One Mission: End AHC!

YOUR ALTERNATING HEMIPLEGIA OF CHILDHOOD FOUNDATION NEWSLETTER www.ahckids.org SEPT. 2015

2000 Town Center ■ Suite 1900 ■ Southfield, Michigan 48075

AHCF President Lynn Egan

AHCF Goes to Washington for 4th Symposium on ATP1A3 in Disease

Egan connects with international researchers

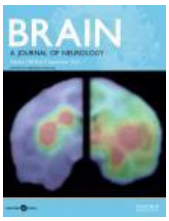
From August 27th to the 29th, the *4th Symposium on ATP1A3 in Disease* was held in Washington, DC. The AHC Foundation was proud to be represented by our president, Lynn Egan as well as sponsor Dr. Kevin Ess from Vanderbilt University.

It was reassuring to hear from Dr. Sweadner that researchers recognize that there is a huge need for preventative strategies. She suggested that preventative measures/treatment are important because of the hypothesis that ongoing episodes over many years may cause some cell damage in the brain.

Another important aspect of the meeting was having several opportunities to network with the researchers during breaks and meal times. Being able to share the parent and foundation perspectives with researchers was essential to communicating our need for treatments.

A very moving part of the meeting was when the AHC documentary was shown at the end of the symposium. It was a very powerful, insightful and emotional movie organized by Siggi Johannesson. It was an honor to help fund the project as well as participate in the filming of it at our 2014 Family Meeting.

For a researchers perspective on the symposium, read Dr. Ess' comments on page 5.



Researchers Take AHC to Heart

Important update on published research

In an Open Access article published in the journal *Brain*, an international collaboration of doctors authored an important article titled, "Faulty Cardiac Repolarization Reserve in Alternating Hemiplegia of Childhood Broadens the Phenotype."

Their research **analyzed ECG recordings of 52 patients with alternating hemiplegia from nine countries.** They found that half the group had resting electrocardiogram abnormalities. These abnormalities were significantly more common in people with alternating hemiplegia than in an age-matched disease control group of 52 people with epilepsy.

The research concluded, "dynamic electrocardiogram and neurological features point to periodic systemic decompensation in ATP1A3-expressing organs. Cardiac dysfunction may account for some of the unexplained premature mortality of alternating hemiplegia. Systematic cardiac investigation is warranted in alternating hemiplegia of childhood, as cardiac arrhythmic morbidity and mortality are potentially preventable."

You can read this article at:
http://brain.oxfordjournals.org/content/brain/early/2015/08/19/brain.awv243.full.pdf

For insight on what this new research means to you, read Dr. Matt Sweney's comments on page 3.

Andrasco and Platt Families Host another Great Event in September

10th annual AHCF Chicago Walk a huge success!

On September 20th, Gene and Kelly Andrasco and Andy and Vicky Platt hosted the 10th annual walk in Lake Zurich, Illinois to honor their daughters, Kiley (14) and Emma Rose (13).

The walk is even more meaningful as we were joined by additional AHC families from the Midwest, Sharon Ciccodicola from the foundation, and doctors Al George, Kenneth Silver, and Sho Yano.

With donations still rolling in, it is anticipated that the walk will break $30,000 again this year. That will mean, that over the last ten years of this walk, donations to **the AHC Foundation will total over $300,000.**

In addition to being a fundraiser for AHC research, **the walk is a celebration of our AHC community.** It is a time for having fun and enjoying everyone's company.

A "selfie" contest was also held to help spread the word about AHC on social media. The picture on the left was our winner and they received a prize package of gift cards worth $75. Congrats Vaselopulos family!

It was a great day and we got to share our mission of ending AHC with a lot of wonderful people.

Be sure to join us next year as we begin our second decade of funding research to help the entire AHC community.

International Consortium for the Research on AHC (IAHCRC) Publishes Important New Article

Doctors around the world are working to end AHC!

On September 26, an Open Access article was published in *Orphanet Journal of Rare Diseases* by the International Consortium for the Research on AHC titled, "Clinical Profile of Patients with ATP1A3 Mutations in Alternating Hemiplegia of Childhood—a Study of 155 Patients."

OJRD ORPHANET JOURNAL OF RARE DISEASES

Clinical data from an international cohort of 155 AHC patients (84 females, 71 males; between 3 months and 52 years) were gathered using a specifically formulated questionnaire and analyzed relative to the mutational *ATP1A3* gene data for each patient.

A table summarizing some of the article's conclusions is continued on Page 3

IAHCRC Article Continued from Page 2

Additional File 5: Clinical phenotype of patients with the three most common mutations, and of patients without, and with mutations, in the *ATP1A3* gene.

Clinical phenotype	p.Glu815Lys	p.Asp801Asn	p.Gly947Arg	*ATP1A3* negative	*ATP1A3* positive
Number of patients percentage	16% (22/132 mutated patients)	43% (57/132 mutated patients)	11% (15/132 mutated patients)	15% (23/155 total patients)	85% (132/155 total patients)
TYPE OF FIRST PAROXYSMAL EPISODE					
Abnormal ocular movements	42% 8	27% 14	38% 5	5% 1	34% 41
Hemiplegic or bilateral plegic	21% 4	25% 13	0% 0	26% 5	21% 25
Tonic/Dystonic attacks	16% 3	33% 17	30% 4	26% 5	23% 28
PAROXYSMAL EVENTS (OTHER THAN EPILEPSY)					
Hemiplegic episodes (6-12 years)	100% (14/14)	94% (36/38)	91% (10/11)	94% (16/17)	95% (100/105)
Dystonic episodes (6-12 years)	71% (10/14)	74% (26/35)	82% (9/11)	70% (12/17)	77% (66/85)
Abnormal Ocular Movements during lifetime	100% (22/22)	98% (55/56)	93% (14/15)	82% (19/23)	98% (127/129)
Abnormal Ocular Movements (6-12 years)	57% (8/14)	58% (21/36)	45% (5/11)	59% (10/17)	56% (47/83)
COGNITION - BEHAVIOUR					
Intellectual Disability during lifetime	100% (22/22)	98% (56/57)	100% (15/15)	91% (20/22)	95% (124/130)
Verbal Communication Disorder during lifetime	47% (10/21)	58% (32/55)	43% (6/14)	57% (12/21)	53% (66/123)
Behavioral Troubles (during lifetime)	47% (10/21)	58% (32/55)	43% (6/14)	57% (12/21)	53% (66/123)
MOTOR DISABILITY					
Ataxia during lifetime	41% (7/17)	71% (38/53)	57% (8/14)	37% (7/19)	60% (70/116)
Dystonia during lifetime	68% (15/22)	73% (42/57)	86% (13/15)	57% (12/21)	74% (96/129)
Other/Complex movement disorder during lifetime	68% (15/22)	52% (29/56)	80% (12/15)	62% (13/21)	60% (77/127)
Movement disorders (all) during lifetime	100% (20/20)	94% (52/55)	100% (15/15)	82% (18/22)	95% (121/127)
EPILEPSY					
Epilepsy during lifetime	82% (18/22)	55% (31/56)	40% (6/15)	50% (11/22)	59% (76/129)
Status epilepticus during lifetime	38% (8/21)	21% (12/56)	20% (3/15)	19% (4/21)	24% (31/127)
AUTONOMIC DYSFUNCTION					
Autonomic dysfunction during lifetime	95% (21/22)	74% (37/50)	71% (10/14)	77% (17/22)	76% (89/117)

The electronic version of this article can be found online at: http://www.ojrd.com/content/10/1/123

French Researchers Are Busy Publishing New Articles

Two more articles are coming out in October!

Article #1

In an upcoming issue of *Developmental Medicine and Child Neurology*, researchers emphasize, "the possible role of brain energy deficiency in patients with ATP1A3 mutations.

Rather than multiple overlapping syndromes, ATP1A3-related disorders might be seen as a phenotypic continuum."

Watch for both articles next month.

Article #2

In an upcoming issue of *The EMBO Journal,* researchers "show that freely diffusing α3-NKA are trapped within α-syn clusters resulting in α3-NKA redistribution and formation of larger nanoclusters.

This creates regions within the plasma membrane with reduced local densities of α3-NKA, thereby decreasing the efficiency of Na+ extrusion following stimulus."

Matthew T. Sweney, MD MS
Asst Prof, Division of Child Neurology
Departments of Pediatrics and Neurology
PCH, University of Utah

Brain Article Leaves Many Families Wondering

Help understanding recent cardiac article!

Greetings from the Medical Advisory Board! We have heard much interest regarding the recent article published in *Brain* by Jaffer et al, in August. It presents data from a study in which the EKG results from 52 patients with confirmed ATP1A3 mutations were reviewed.

Investigators found interesting results that suggest there may be cardiac dysfunction associated with ATP1A3 mutations, specifically regarding the heart's ability to recover with each heartbeat ("impaired repolarization reserve") and that this dysfunction may worsen with age.

The authors suggest that this might have a bearing on premature mortality that has unfortunately been reported by families affected by AHC. The study also suggests that similar findings have been seen in other disorders involving "channelopathies" of heart tissue. **Although this study provides a valuable piece of information in moving broader ATP1A3 research forward (especially in the push to better understand the impact of ATP1A3 on organs outside of the nervous system), the impact on day-to-day management of children with AHC is less clear.**

After discussing the findings with colleagues in pediatric cardiology, **the "take home" points for families dealing with AHC are fairly limited.**

Currently, widespread testing of cardiac function with prolonged monitoring is not routinely recommended, although it may be a target of future research. For now, if there is a clinical suspicion of possible heart problems in a child with AHC, a good place to start is with a routine EKG, which usually can be done in the outpatient setting.

From there, input from a pediatric cardiologist would be most helpful in guiding any additional testing. We are hopeful that this is just the beginning of the next wave of ATP1A3 research, and that other pediatric and adult subspecialists will join in better understanding this complex disease.

Keeping up with AHC research can be challenging, but staying connected with the AHC community and the AHC Foundation will always help!

Kevin C. Ess, MD, PhD
Vanderbilt University
Associate Prof, Pediatrics & Neurology
Chief, Pediatric Neurology

Hear What Happened in Washington at the 4th Symposium on ATP1A3 in Disease

Dr. Kevin Ess meeting summary for parents

Friday August 28th - The meeting was strategically held in Bethesda MD, just down the street from NIH. The initial talk was given by **Dr. Walter Koroshetz, Director of the NINDS, NIH.** Dr. Koroshetz is relatively new to his position but a respected Neurologist and Neuroscientist who has been at NINDS for several years.

I have never heard him talk for so long! He usually gives a 10-20 minute overview but his opening talk went on for about one hour. He very nicely addressed the current state of Neuroscience research and the stark funding issues facing scientists.

He offered some hope that the CURES2015 bill (#CURES2015) had bipartisan support and might be passed in 2016. This would be amazing given the election cycle we are in. If the bill if passed, it would substantially increase NIH funding. He closed with frank acknowledgement of the challenges of rare diseases and the highly important role of patient advocacy organizations.

Dr. Mohamad Mikati gave an overview of clinical definitions including discussions about epilepsy in AHC. He also proposed renaming AHC to broaden the definition to encompass other *ATP1A3* related disorders. This included a proposal to change the C in AHC to stand for "Complex". The group was not receptive to this and argued that this field was moving so rapidly that we should wait before making any nomenclature changes. There seemed to be consensus about this point.

Dr. Tsveta Schyns announced the 2016 Meeting would be held August 24-26th in London, UK and asked for help in organizing this and maybe having a European based AHC group take responsibility. Again, lots of discussion and concerns about this. Argument were made for "inclusion" and "democracy". However, not much resolution was made on this topic.

There was further discussion on development of an app "AHC Tracker". General consensus about this idea is need. **Drs. Henrik Rosewich, Mikati, and Allison Brashear** indicted willingness to work on this.

Further discussion was held about the need for biomarkers in AHC research.

Dr. Helen Cross discussed findings about ECG and concern for sudden unexpected cardiac death, possibly underscoring a function for ATP1A3 in the heart.

Several new variants/mutations were reported, T360R, Q140H, and G325A of the *ATP1A3* gene.

CONTINUED ON PAGE 6

Dr. Kevin Ess Meeting Summary for Parents CONTINUED…

A subtype of AHC was recognized with a suggested name of DEMO for Dystonia/Dysmorphism, Encephalopathy, MRI abnormal, and no hemiplegia.

Another possible subtype associated with R756H was described with the awkward name FIPWE for Fever Induced Paroxsmal Weakness Encephalopathy by **Dr. Sho Yano**, a Child Neurology Resident at the Univ. Chicago.

Saturday August 29th -Data from D801N, D801Y brain slices was presented by **Dr. David Goldstein**. They used multi electrode arrays (MEA) on an Axiom Bio Maestro machine. This seemed to be preliminary work and concluded with "no MEA phenotype" was found.

A neuroblastoma model of AHC was presented by **Dr. Danilo Tiziano.** They used SH-SY5Y cells and introduced ATP1A3 wild-type or mutant genes. The cells were introduced to differentiate with retinoic acid, some lethality was seen upon neuronal differentiation of the mutants.

Dr. Mohamad Mikati gave an update on Atp1a3 mutant mice. He reported mostly published data but mentioned progress on D801Y, D801N, and E815K knock-in mice. Details of the data shared was sparse, likely because most is unpublished. There was mention that E815K mice are difficult to breed and have a more severe phenotype than D801N mice. Some data implicating the GABA system was presented using bicuculline that normalized polyspikes when compared to number of polyspikes seen in wild-type mice. A suggestion that parvalbumin (GABAergic) cell numbers are reduced in these mouse models of AHC.

There was a nice discussion about D801Y mice from **the Lykke-Hartmann lab**. They reported that no seizures were seen.

Dr. Steve Petrou presented the possible use of triheptanoin in mouse models and AHC and the application to patients.

Closing Keynote Address was by **Dr. Kevin Eggan**. He gave a very nice overview of his research and how the AHC community can work together. He showed some exciting techniques and approaches to explore neuronal dysfunction.

The last aspect of the Symposium was about plans for the next meeting in London 2016. Various scientists were asked to speculate on what they would present next year.

Finally we watched the premiere of the **AHC documentary "Human Timebombs" directed by Águsta Fanney and produced by Sigurour H. Johannesson. This was a very moving depiction of AHC and ended with a standing ovation by the audience.**

The AHC Foundation wishes to thank Dr. Ess and all of the researchers and physicians who attended this important symposium. Your time and hard work is greatly appreciated!

Leverage your personal contacts all around the country and ask them to participate in any one of the upcoming events. Share your passion for achieving our **One Mission: End AHC!**

Families are Getting Ready for the Most Important Time of our Year

Fundraising season is stepping off big in New York

DINE & DANCE

FRIDAY, NOVEMBER 6, 2015

Join Paul & Renee Hodes in New York State for their Second Annual Event

Dine and Dance to End AHC is a social evening of dinner dancing, and fundraising in honor of their daughter Lisa. Attendance at the event, a 50/50 Raffle, and general donations raise funds that go directly to funding research that will bring

all AHC kids closer to a treatment or a cure.

For more information go to:

http://ahckids.org/dinedance/

Words of Wisdom

"I am only one; but still am one.

I cannot do everything, but still can do something.

I will not refuse to do the something I can do."

Helen Keller

This newsletter is full of articles discussing advances taking place all across the world And, **this is an incredibly exciting time for AHC research and everyone in our community!**

Let's keep the momentum going by sharing this exciting news with our friends and family.

As the main fundraising season approaches, it is essential that our supporters know how determined our community is to find those viable treatment options for AHC patients.

There are numerous ways to help support research efforts throughout the year.

Keep watching for more information from the AHC Foundation as we work towards

our

One Mission: End AHC!

We have a day for giving thanks.
We have two for getting deals.
Now, we have #GivingTuesday,
a global day dedicated to giving back.

Join us in the fun on Tuesday, December 1st
As we give back to the AHC community.

Black Friday. Cyber Monday.

#GIVINGTUESDAY

December 1, 2015

Contact Vicky Platt to start planning now
vicky@ahckids.org