SYMPOSIUM ON AHC

9 February 2019

Hospital Sant Joan de Déu, Barcelona

SYMPOSIUM ON AHC

Hospital Sant Joan de Déu

9 January 2019, 8:30 – 17:00

8:30 **Registration**

9:00 **Opening and Welcome**

Bridget Vranckx, *President of AESHA (Spanish Association of AHC)*

Dr. Jaume Campistol, *Paediatric Neurologist, Hospital Sant Joan de Déu*

Morning Session - Chair *Dr. Jaume Campistol*

9:10 **The importance of research in rare diseases**

Jordi Cruz, *FEDER (Spanish Federation of Rare Diseases)*

9:20 **AHC: Current situation and understanding of the disorder**

Dr. Carmen Fons, *Hospital Sant Joan de Déu (Barcelona, Spain)*

9:45 **Family associations' role in research for AHC**

Rosaria Vavassori, *IAHCRC (International Consortium for the Research on AHC)*

10:15 **OBSERV-AHC Prospective Observational Natural History and Therapy Study**

Dr. Mohamad Mikati, *Duke University School of Medicine (Durham, USA)*

11:00 Coffee-break

11:30 **Behavioural disorders and psychiatric comorbidity in AHC**

Dr. Eleni Panagiotakaki, *Centre Hospitalier Universitaire de Lyon (France)*

12:00 **Therapeutic alternatives in AHC**

Dr. Elisa De Grandis, *Università degli Studi di Genova (Italy)*

12:30 **Medium throughput screening of candidate compounds to the treatment of AHC**

Prof. Francesco Danilo Tiziano, *Institute of Genomic Medicine of Catholic University (Rome, Italy)*

13:00 **AAV9 gene therapy project**

Video presentation

13:15 **General Discussion**

13:45 Lunch

Afternoon Session – Chair *Dr. Carmen Fons & Albert Vilamala*

15:30 **Meet the Experts: Dr. Mohamad Mikati, Dr. Eleni Panagiotakaki, Dr. Elisa De Grandis**

17:00 **Closing Remarks**

Organizing Committee

Dr. Carmen Fons, *Head of the Paediatric Neurology Service, HSJD*

Dr. Jaume Campistol, *Paediatric Neurologist, HSJD*

Bridget Vranckx, *President of AESHA*

Marc Gambús, *Secretary and Treasurer of AESHA*

Albert Vilamala, *Member of AESHA Board*

Dr. María Carme Fons Estupiñà

Head, Neurology Department, Hospital Sant Joan de Déu, Barcelona, Spain

Education

- PhD in Neurosciences. University of Barcelona , 2010
- Fellowship in Pediatric Neurology. SJD Barcelona Children's Hospital and University of Barcelona, 2006
- Specialist in Pediatrics. Lozano-Blesa University Clinical Hospital, Zaragoza, 2005
- Bachelor of Medicine and Surgery. Rovira & Virgili University (URV), 2000

International Experience

- Post-Doctoral Research Fellow in Fetal Neonatal Neurology. Boston Children's Hospital. Harvard University, Boston, Massachusetts, USA 2010-2011
- Special medical training in Pediatric Neurology. Neurology Department. St. Christopher's Hospital for Children. Philadelphia. USA. 2003

Scientific and teaching activity (summary)

- Presentation of numerous papers, oral communications and posters at national and international scientific conferences and meetings (+91)
- Author of scientific papers in national and international journals (+41) and book chapters (5)
- Participation in national and European research projects (7):
- Lecturer in the Master's Degree Course in Pediatric Neurology. University of Barcelona (UB)
- Clinical lecturer for the Undergraduate Degree in Medicine. University of Barcelona (UB)

AHC: Current situation and understanding the disease. Past, present and future

AHC is a rare neurological disorder that was first described by Verret and Steel in 1971 as a type of hemiplegic migraine. Later, in the 80's, Krakelog and Aicardi defined the diagnostic criteria of the disease. A huge advance in the knowledge of the disease has been evident since 2005 when the European Union funded the ENRAH for SMEs project (2005-2007), and which main goal was to develop a web based multi-centric register of the disease and to promote the clinical research. 158 patients from 8 countries were collected and as a result of the project, a description of the natural history of the disease was described (Panagiotakakai, 2010). In 2012, De novo mutations in ATP1A3 were demonstrated to cause AHC (Heinzen et al.). Following the evidence of a genetic cause of AHC, a new era focused into the research of physiopathology mechanisms, genotype-phenotype correlations and treatment options began. The IAHCRC was created to promote and accelerate collaborative research on ATP1A3 related disorders. Several research projects based on Genotype-Phenotype correlations, cardiac abnormalities have been published and will be discussed. The near future will be dedicated to find personalized treatments to cure or improve the quality of life of the patients.

Mrs. Rosaria Vavassori, Dr. Eng.

Data manager IAHCRC International Research Consortium for AHC

- Mrs. Vavassori received her graduation in Electronic Engineering in 1986 at the Polytechnics University of Milan, with a specialization in Computer Science.
- She worked at Honeywell Information Systems Italy (Manufacturing Division), then at Siemens Telecommunication Italy, as Director of the Workflow and Product Data Management Systems Department, until 2000.
- She founded the Italian Patient Association for AHC in 1999 and was its president until 2014.
- Mother of an AHC patient, she founded the Italian Patient Association for AHC in 1999 and was its president until 2014. During her presidency, she initiated and coordinated I.B.AHC - Italian Biobank and Clinical Registry for AHC.

- As patient representative, she participated in the EU-funded Projects “ENRAH for SMEs” (FP6, 2005 – 2009) and nEUroped (PH, 2008 -2011) and as IT professional, she was the Data Manager of the European Registry created for these two Projects, until 2013.
- In 2013 together with Prof. Alexis Arzimanoglou she initiated the IAHCRC International Research Consortium for AHC and all the ATP1A3 diseases and in 2014 she was appointed as its Data Manager.
- In 2017 she started the coordination of the Project IAHCRC-CLOUD, to create an on-line Platform serving the data collection and sharing for the Studies carried out by the centers of the Consortium.
- Currently she is in charge of the project management for the Study OBSERV-AHC, a two years observational therapy and natural history Study on AHC, whose data will be collected in the Platform.

Family associations’ role in research for AHC

Family associations have always had an active role in research on AHC, since the very first studies launched in early 2000 in the USA and Italy.

Families are engaged in many different ways, all of them strategic for the progress of the research on a disease as rare as AHC. Their contribution is essential not only in typical activities of raising awareness and funding research projects, but also in developing collaborative networks among basic research and clinical centers, and in finding new partners from industry and public institutions. They promote and actively support the sharing of ideas, information and data among all the stakeholders, also by means of informatics and resource management tools such as Clinical Registries and Biobanks. Bringing their experiential knowledge of the disease in all its practical issues, they are getting more and more involved in the definition of priorities in research, in the design and realization of new studies and in the actualization of the results of such studies in the clinical practice.

The EU-funded projects ENRAH for SMEs (2005 – 2007) and nEUroped (2008 – 2011) have been positive experiences of family engagement, with the participation of many family associations, also with coordination and management roles, together with the clinical reference centers and genetic laboratories of ten European countries. Thanks to the collaborative network created by these two projects, the large-scale international study was carried out in 2012 that led to the identification of the mutations in the ATP1A3 gene as main cause of AHC.

Afterwards, the IAHCRC International Consortium for the Research on AHC was formally created, in whose activities and studies the family associations are involved at all levels as supporting partners.
In particular, the associations collaborate for the informed recruitment of their families in the Studies of the Consortium, and can support them in providing their own part of data.

The IAHCRC-CLOUD Project has been recently launched, to facilitate this process by establishing an on-line, independent Platform for the secure and ethical data collection and sharing, open to the peer contribution of all stakeholders, including patients. The Platform is aimed to serve the multicentre Studies of the IAHCRC Consortium, such as the observational therapy and natural history Study OBSERV-AHC.

Dr. Mohamad Mikati

Duke University Scool of Medicine (Durham, EEUU)

Dr. Mikati's clinical research has centered on characterization and therapy of pediatric epilepsy and neurology syndromes, describing several new pediatric neurological entities with two carrying his name (POSSUM syndromes # 3708 and 4468), developing novel therapeutic strategies for epilepsy and related disorders particularly Alternating Hemiplegia of Childhood, and applying cutting edge genetic and Magnetic Resonance Imaging techniques to drug resistant pediatric epilepsy. In the laboratory he has elucidated mechanisms of seizure related neuronal injury, particularly those related to the ceramide pathway, and demonstrated neuroprotective effects of several agents including erythropoietin. Most recently he has concentrated his laboratory research on the pathophysiology of ATP1A3 dysfunction in the brain as model for epilepsy and of Alternating Hemiplegia of Childhood.

He has more than 210 peer reviewed publications, 300 abstracts 40 chapters one book and two booklets. He also has more than 6,214 citations in the literature with an h-index of 46 and an i-10index of 127. Dr. Mikati has written chapters on epilepsy and related disorders in the major textbooks of Pediatrics and Pediatric Neurology including Swaiman's Pediatric Neurology and Nelson's Pediatrics.

Before joining Duke in 2008 he had completed his M.D. and Pediatric training at the American University of Beirut, his Neurology at the Massachusetts General Hospital, his Neurophysiology at Boston Children's Hospital and had been on the Faculty at Harvard as Director of Research in the Epilepsy Program at Boston Children's Hospital and then as Professor and Chairman, Department of Pediatrics, Founder and Director of the Adult and Pediatric Epilepsy Program at the American University of Beirut.

Dr. Mikati has had several international leadership roles including being President of the Union of the Middle Eastern and Mediterranean Pediatric Societies, on the Standing Committee of the International Pediatric Association, Officer of the International Child Neurology Association, Member of the Pediatric Content and Scientific Program Committees, Child Neurology Society International Affairs Committee Consultant to UNICEF, WHO, and the American Board of Pediatrics, and being one of only two Pediatric Neurologists, initially chosen worldwide, on the WHO advisory committee for the International Classification of Disease being the head of the neuromuscular group in that committee. He is also a cofounder of the International Alternating Hemiplegia of Childhood Research Consortium and Deputy Scientific Coordinator of the Consortium. He is also a member of the Planning Committee for the International ATP1A3 Disease Group. He has received several national and international honors including, among others, Merritt Putnam American Epilepsy Society Fellowship Award, Harvard Community Health Plan Peer Recognition Award, Debs Research Award, Hamdan Award for contributions to Medicine, Hans Zellweger Award for contributions to Pediatric Neurology, Patient Choice Award, American University of Beirut Alumni Achievement and Service Award, and the Michael Frank Award for research and lifetime contributions to the field of Pediatric Neurology. His name consistently appears in America's Top Doctors Series

Dr. Mohamad Mikati

Duke University Scool of Medicine (Durham, EEUU)

OBSERV-AHC Prospective Observational Natural History and Therapy Study

Among the important current needs for research in Alternating Hemiplegia of Childhood (AHC) are the following four clinically important goals:

1. Collect prospective data regarding prognosis and its predictors (other than the known prognostic correlations of certain gene mutations) including initial disease severity parameters and subsequent flunarizine therapy (does flunarizine therapy affect long term developmental and other outcome or it only affects the frequency of the AHC spells during its intake?)
2. Determine what is the relative efficacy of various therapies that are being tried on an ad-hoc basis by different clinicians (e.g. keto diet, Cannabidiol, VNS)?
3. Establish validated and reliable procedures in data collection and analysis that are useful for future prospective therapeutic trials of AHC.
4. Establish a prospective natural history data base that could be used as a potential historical comparison for future interventional studies.

Whereas some, important, cross sectional studies did not demonstrate that AHC is a progressive disease, prospective studies are needed to determine if this is, in fact, the case or not. Performing such studies is critical in view of the demonstrated regression in many patients reported by multiple investigators, the recent recognition that ATP1A3 dysfunction contributes to regression in neurodegenerative disease like Parkinson's and Alzheimer's and due to the inherent limitations of cross sectional studies. There are also recent studies to indicate that there are pervasive neuropsychological and motor impairments in AHC and these need to be determined if they are progressive or not. Relevant studies will be reviewed and then the Observ-AHC study, which aims to address the above much needed goals, will be presented. It is a multicenter study of the International Alternating Hemiplegia of Childhood Consortium (IAHCRC) that leverages the collaboration of multiple clinical centers: Duke, Lyon, Genoa and Barcelona with its database being housed in I.E.ME.S.T in Palermo, Italy. This is a 2 year prospective study which also includes retrospective data collection components (historical data about disease severity and clinical course will also be collected). It aims to recruit patients who fit the Aicardi AHC clinical criteria, of any age. Patients seen during the first year will have their baseline data, regarding various disease manifestations, entered. Subsequent follow up data in one year (and from any additional encounters in between) will be entered also. Follow up visits will be performed according to the clinical needs of each patient. The training of the caregivers will be through the Video-Library (two sets one initial for training and the other from study participants), to learn how to classify the episodes they will have to record for the study and to use in validity and reliability testing. Data analysis will be targeted at achieving the above goals. The expectation is also that the study would continue beyond two years for at least 5 years in order to collect more prospective information. It is also hoped that in the future other centers in the IAHCRC will participate in order to strengthen the power of the findings and to be able to answer more granular questions regarding the natural history of various aspects of the disease.

Dr. Eleni Panagiotakaki, MD PhD

Department of Clinical Epileptology, Sleep Disorders and Functional Neurology in Children HFME, Centre Hospitalier Universitaire de Lyon (France)

Academic Qualifications (most current date first):
Degree/Certification PhD in “Correlation of the genotype in Wilson’s disease (gene ATP7B) with clinical and biochemical phenotype. 2009 University of Athens, Faculty of Medicine, Greece.
French inter-University Diploma of Pediatric Neurology. 2007 University of Picardie, Jules Verne, Amiens, France.
French inter-University Diploma of Epileptology. 2005 University Henri Poincaré, Nancy 1, France.
Board certified in Paediatrics. 2003 Faculty of Medicine, Athens, Greece.
Doctorate of Medicine. 1993 Faculty of Medicine, Patras, Greece.

Behavioural disorders and psychiatric comorbidity in AHC

ATP1a3 is the main subunit of the Na+/K+-ATPase pump that is expressed in neurons. It is present in multiple brain areas, including the hippocampus, cortex, cerebellum, and basal ganglia. This pump consumes about 50% of the energy of neurons and is vulnerable to metabolic stress.

Mutations in the ATP1A3 gene are responsible for various neurological disorders as: rapid-onset dystonia-parkinsonism (RDP), alternating hemiplegia of childhood (AHC), CAPOS, RECA, and also childhood onset schizophrenia, introducing the idea that defecting function of this subunit can be related to psychiatric disorders. This is further underlined by recent works, which suggest that RDP patients may exhibit an elevated prevalence of mood disorders (50%) and psychosis (19%) as well as impairment in attention, compared to relatives without an ATP1A3 mutation. Repetitive behaviors and social difficulties resulted in a diagnosis of autism spectrum disorder have also been described in patients with CAPOS.

Noteworthy, a particular behavioral phenotype is evident in multiple mouse models of AHC. Behavioral anomalies evident in Mashl+/ mice included increased levels of spontaneous activity as well as decreased avoidant and anxiety-like behaviors. Such behavior has been noted in other mouse models of ATP1a3 dysfunction, including in the Myshkin mouse model of AHC and in the Atp1a3tm1Ling/+ mouse, which has an increased susceptibility to depression-like endophenotypes induced by chronic variable stress. These characteristics have an analogy with the behavioral features that can also be seen in AHC patients.

AHC patients manifest a wide range of behavioral and psychiatric disorders including impulsivity, lack of attention control, problems with communication, obsessionality, and short-temperedness. Most patients have behavior problems, usually consistent with ADHD superimposed on cognitive impairment. These include aggression toward self or others. Some genotype-phenotype correlation tendencies have been reported as behavioral disorders found more commonly in patients with the p.Asp801Asn mutation (in more than half the patients) compared to those with the other two frequent mutations (p.Glu815Lys and p.Gly947Arg). Developmental, neuropsychological, and psychiatric evaluations are helpful to address these issues.

On the light of these findings associating psychological disorders with ATP1A3-related disorders, we can rise the reverse hypothesis : that ATP1A3 mutations may also be found in patients with psychiatric conditions, associated to less severe types of movement disorders paroxysmal or not.

In conclusion mood disorders including depression, social phobia, anxiety, bipolar disorder, and psychosis are common comorbidities in AHC and other ATP1A3-related disorders. Based on recent research findings, they do not only appear as a psychological and social reaction towards a chronic, severe and disabling disorder, but are directly related to the defective expression of the ATP1a3 subunit in the brain.

Dr. Elisa De Grandis

MD, PhD, IB.AHC Italian Consortium
Università degli Studi di Genova, Italy

Dr Elisa De Grandis is a clinical researcher working in the University of Genoa, Division of Child Neuropsychiatry. After the degree in Medicine and Surgery in 2001, she started the residency training in Genoa and developed a deep interest in Child Neurology, and in particular in the field of Movement Disorders. At the end of the residency training, she spent 4 months in Queen Square, National Hospital of Neurology and Neurosurgery focusing on the semeiology of extrapiramidal disorders. During her Neurosciences PhD course, she attended for nearly 2 years the Division of Pediatric Neurology Service and Movement Disorders Clinic, Sant Joan de Dèu Hospital, University of Barcelona. During this period, she gained further clinical and research experience on movement disorders in childhood.

She has always been deeply committed to the care of rare neurological disorders and their related disability and in particular of Alternating Hemiplegia of Childhood (AHC), collaborating with the Italian Association of Hemiplegia od Childhood – AISEA since 2002.

She is author of 8 indexed scientific publications on AHC.

She has been recently confirmed as Coordinator of the Italian Node of the IAHCRC International Consortium for the Research on Alternating Hemiplegia of Childhood (AHC) and she is Data Manager and Scientific Coordinator of the Italian Biobank and Clinical Registry of the Italian Association of Alternating Hemiplegia of Childhood.

Therapeutic alternatives in Alternating Hemiplegia of Childhood

Since phenotype variability of AHC is extensive, drug therapy is often difficult and challenging. Several drugs have been used since AHC was first described, mainly to control the paroxysmal attacks that represent the most disturbing symptoms.

A revision of the existing literature will be provided. A recent review of the pharmacological data regarding the prophylactic and acute treatment of the Italian cohort of patients will be presented and discussed.
Further studies on the response to treatment in a cohort of AHC patients affected by the ATP1A3 mutation, in light of the recent discovery of the biological basis of the disorder, are needed to provide the rationale for the use of newer and more efficacious molecules.

Prof. Francesco Danilo Tiziano

Associate professor at the Institute of Genomic Medicine of Catholic University (Rome, Italy)

Together with Fiorella Gurrieri, I have been involved in the identification of ATP1A3 as one of the causative genes of AHC. Currently I am co-PI in the medium throughput screening program. Beside AHC, my main field of research is spinal muscular atrophy (SMA). I have been among the stakeholders of the identification of effective treatments for the condition, and leader in the research field of biomarkers for the condition. Currently, I am the PI of the first national newborn screening program for SMA and among the first worldwide. This pilot project will start soon and will involve about 140k neonates over the next two years.

Medium throughput screening of candidate compounds to the treatment of AHC

Abiusi E.[1], Novelli A.[1], De Billy De Crispin E.[2], Piacentini R.[3], Diano F.[1], Cocco S.[3], Di Pietro L[1], Ripoli C.[3], Gemei M.[4], Beccari A.[4], Antonini L.[5], Ragno R.[5], Gurrieri F[1], Tiziano FD[1],

[1]: Institute of Genomic Medicine, Catholic University of Rome, Italy; [2]: Department of Hematology/Oncology and Stem Cells Transplantation, Bambino Gesù Children Hospital, Rome, Italy; [3]: Institute of Human Physiology, Catholic University of Rome, Italy; [4]: Dompè Pharmaceuticals, Milano; [5]: Dep. of Pharmaceutical Chemistry and Technology, Sapienza University, Rome, Italy, [6]: Alchemical Dynamics, Roma; [7]: Fondazione Policlinico Universitario IRCCS "A. Gemelli", Roma.

We are currently performing a medium throughput screening of candidate compounds to the treatment of AHC, by using a cellular model of the condition that we have recently developed and characterized. Our model is based on a human neuroblastoma cell line (SH-SY5Y), expressing the most common *ATP1A3* variants found in AHC patients (E815K, D801N, G947R) plus the D801Y mutation, found in DYT12 patients.

We are testing 2000 compounds that were selected among molecules registered for other disorders (about 1300 molecules) and about 700 compounds safe-in-man, even if not registered as drugs. We have chosen this strategy for several reasons:

1) compared to other therapeutic approaches, the identification of an effective small molecule may provide clinically relevant improvements, independent of the mutation found in the single AHC patient;
2) the use of potential candidates may be extended to other disorders that display similar accessual phenotypes;
3) the approach of safe-in-man molecules/registered compounds may help to skip the phase I studies, accelerating the preclinical and clinical studies.

So far, we have characterized the cellular model and obtained relevant results. First, our data indicate that AHC mutations have a gain-of-function effect: even if mutated cells have a normal background expression of the endogenous *ATP1A3* gene, the presence of the AHC mutations induce a clear cellular phenotype, including the accumulation of Na^+ and Ca^{2+}, as well as the reduction of the membrane resting potential. Upon differentiation, cell lines bearing *ATP1A3* mutations started dying few days after the initiation of the protocol.

The phenotypic characteristics we found in mutated cells can be easily evaluated by high-throughput screening platforms. In particular, fluorescent probes could easily track Na^+ accumulation and allowed to clearly discriminate mutated from naïve cells. We expect that an effective compound will promote the scavenging of ion accumulation, thus restoring a normal cellular phenotype. This approach will be used as a first tier selection of candidate compounds: we will also evaluate the ability of candidate molecules to revert the death phenotype upon differentiation.

This work was supported by AISEA.

More information

IAHCRC International Consortium for the Research on Alternating Hemiplegia of Childhood (AHC) : iahcrc.net

AHC Federation of Europe: ahcfe.eu

AHC International Media: ahcim.com

Documentary: humantimebombs.com (subtitles in 10 languages)

International Patient Organizations:

Cure AHC: American Patient Association for AHC, Raleigh, NC, USA

AHCF: Alternating Hemiplegia of Childhood Foundation, Southfield, MI, USA

Assocation Canadienne de l'Hémiplégie Alternante: Québec, Canada

AFHA: French Patient Association for AHC, St Germain lès Arpajon, FR

AHC Association of Iceland: Reykjavík, Iceland

AHCUK: AHC Support Group, UK

AHC Vereniging Nederland: Dutch Patient Association for AHC, The Netherlands

AESHA: Spanish Patient Association for AHC, Barcelona, Spain

AISEA: Italian Patient Association for AHC, Rome, Italy

AHC Kids DK: Danish Patient Associtaion for AHC, Denmark

AHC Deutschland: German Patient Associtaion for AHC, Germany

Alternating Hemiplegia Society of Ireland: Ireland

Polskie Stowarzyszenie na Rzecz Osób z AHC: Polish Patient Assocation of AHC, Poland

JAFA: Japan AHC Family Association, Tokyo, Japan

THANK YOU

GRACIAS