REPORT ON ATP1A3 CONFERENCE

The Third Symposium on ATP1A3 in Disease was held August 29-30, 2014 in Lunteren, The Netherlands. The meeting was held jointly with the first day of the 14th International Conference on Na/K ATPase. This joint arrangement was designed to stimulate discussions between clinicians, geneticists and scientists working on these genes and related disorders. During the two-day conference, there was clear evidence of intermingling of researchers who are experts in the more basic scientific aspects of ATP1A3 with others more focused on AHC and related diseases. Overall, the conference was deemed highly successful.

Progress has been made in several important areas including advances in recognizing an expanded range of clinical disorders associated with ATP1A3 mutations, development and characterization of various mouse models of AHC, continued progress toward understanding the basic molecular defect underlying AHC and RDP, and preliminary work toward identifying potential treatments.

The evening before the conference, a group dinner followed by a short program allowed parents and researchers to exchange ideas. There was brief discussion about the potential value of medicinal marijuana or cannabidiols in treating AHC, an idea stimulated by current trends in epilepsy therapy. Additional topics receiving attention were the need for more research into behavioral aspects of AHC, the basis for relief of symptoms by sleep and the need to understand the mechanisms of triggers. The program ended with the showing of videos produced by the Icelandic AHC foundation to raise awareness about this condition.

Progress in defining the clinical spectrum of ATP1A3 disease

New clinical subsets of ATP1A3 were revealed at the conference. The disorder called CAPOS for Cerebellar Ataxia, Pes cavus, Optic atrophy and Sensorineural hearing loss has been diagnosed in several families. All families have the same ATP1A3 mutation (E818K). Unlike AHC and RDP in which most mutations are de novo, this mutation can be transmitted within families. Although CAPOS was described as a distinct entity, there is also evidence of clinical overlap with AHC and RDP. Preliminary study of the molecular defect caused by E818K suggests overlap with features of AHC mutations.

There may be other clinical entities associated with ATP1A3 mutations. Drs. Brashear and Sweadner presented information about three cases with a wide range of neurological symptoms that were brought to their attention because of incidental discovery of ATP1A3 mutations. One adult male with severe ataxia and an inability to walk was referred from the NIH Undiagnosed Diseases Program. Two other infants with either severe apnea (non-breathing) or seizures also were found to have novel ATP1A3 mutations. Additional genotype-phenotype correlations were also recognized by Duke investigators. These new cases suggest a wider clinical spectrum of ATP1A3-associated disease.

One presenter discussed the possible occurrence of abnormal electrical activity in hearts of AHC patients. An extensive study of electrocardiographs (ECG) revealed some consistent abnormalities among patients, although the clinical significance of these findings is unclear.

There are now more than 70 known ATP1A3 mutations and a suggestion to build a web site to collect information about these findings was embraced by the group. There remains a small

subset of AHC and RDP patients in whom no ATP1A3 mutation has been found and there are efforts to look for a second AHC gene in these families.

Progress in understanding the molecular defect

Several groups have employed various cellular models to understand the basic molecular defects caused by ATP1A3 mutations. The emerging consensus appears to be that mutations associated with AHC and RDP are predominantly loss-of-function. Additionally, there may be some properties of the ATP1A3 pump protein that are preserved in some cases and this fueled speculation of mechanisms responsible for greater clinical severity of certain mutations such as E815K. There have been preliminary efforts to identify drugs that can restore ATP1A3 function. In work funded by the AHCF done by the Vanderbilt and Northwestern University teams, there is evidence that it may be feasible to restore normal ATP1A3 protein levels to the cell membrane.

Progress with mouse models

Exciting work was presented at the conference related to the development and characterization of mouse models of AHC. The Duke group presented their results with a new mouse having the D801N mutation. These mice exhibit many features of AHC including attacks of hemiplegia, quadriplegia, dystonia, hyperactivity and seizures. They are also working toward development of another mouse model with the E815K mutation.

Two groups presented additional studies of the D801Y mouse developed at Aarhus University in Denmark. Although in humans D801Y is associated with RDP, the mouse exhibits characteristics more closely aligned with AHC. Some of the behavioral abnormalities exhibited by the mice somewhat resemble other animal models with defect in dopamine transport. Because of this similarity, the Danish researchers tested a drug (haloperidol) that modulates the activity of dopamine in the brain. Preliminary evidence suggests that D801Y mice treated with haloperidol may have less hyperactivity.

Progress in working as a team

Throughout the conference, there was a consistent emphasis by presenters and participants to work together as much as possible. These efforts included developing consensus guidelines for genetic testing and clinical management, and defining measurable indices of symptoms and clinical outcomes. Dr. Rosewich informed the group about the effort started at the AHCF Family Conference held in June 2014 to write a consensus paper about AHC and RDP management then invited the rest of the research community to contribute. There was a spirited discussion about fund raising strategies but no specific recommendations were made.

Future Conference

Planning is underway for the 4th Symposium on ATP1A3 in Disease to be held in Bethesda the last week of August 2015. A small grant has been submitted to the NIH by CURE AHC to help fund the conference.