effort for the first 90 years has now taken off. In the past 15 years, MRIs have rapidly improved and revealed to us even more findings associated with CAA. Even though we still don't fully understand the biology of the disease, it has become more well-known and even gained the attention of drug companies, who are attempting to design treatments to slow disease progression. The disease is being researched all over the world, and there is now a bi-annual International CAA Conference, which next will be held in Boston in 2016. We are hopeful that the years to come will provide new insights into this disease and answers regarding how to best treat, prevent, and care for those who are affected.

"Like" us on Facebook for updates and more information about CAA!
https://www.facebook.com/CerebralAmyloidAngiopathy

Cure

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PATIENT SPOTLIGHT:

This edition *of Pathways to a Cure features Joe, a 64 year old man from Barre, VT. He and his wife Marie are the proud parents of two children. He currently works as a high school social studies teacher in VT. Joe has been very active with the J.P. Kistler Stroke Research Center, having participated in several of our genetic and imaging research studies.*

How did you come to find out about your CAA?

After a month of chronic headaches in 2013, I underwent several tests including a biopsy and an MRI, which showed minor brain bleeds. Just a week later, I had a hemorrhagic stroke. After the stroke, a local neurologist recommended I go to MGH for a brain biopsy to determine the cause – mainly because they had found cancer in my kidney during the earlier extensive testing, and wanted to now rule out brain cancer. Everyone at MGH agreed that I did not have brain cancer but instead something called CAA.

What did you find to be the most challenging aspect of the diagnosis?

Initially, the long-term fear of dementia was my foremost concern. When my doctor explained that CAA does not have the same timeline associated with Alzheimer's disease, I felt relieved; though would have been happier if I had treatable migraines. Since the diagnosis, I have felt the greatest impact on my teaching; I'll retire after this school year and am very wistful about doing so. Before getting ill, I figured on at least a couple more years of teaching than I'll have, but I'm trying to look forward to gardening, canning foods, and walks with our dogs. I also hope that the near future might hold grandchildren, and I look forward to spoiling them.

What inspired you to be so active in research, and how has the experience been thus far?

I've had a fair number of health issues and have been very well served by medical science. The fact that I'm in halfway decent shape is due to the work of the medical community over many decades and those who have participated in research. The many brain scans that have been part of this research have been fascinating, and understanding more about the science firsthand has given me something interesting to share with my students. I'm not recommending that anyone have a stroke to learn all of this cool stuff, but if you're going to be dealt a lot of lemons, you might as well make lemonade.

Do you have a particular support structure you'd like to tell us about?

The greatest help came from my wife, Marie. After the stroke, I was largely unable to drive, but thanks to her, I was able to get to my many appointments. Since then, Marie has continued to help with my language, which still has numerous small tics. Finally, I owe more than I can say to a young neurologist in Vermont, whose listening and encouragement helped me to share my fears about CAA and my future.

What advice would you give to others who have CAA?

This is ghoulish but ... "Have a living will while you still can." Tell your next of kin your desires while you are still in a position to make important decisions. Apart from that, try to be upbeat and enjoy the blessings you have today. In fairness, I haven't been pushed that far down the road from this disease; that said, expressing your love to family and friends can brighten most anyone's day.

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Contact Information:

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

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**

1st Annual Stroke Research Team Picnic – Brookline, MA; Goodbye lunch for a long time team member; Dr. Greenberg and Dutch fellow, Susanne J. van Veluw, PhD at her thesis defense – Utrecht, Netherlands; *U.S. News & World Report* names MGH the top hospital in the nation

"Thank you for your commitment to CAA research!"

From all of us at the J. Philip Kistler MGH Stroke Research Center