One Mission: End AHC!

YOUR ALTERNATING HEMIPLEGIA OF CHILDHOOD FOUNDATION NEWSLETTER September 2016

2000 Town Center ■ Suite 1900 ■ Southfield, Michigan 48075

PATH to a CURE
Report from 5th ATP1A3 Meeting London

Written by Kevin Ess, MD, PhD and Alfred George J, MD.

The **Fifth Symposium on ATP1A3 in Disease** was held in London UK August 25-26th 2016. The conference was very successful with lots of exciting results and sense of increasing teamwork and collegiality with groups throughout the world.

The opening talk on Day 1 was given by **Dr. Brashear** who provided a clinical review of typical and atypical ATP1A3-associated disorders. Presented brain MRI data from RDP patients, looking at cerebellum, basal ganglia, and thalamus volume along with performance during card sorting tasks. **Dr. Sweadner** then reviewed mouse models representing different genetic disorders of Na, K-ATPases with an emphasis on potential disease mechanisms. She also discussed the spectrum of known mutations in ATP1A2 and ATP1A3 with an emphasis on what can be learned by comparing the locations of these mutations between the two genes.

Drs. Doummar, Rosewich, Bhatia and Scharf reported on unique features of ATP1A3-associated diseases. ATP1A3 can cause an early onset epileptic encephalopathy without hemiplegic attacks. There are now 22 known cases of CAPOS syndrome and they all have the same ATP1A3 mutation (E818K). A potential new mechanism to explain optic atrophy in this disorder was discussed. A case with painful dyskinesia and dystonia was presented. Finally, there was evidence discussed that ATP1A3 can be the target of an autoimmune disorder in adults that is associated with cancer. **Dr. Caski** discussed cardiac involvement in AHC emphasizing his 2015 publication reporting ECG abnormalities.

Kevin C. Ess, MD, PhD
Vanderbilt Univ.
Nashville TN

A video review session was led by **Dr. Mikati** to seek consensus for describing movements and seizure manifestations of ATP1A3 disorders. There was specific discussion of spells of altered consciousness in AHC that are not accompanied by abnormal EEG findings. A comment about the similarity of clinical presentations to anti-NMDA encephalitis led to a stimulating discussion about testing ATP1A3 mutation-negative kids for anti-NMDA and anti-alpha3 antibodies. There was consensus to generate a video library for review by experts in the field.

Alfred L. George, Jr., M.D.
Northwestern University
Chicago, IL

Two presentations focused on different aspects of genetics related to AHC. **Dr. van den Maagdenberg** gave an informative update on the search for a possible second AHC gene. In ATP1A3 mutation negative patients, further sequencing identified a few patients with ATP1A3 mutations (false-negative initial sequencing). In other families, new gene variants were discovered but further validation is needed. **Dr. Kearney** reviewed related work in Dravet Syndrome using mouse models to discover genetic modifiers. A similar strategy using ATP1A3 mouse models is feasible to discover genetic pathways and disease modifying therapies.

Mouse models continue to provide novel information about ATP1A3-related disorders. **Dr. Lykke-Hartmann** provided an update on the ATP1A3 D801Y mouse model. She focused her presentation on abnormal gait and balance evident in the mice and the corresponding defects in cerebellar neuron function. **Dr. Piggins** presented data on the Myshkin mouse (mutation ATP1A3-I810N) focusing on circadian rhythms. These animals are hyperactive with poor circadian control and quicker adaptation to alterations in day-night changes (e.g., they "don't have jet lag"). A discussion ensued about whether patients with AHC also have day/night issues. **Dr. Clapcote** discussed other published work on the Myshkin mouse.

PATH to a CURE
London Report Continued

Two presentations focused attention on other proteins that may interact with ATP1A3. **Dr. Hoshi** presented data that ATP1A3 interacts with amyloid beta protein and discussed possible involvement of the protein in Alzheimer's disease. **Dr. Melki** presented other data reporting interactions between ATP1A3 and a protein (α-synuclein) involved in Parkinson disease.

There were presentations focusing on the structure and function of ATP1A3. **Dr. Vilson** reviewed structural and functional aspects of Na,K-ATPases focusing on perturbation to sodium ion binding. Dr. Koenderink discussed his research findings from work that was supported in part by AHCF. He illustrated different molecular mechanisms that stem from ATP1A3 mutations. There does not appear to be a clear correlation of pump function within phenotype or severity. **Dr. George** outlined AHCF funded work being done at Vanderbilt and Northwestern using patient-specific induced pluripotent stem cells made into neurons. Functional data on these neurons were presented.

The keynote presentation of Day 2 was given by **Dr. Muntoni**. He shared decades of experience of mechanistic discovery and therapeutic search in Duchenne Muscular Dystrophy. The difficult and often prolonged journey from gene discovery to effective therapy was stressed, as lessons learned may apply to ATP1A3 related disease manifestations.

Additional presentations discussed different treatment strategies. **Dr. Fedosova** discussed the binding of cardiotonic steroids to Na, K-ATPases and speculated that it may be feasible to develop ATP1A3-selective drugs. **Dr. Cross** discussed the use of a ketogenic diet in AHC. Dr. de Grandis reviewed studies on flunarizine and antiepileptic drugs for AHC. Several studies have been done but all had small numbers of subjects and suboptimal experimental designs. Finally, **Dr. Roze** reviewed his on-going clinical trial experience in AHC involving 10 patients. His clinical trial explores the use of the fatty acid analog triheptanoin based on a hypothesis of altered energy usage in the brain underlying AHC. Findings from this clinical trial may be revealed by the end of 2016.

The **6th Symposium on ATP1A3 in Disease** will be held 21-22 September 2017 in Tachikawa City Tokyo, Japan. The Steering Committee for the 2017 meeting will consist of Drs. Ess, Mikati, Rosewich and Schyns, and Mr. Wuchich.

Thank you to all the London participants and those working to make the next meeting in Japan a success.

INFO EXCHANGE
Flunarizine Update

Families have reported that there have been some delays recently with shipments of Flunarizine coming from Canada and abroad. Some delays are due to customs issues and some postal issues.

This is a friendly reminder to all families to check your supply, order early and order extra if possible. If you find yourself running into unforeseeable issues, please contact us.

PATH to a CURE
AHC gets Global Attention in September

The 12th European Congress on Epileptology took place on September 11th through 14th in Prague, Czech Republic.

On Tuesday, September 13th, a session titled, "ATP1A3 related epilepsies: novel phenomena, therapeutic insights and underlying pathophysiology" was chaired by: Alexis Arzimanoglou (France) and Catherine Chiron (France). Discussions during this session included:

Epilepsies in Alternating Hemiplegia of Childhood and other ATP1A3 related diseases – Eleni Panagiotakaki (France) & **Hendrik Rosewich (Germany) (AHCF Medical Advisory Board)**

Acute and long term management of seizures and related disorders in alternating hemiplegia of childhood – Federico Vigevano (Italy)

Underlying pathophysiology of ATP1A3 related epilepsies: animal models and the promise of novel therapies – Mohamad Mikati (USA)

Thank you to all of these presenters for keeping AHC in front of a global audience.

AHCF in ACTION
Strategic Alliance Partnership Formed

Rare Disease Report (RDR) is an organization that hosts a website and weekly e-newsletter that offers an independent voice for the Rare Disease Community. It strives to bring together medical, scientific, investment, regulatory, and advocate professionals interested in rare diseases and orphan drugs. RDR provides rare disease information to 30,000 doctors each week.

The purpose of the partnership is to **increase awareness and knowledge regarding rare diseases** in general and AHC specifically, among physicians, other medical professionals, and the public. Our role will be to supply a monthly article to RDR.

These articles will be featured online and showcased in **the weekly newsletter which has an audience of 80,000 clinicians!** The article can be written by an AHC patient, parent, scientist, board member or clinician and will be geared toward clinicians reading something they did not know before, for instance a different aspect of AHC, and since there are many aspects to AHC we should have much to write about!

We also will have a page on the RDR website where we can host AHC videos and interviews. We will identify prominent AHC dedicated scientists, clinicians, and advocates to be filmed by the RDR communications team 4 times a year for placement on the site. RDR also posts on 22,000 social media outlets; so spreading awareness takes on a whole new meaning.

If you have any interesting ideas for an article please contact Sharon@ahckids.org.

Flower Power is BACK for 2016!

Order your bulbs for Fall planting, and receive Blooms for Hope in the Spring. Hope for a good new year, and Hope for our AHC kids. 50% of your purchase will come to us for use in funding research! Research that will make an impact on our mission to END AHC for all kids and their families.

Join us in planting our Blooms for Hope this year.

http://www.flowerpowerfundraising.com/campaign?campaign_id=23848

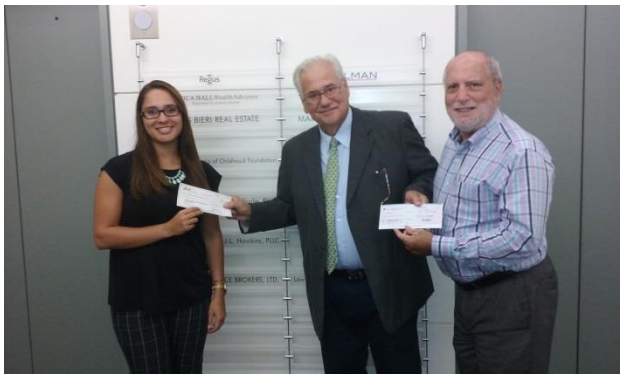
AHCF in ACTION

Grant Presented at Foundation Office in Michigan!

Earlier this month AHCF was selected to receive an award from the **2016 Selective Insurance Group Foundation Matching Grant Program.**

Our Insurance Company, "Allied Insurance Managers," recommended us for the award and donated $250.

The Selective Group Foundation matched the $250 donation by Allied Insurance for a total of $500!



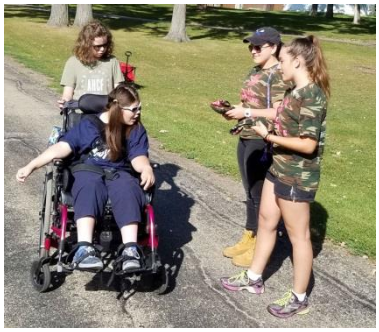
The check was hand delivered by Paul Murad and Madison Morton from Allied Insurance to Pasquale Ciccodicola, the AHCF attorney. **Thank you so much!**

DOUBLE the FUNdraising

11th Annual Chicago Walk a Huge Success in September

The 11th Annual Chicago Walk was held in Lake Zurich, Illinois on Sunday, September 18th at Paulus Park. The walk was hosted in honor of Emma Platt (14) and Kiley Andrasco (15) by their parents, Andy & Vicky Platt and Gene and Kelly Andrasco.

The weather was perfect and there were walkers of every age enjoying the park, lake, bocce courts, raffle baskets, and fun.

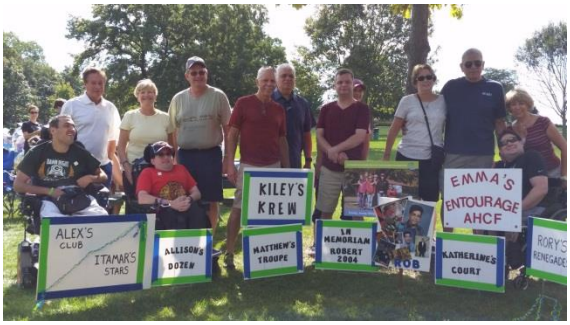


This year, the local community really came out to support the walk. Ladies from the Lake Zurich LaCrosse team were on hand to present Kiley and Emma with special t-shirts and to make them "honorary" team members for a day. These young ladies were amazing.

Students from Lake Zurich High School also came out to help with anything and everything that needed a strong pair of hands. Setting up tents, moving tables, carrying boxes; it was all done with a great attitude and generosity of spirit.

The best part of the walk was having an opportunity to come together as a community and feel the love of friends and family.

Pictured right are Robert's friends and family who came to the walk to celebrate his life and remember him in an uplifting and positive manner. It was a wonderful event filled with wonderful people.



DOUBLE the FUNdraising
3rd Annual Dine and Dance to End AHC – This November

Dine and Dance To End AHC

Hosted by Renee and Paul Hodes
When: Friday November 4th at 7:00 pm
Where: Sinapi's Ceola Manor
489 E. Main St., Jefferson Valley, NY

Join us for an affair to remember at our 3rd annual
Dine and Dance to End AHC

50% of those affected by rare diseases are children, please help us make an impact by funding research for a cure to END AHC for Lisa Marie and those afflicted by it.

Appetizers, Open Bar, Dinner, Dancing to DJ Chris, Raffles and much more!

Tickets $75 per person

To purchase tickets or to make a donation please visit our website at www.ahckids.org. Checks can be written out to AHCF and mailed to Renee Hodes at 3747 Barger Street Shrub Oak NY 10588

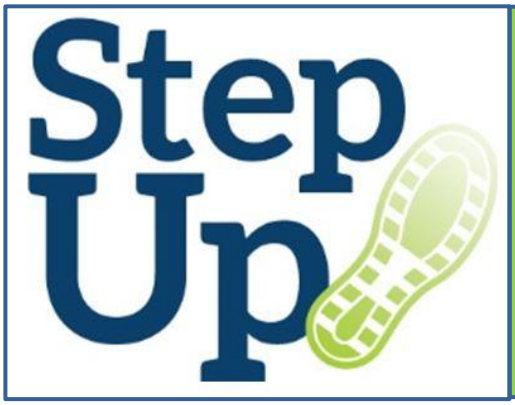
For Sponsorship information or to make a donation to our raffle contact Renee@ahckids.org or call 914-299-5413

All proceeds to benefit the Alternating Hemiplegia of Childhood Foundation

Be a part of the exciting New York event this November.

Join AHC families and friends to celebrate the AHC community & champions.

The Hodes Family welcomes you to invite your family and friends who live in the area to be part of this amazing evening of fun!



Step Up to End AHC!

We are very excited about our end of the year campaign "Step up to End AHC"
With your participation, you will not only help this foundation, but the entire AHC community.
Together we can End AHC.

Target date October 15th - Look for more information soon!

PATH TO A CURE
New Research is Working towards Answers for AHC!

INTERNAL MEDICINE
THE JAPANESE SOCIETY OF INTERNAL MEDICINE
ONLINE ISSN: 1349-7235 PRINT ISSN: 0918-2918 (As of October 04, 2016) Registered articles: 9,926

Researchers are hard at work; looking for answers to the hardest AHC questions. Here are the citations to research published over the last two months. When available, a link to the full text article is included.

Neurological disease mutations of α3 Na+,K+-ATPase: Structural and functional perspectives and rescue of compromised function.
By: Holm R, Toustrup-Jensen MS, Einholm AP, Schack VR, Andersen JP, Vilsen B.
Biochim Biophys Acta. 2016 Nov;1857(11):1807-1828

Recognizable facial features in patients with alternating hemiplegia of childhood.
By: Gurrieri F; Tiziano FD; Zampino G; Neri G.
American Journal of Medical Genetics. Part A, 2016 Oct; Vol. 170 (10), pp. 2698-705

De novo p.Arg756Cys mutation of ATP1A3 causes an atypical form of alternating hemiplegia of childhood with prolonged paralysis and choreoathetosis.
By: Kanemasa H; Fukai R; Sakai Y; Torio M; Miyake N; Lee S; Ono H; Akamine S; Nishiyama K; Sanefuji M; Ishizaki Y; Torisu H; Saitsu H; Matsumoto N; Hara T,.
BMC Neurology, 2016 Sep 15; Vol. 16, pp. 174.
Fulltext available at:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5025569/

A novel de novo mutation in ATP1A3 and childhood-onset schizophrenia.
By: Smedemark-Margulies N; Brownstein CA; Vargas S; Tembulkar SK; Towne MC; Shi J; Gonzalez-Cuevas E; Liu KX; Bilguvar K; Kleiman RJ; Han MJ; Torres A; Berry GT; Yu TW; Beggs AH; Agrawal PB; Gonzalez-Heydrich J.
Cold Spring Harbor Molecular Case Studies, 2016 Sep; Vol. 2 (5)
Fulltext available at:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5002930/pdf/Smedemark-MarguliesMCS001008.pdf

Cognitive deficits caused by a disease-mutation in the α3 Na(+)/K(+)-ATPase isoform.
By: Holm TH, Isaksen TJ, Glerup S, Heuck A, Bøttger P, Füchtbauer EM, Nedergaard S, Nyengaard JR, Andreasen M, Nissen P, Lykke-Hartmann K.
Sci Rep. 2016 Aug 23
Fulltext available at:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4994072/

Alternating Hemiplegia with Ipsilateral Supranuclear Facial Palsy and Abducens Nerve Palsy Caused by Pontine Infarction.
By: Maeshima S, Tsunoda T, Okamoto S, Ozeki Y, Sonoda S.
Intern Med. 2016;55(15):2073-5.
Fulltext available at:
https://www.jstage.jst.go.jp/article/internalmedicine/55/15/55_55.6603/_article