The History of Alternating Hemiplegia of Childhood Foundation (AHCF)

They met at Boston's Children's Hospital, both their children having been diagnosed with Alternating Hemiplegia of Childhood (AHC). Kathy and Steve Hurley (Massachusetts) and Dennis and Elsie Kiernan (Virginia) thought they were the only parents with children who had AHC. The Kiernan's were to head home after their son's hospital stay however the Hurley's convinced them to stay with them for a few days. From an idea at the kitchen table to fruition, the International Foundation for Alternating Hemiplegia of Childhood (IFAHC) was registered with the Commonwealth of Massachusetts in June 1993. This was made possible by Steve's childhood friend, Joe Stanton, an accountant, who assisted them in filing all the necessary paper work. As their children's neurologist, Dr. Mohammad Mikati was very interested in AHC and became the Chairman and Advisor to the Board of Directors from 1993-1994.

In early 1993, Lynn and Mark Egan (California) received a call from their neurologist who had seen an ad in a medical journal looking for participants in a research study for AHC. Shortly after this, Laurie and Ray Baker (Wisconsin) contacted Dr. Mikati. Laurie asked if Dr. Mikati knew of any patients with AHC and did he have a list of neurologists who were following AHC patients. Dr. Mikati was instrumental in connecting Lynn and Laurie. In late 1993, Richard George (Michigan) contacted the Hurley's. Richard and his wife Rhonda, were recommended to Dr. Mikati by their neurologist. Once they returned from Boston, they contacted Dr. Harry Chugani of Children's Hospital of Michigan who was following two patients. The Hurley's heard from other families as well– the Wisyanski's from Pennsylvania and the Peckinpaugh's from Indiana. For the next two years, the IFAHC began to network, building a database through phone calls and letter. There were now 36 families worldwide!

With the departure of Dr. Mikati to Lebanon in 1995, the search began for another researcher who was interested in AHC and working with the IFAHC to find a treatment and ultimately a cure. Dr. Chugani was interested in AHC and PET studies (*Journal of Child Neurology*, (Volume 17, Number 4, April 2002) and in 1995 was awarded a $19,000 grant to evaluate treatment approaches and the underlying cause of AHC.

A meeting was organized by the Baker's, Egan's and George's for the core participants within the foundation. In April of 1995, Steve and Kathy Hurley, Denise and Elsie Kiernan (and son Jimmy), Greg and Donna Cyr, Kevin and Carol Prunty, Catherine Mathews, Richard and Rhonda George, Neal Jackson, Laurie Ingwell, Ray Baker and Lynn and Mark Egan traveled to Detroit. There were 8 Board of Directors and a Medical Advisory Board of 10; which included Dr. Fred Andermann, Dr. Kenneth Silver, Dr. Jean Aicardi, Dr. Federico Vigevano, Dr. Norio Sakuragawa and several others.

At the conclusion of this meeting, Dr. Chugani was on board and would begin to recruit patients to participate in his study of MRS and serotonin PET scans. Later that year, Richard George started the Alternating Hemiplegia Foundation (AHF). The focus of the AHF was fundraising and the AHF and the IFAHC jointly awarded Dr. Chugani a second grant of $30,000. By the end of 1995, Janssen Pharmaceuticals, the maker of Sibelium (Flunarizine), discontinued their eight year study on the efficacy and use with AHC. The database of families had grown to 67 worldwide!

Richard and Rhonda George were the major fundraisers for AHC from 1994-1997. After completing five events, they raised $192,000!! Greg and Dawn Wisyanski and Rich and Dana Tasi sent out annual appeal letters and raised $23,400! Greg also got the United Way started in the Tri-State area of Connecticut, New York and New Jersey. Other families also organized fundraisers – the Peckingaugh's of Indiana raised $1,800; the Prunty's raised $2,500; the Coopers raised $4,500 and Dave and Cindy Ryan started their annual fundraiser that **continues** to raise thousands of dollars each year!! There were many others who raised funds during these early days too – thank you!

As parents of a newly diagnosed little girl, Laura and Kim Cooper, from Woodenville, Washington, understood the urgency of raising funds for research. They were new to the foundation and with the support of the AHF and IFAHC, they organized a workshop/symposium held in Seattle, Washington in May 1997. Symposium participants were: Dr. Jean Aicardi, Dr. Fred Andermann, Dr. Eva Andermann, Dr. Harry Chugani, Dr. Diane Chugani, Dr. DaSilva, Dr. James Garbern, Dr. Giuseppe Gobbi, Dr. Renzo Guerrini Dr. Michael Johnston, Dr. Louis Ptacek, Dr. Gregory Moore, Dr. Jong Rho, Dr. Steven Roach, Dr. Harvey Sarnat, Dr. Philip Schwartzkroin, Dr. Ken Silver and Dr. Mary Zupanc. The goals of the symposium were to discuss the underlying cause of AHC, how neurologists around the world were treating AHC, what drugs were being administered, national and international collaboration in studies and treatment, and how the foundations might facilitate research.

These medical community participants unanimously agreed that there should **Not** be two separate AHC organizations. For the sake of the children, they recommended that the two foundations merge into one organization. A major outcome of that meeting was the establishment of the first Bio-Bank for the collection of samples from AHC patients and their families. This was under the direction of Dr. Louis Ptacek, a neurologist and geneticist from the University of Utah.

The IFAHC continued to build a database of families, launched its first website in 1997, and focused on awareness through a newsletter, provided family support, and conducted some fundraising. The Board members changed over the next few years with Neal Jackson stepping in as president after Steve Hurley left the position in 1997; Greg Wisyanski moved from treasurer to president in 1998-1999

and Lynn Egan took over in 2000. Organized by the Prunty's and Ryan's in June 1999, the first 'Midwest Family Gathering' was held in Rockford, Illinois. Thirteen families attended. There were now 206 families worldwide!!

In June 2000, the second 'Midwest Family Gathering' was held. The AHF funded two research grants in the amount of $77,485.00. The first grant was, "Toward a Molecular Understanding of AHC," by Dr. Louis Ptacek. This research was the natural extension and continuation of the DNA blood collection project which Dr. Ptacek had been conducting for over a year. The second grant was, "The Effects of Flunarizine of Neocortical GABAergic and Glutamatergic Function," by Drs. Johannes van Brederode and Jong Rho.

Their principal goal of the proposed studies were to examine the effects of flunarizine on excitatory and inhibitory local synaptic circuits in the deep layers of the motor cortex from normal juvenile mice. The motor cortex was chosen because of its probable direct involvement in hemiplegic attacks seen in AHC patients. By the end of 2000, the AHF had a six month update from Dr. Ptacek. They were focusing and working on trying to find the breakpoint on chromosome 9 in a family whom a translocation of chromosomes 3 and 9 were found.

Dr. Kathryn Swoboda, while still a genetics fellow in Boston, had been discussing the project with Dr. Ptacek in 1997. Dr. Swoboda was instrumental in collecting the very first familial case from Boston which she sent to Utah to launch the database even before she arrived in Salt Lake City in 1998. Once Dr. Swoboda arrived in Salt Lake City, Dr. Ptacek and Dr. Swoboda wrote a NIH grant and received a K award in 1998 to work on the project and paroxysmal dyakinesia project. They also jointly wrote a grant to the Dystonia Medical Research Foundation to get additional funding to begin collecting clinical records and blood samples from patients and their parents making cell lines.

The IFAHC and AHF had worked together for 8 years. Heeding the recommendation of the medical community, and realizing that we were wasting valuable resources, Richard George, Kim Cooper, Carol Presunka, and Lynn and Mark Egan met in San Francisco, CA in March 2001. It was decided to become one organization and combine resources. And so the IFAHC merged with the AHF and the **Alternating Hemiplegia of Childhood Foundation (AHCF) was established**.

With Dr. Ptacek moving to San Francisco, the AHC Gene Project transitioned to a completely independent neurogenetics laboratory at the University of Utah and Dr. Swoboda became the primary investigator in 2002. Dr. Swoboda traveled to France and held an impromptu meeting in New York prior to the family meeting later that year in Chicago. At each of these meetings, she continued to gather information for the clinical database and bio-bank held in Salt Lake City. And in 2003, families traveled to Salt lake City for another family meeting.

A measure of the growing interest of AHC internationally was the collaboration between scientists in Los Angeles, Boston, Italy, and France. Dr. Swoboda was awarded $66,890.00 each year, for the next three years ($200,670.00 total), to identify the genetic cause of Alternating Hemiplegia of Childhood. During this period, in an exhaustive search of 50 candidate genes, they identified families with specific mutations, the CACN1A1 calcium channel gene, the ATP1A2 gene, and mutations in the glutamate transporter SLCIA3. However, to date, have found fewer than 5% of our AHC patients having one of those mutations. Thus, this work will continue, using newer more sophisticated gene chip techniques to help scan the entire genome for possible small changes in the genetic code that makes up our DNA.

Sharon Ciccodicola became the Medical Liaison in November 2004. We had a great turn out at the 2005 Family Meeting held in Boston, Massachusetts, with 22 new families in attendance, and representation from Asia, Europe, Africa and North America. Data collection continued and the meeting highlighted school intervention for parents and a presentation on neuropsychology by Josh Magleby, M.S. He was actively testing affected children and their siblings throughout the conference for many long hours. Breakout groups helped parents explore many issues relevant to AHC.

Following his work at the 2005 family meeting, in March 2006 the AHCF board, at its annual meeting, decided to award Dr. Josh Magleby, Ph.D., $3,100.00 to conduct a Cognitive and Behavior study. The proposed study hypothesized that children and adolescents diagnosed with AHC display unique cognitive and behavioral sequelae that separate AHC from other similar disorders.

In conjunction with the 10th International Child Neurology Congress, the International Symposium on Alternating Hemiplegia was held in Montreal in June 2006. Organized by Drs. Fredrick Andermann, Kenneth Silver, Kathryn Swoboda, Eva Andermann, parent Lynn Egan and sponsored by the AHCF, the symposium brought renewed interest to AHC with an emphasis toward pathophysiology, expanding the gathering of data, and including samples from patients who had passed. There were over 120 delegates worldwide. In September 2006, the first AHC walk was held in Chicago, Illinois.

In 2007, the AHCF awarded Dr. Swoboda a three year grant covering the period from July 1 2007 – June 30 2010. The first year of the grant cost $203,339.00. The second year cost was $208,739.00 and the third year was budgeted for $214,334.00. However, we found ourselves only able to fund $134,000.00 with Dr. Swoboda making up the rest.

During this grant period these were the following aims:

1) <u>Ongoing efforts to identify the genetic mechanisms involved in disease pathogenesis.</u>

a) Candidate Gene Analysis:

The work of evaluation of candidate genes continued in collaboration with researchers at Harvard University and UCLA, focusing on chromosome abnormalities identified in AHC patients that may provide clues to a causative genetic mechanism. Neighboring genes in these regions were also examined to decode the message looking for any small errors that could be interfering with function while additional candidates continued to be examined.

b) Implementation of new gene chip technologies:

The University of Utah took advantage of a new technology which allowed an unprecendented search for small deletions across the genome. This work was performed in collaboration with Dr. Arthur Brothman, a cytogeneticist who was experienced in the use of this novel and powerful new technology.

2: Development of a fellowship program designed to attract new and talented young physicians to AHC research. Providing Neurology Fellows with a year of intense focused effort on an AHC-related project to advance medical research and knowledge of AHC for the benefit of AHC patients and families as well as increase awareness of AHC in the medical community. This first Fellow was Matthew Sweeney whose fellowship resulted in the publication of the paper, "Alternating Hemiplegia of Childhood: Early Characteristics and Evolution of a Neurodevelopmental Syndrome" in the journal *Pediatrics*. His interest in AHC remains strong and he is currently serving on our Medical Advisory Board.

3) Pilot Clinical Drug Trial - Open Label Phase I/II Pilot Clinical Trial for the Treatment of Alternating Hemiplegia of Childhood with Gammahydroxybutyrate
The trial enrolled six clinical subjects with AHC, ages 1 - 4 years, and an additional six clinical subjects with AHC of all ages. Enrollment occurred over a 2 1/2 year period, with data analysis following.

The trial was divided into 2 phases – Phase 1 - In Hospital Initiation of Therapy and Phase 2 – Maintenance Therapy. The trial involved intense participation from the parents and was overseen by Dr. Aga Lewelt our second Fellow. Although the project had an end date of 6/30/2010, a No-Cost Extension was requested until 6/30/2011 to finish the project with full enrollment requiring no additional funds from the AHCF. This was granted, and Dr. Lewelt presented an abstract of the results of the clinical trials at the American Academy of Neurology Annual Meeting, April 28, 2012.

In addition to the above the grant funding allowed us to hire a Study Coordinator/Research Associate who was dedicated to AHC alone.

In July 2008, we held our next Family Meeting in Chicago, Illinois with a great turnout and many new families. Data collection continued and topics included research updates and fundraising with highlighted topics for the parents with professionals in behavior and estate planning for special needs persons. A medical panel fielded questions from the parents.

In February 2010, the Board voted to hire Sharon Ciccodicola on a contract basis to become the AHCF coordinator in addition to acting as the foundation's medical liaison. 2010 also brought other changes to the executive board. Richard George stepped down after 15 years as president of the AHF/AHCF in June, and the search for a new president rendered the appointment of Jeff Wuchich, who accepted in August. Jeff brought his networking and social media skills to the foundation.

This was also the first year that the foundation entered contests to win grants. Our first award was $20,000 which was won from Chase Community Giving in July, 2010. This grant was used for Dr. Sandra Reyna to perform administrative, managerial and scientific functions throughout the course of the AHC SO study and upcoming AHC projects.

This impetus propelled the foundation to our biggest challenge yet! Just after the Chase contest ended, Sharon Ciccodcola, saw an ad for the Pepsi Refresh contest and simultaneously was contacted by 2 AHC families wondering if we could take this on. Dr Sandra Reyna helped fill out the application spelling out specific medical needs and attainable goals. The project was titled "Find a Path to the Cure for AHC". Jeff entered the application right at midnight and we were on our way!

The response and support was incredible! Board members, researchers, families, friends and strangers voted us to victory. US servicemen voted on a carrier in the Atlantic, dozens of people handed out our cards to strangers and put hundreds of flyers on cars, Professors made their class text votes before the end of class, our foreign foundation friends contacted their families in the states to vote, Dr. Swoboda handed out cards while she was running a marathon, schools our AHC kids attended participated, parent's alumni schools and associations made announcements and put up posters to vote, neurologists and business' alike sent out mass emails, churches made announcements during their services, and every board member spent many long hours spreading the message via calls, facebook, local print and visual media. Many families made videos with the Zach Rap being a highlight! With the help of all of these families, friends, our medical team and so many more, we won $250,000! The $250,000.00 Pepsi Grant went directly to Dr. Swoboda and in collaboration to the Institute of Systems Biology and Complete Genomics to identify the gene, or genes, causative for AHC as the critical step in understanding pathogenesis.

In 2011, the clinical trials of the Sodium Oxybate study were in the final stages. The AHCF awarded an extended research agreement in the amount of $25,000.00 to Dr. Reyna to provide remaining consultation, supervisory and advisory services in connection with the clinical drug trials through 12/31/2011. In July 2011, a Family Meeting was held in Raleigh, N.C., with 34 families in attendance. Data collection continued, the AHCF sponsored a luncheon, and experienced parents participated in a parent's panel. The Foundation grew to 13 board members, the Medical Advisory Board expanded and was reengaged, and collaborations were

established with AHC foundations from across the globe. We now knew of approximately 750 patients worldwide.

In January 2012, the ATP1A3, the first AHC gene mutation was discovered. This was a joint effort by the University of Utah and Duke University. AHCF awarded Dr. Swoboda a $175,000 Bridge grant – Part 1: Clinical and Genetic Studies in AHC and Genotype/Phenotype Correlations and Part 2: Online AHC database: Natural history and Functional Outcomes. The grant covered the period January 1 – June 30, 2012. A No Cost Extension of this grant was requested and granted until September 30, 2012.
A very ambitious family meeting was held in San Francisco at the end of June. Meetings were held with the AHCF board of directors, the AHCF Medical Advisory Board and the International AHC associations. Families attended from 7 different countries. Panels of AHC young adults and a sibling support discussion were highlights.

In 2012, the AHCF established a Scientific Advisory Board whose sole objective is to review research proposals.

A $94,535 grant was awarded to Dr. Alfred George, Jr. and Dr. Kevin Ess at Vanderbilt University. It's purpose, to investigate the functional consequences of AHC gene mutations, to identify drugs or drug-like compounds with potential therapeutic effects in restoring normal gene function, and to develop advanced human cell models of AHC based on state-of-the-art induced pluripotent stem cell technologies. This grant is for the period of November 1, 2012 – June 30, 2013.

An award of $51,625 was also given to the Pediatric Motors Disorder Research Program under the direction of Dr. Kathryn Swoboda, specifically for the full genome sequencing to identify additional causative gene(s) in patients without mutations in ATP1A3. The funding period covers October 1, 2012 to April 30, 2013.

In December 2012, the AHCF provided Dr. Sandra Reyna with a grant to attend the AHC Symposium held in Brussels, Belgium. The AHCF also became part of an International AHC Alliance (AHCIA) with 23 countries to facilitate collaboration between organizations and researchers.

If you are interested in more details about the early days, research projects, family biographies, or fundraising accomplishments, please visit us at http://ahckids.org/posts/newsletters/