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The Studies and the Projects of the IAHCRC Consortium, an effective organizational model, for the progress of the collaborative research on the ATP1A3 rare diseases and of the care for the affected patients

Rosaria Vavassori1, Giosuè Lo Bosco1, Alexis Arzimanoglou2, Eleni Panagiotakaki3, Mohammad Miltaki2, Lyndsey Prange2, Arv van den Maagdenberg2, Erin Heinen3, Sanjay Sisodiya2, Simona Balestrini4; all the Centers of the IAHCRC Consortium;

IAHCRC Consortium

The International Consortium IAHCRC for the Research on Alternating Hemiplegia of Childhood (AHC) and other ATP1A3 rare diseases was formed in 2012 to carry out a collaborative research that led to the identification of the ATP1A3 gene as the main cause of AHC (Heinen et al., Nature Genetics, July 2012). The official Charter of the Consortium was definitively approved by its 15 founding members on November 2014.

The Consortium involves clinicians, geneticists and researchers working at University centers in Europe, USA and Australia; it works in close collaboration with health professionals and patient and mixed organizations, most of whom were already collaborating in the EU-funded projects “ENRAH for SMEs” (2005-2007) and “eNeuro” (2008-2011).

Objectives

The IAHCRC Consortium aims to accelerate clinical and basic science research in the field of AHC and of all the ATP1A3 related diseases, and to improve the quality of life of affected patients and of their families.

Its main objectives are:

1. Contribute actively to the collaborative study of the pathogenic mechanisms of the ATP1A3 diseases and to the development of an effective treatment for all of them;
2. Promote a better care for all the affected patients, by developing specific standards for the diagnosis and the management of the diseases and by disseminating the information;
3. Define Common Data Elements (CDE), Protocols and Methods for the production, the assessment, the collection and the sharing of the patient data and of the research information and for the dissemination of the information inside and outside the Consortium;
4. Carry out large-scale collaborative Studies on the ATP1A3 diseases, proposed by any IAHCRC member and compliant to the IAHCRC Charter and CDEs, with the financial and logistic support of patient associations and other private and public supporting partners.

IAHCRC Studies and Projects

In 2013, the Consortium launched further collaborative studies, including the largest international cohort of AHC patients to date, whose results have already been published: the study of the genotype-phenotype correlations (Project GPC-AHC, coordinated by Prof. Alexis Arzimanoglou and Dr. Eleni Panagiotakaki), the study on some cardiac conduction abnormalities of AHC (Project ECG-AHC, coordinated by Prof. Sanjay Sisodiya).

The study for the identification of the secondary gene(s) for AHC (Project GEN2-AHC), the second study of the heart disturbances in the ATP1A3 diseases (Project ECG2_ATP1A3) and the expansion of the IAHCRC CDEs (Workgroup EVCAL_AHC) are all in progress; the observational Study OBSERV-AHC is currently in the pre-launch phase.

Some IAHCRC researchers are also carrying out smaller scale studies independently, at the national level or with external research groups, in Italy, UK, USA that could be preliminary to the launch of new IAHCRC Studies at the international level.

GEN2-AHC Study

* Coordinated by Prof. Arv van den Maagdenberg and Dr. Erin Heinen.

AHC is usually caused by a de novo (not inherited) mutation in the gene ATP1A3; however some children with AHC have no mutation in this gene (so-called ATP1A3-negative patients). We believe these children have AHC because of genetic mutations elsewhere in their DNA.

In this study we are sequencing the DNA of ATP1A3-negative patients with the hope that we will identify the genetic causes of AHC in them. Identifying these mutations will not only allow the families of ATP1A3-negative patients to better understand why their child is suffering from the disease, but it will also teach how AHC is brought about. The identification of new mechanisms, beside potassium pumps that are affected by ATP1A3 mutations, will give new opportunities to identify treatments for children with AHC.

To date we have sequenced 40 ATP1A3-negative patients (and their parents) and found several genetic mutations, including mutations in the gene RHOB2B2, we believe may be responsible for AHC, although more evidence is still needed before a formal claim can be made. Despite this progress there are still patients where we cannot pinpoint the genetic mutation responsible for AHC.

In the coming year we intend to exome sequence even more ATP1A3-negative patients with the most advanced sequencing methods that will detect more types of genetic mutations, in order to identify all the genes involved in AHC.

ECG2-ATP1A3 Study

* Coordinated by Prof. Sanjay Sisodiya and Dr. Sanjay Balestrini.

Outcomes in AHC range from life into adulthood, with comparatively little disability, to premature mortality from sudden death, including sudden unexpected death in epilepsy (SUDEP).

We previously demonstrated that many patients with AHC have ECG changes, varying from repolarization abnormalities, i.e. wave 4 or 5 point changes, to periods of asystole, with an increasing prevalence with age. The ECG abnormalities were dynamic, reflecting characteristics of inherited cardiac channelopathies, and suggesting, along with the paroxysmal neurological features, periodic systemic decurricularization in ATP1A3 expressing organ systems.

Given these findings, systematic cardiac investigation is warranted in this condition, as cardiac arrhythmia morbidity and mortality are potentially preventable (with implantation of a cardiac pacemaker or defibrillator). Also, certain drugs should be avoided in view of the increased risk of precipitating serious arrhythmias.

We are now carrying out a second study enlarging the cohort (113 cases) and including cases with other ATP1A3 related phenotypes: cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss (CAPOS); and rapid-onset dystonia–parkinsonism (RDP). We are investigating the cardiac phenotype further, collecting data also on prolonged ECG monitoring, echocardiography and other cardiological evaluation tests. This will validate our previous findings and give more insight on the phenotype-genotype correlation in AHC and other ATP1A3-associated syndromes.

OBSERV-AHC Study

* Coordinated by Prof. Mohammad Miltaki and Dr. Lyndsey Prange.

This is a study that leverages the collaboration of multiple clinical centers in Europe, the USA and possibly elsewhere to collect data regarding the natural history of the disorder (paroxysmal and disability related) and regarding various therapies that are being attempted by different clinicians and analyze them for:

1. the efficacy of specific agents and for the predictors for long term outcome (most specifically of florazine therapy).

The study also aims to establish the following:

1. procedures for prospective data collections that could be used in future controlled trials
2. a prospective data base that could be used as a potential historical companion for future investigations.

The collaboration will create the framework for hopefully anticipated future multicenter therapeutic trials.

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Cure AHC, USA www.cureahc.org
AFHA, France www.afha.org
AESH, Spain www.aesh.org
AHC Iceland www.ahc.is
AHCUK, Great Britain www.ahcuk.org
AHC Vereniging Nederland www.ahckids.nl
AHC-PL, Poland www.ahc-pl.org
AISEA, Italy www.aiseaenlus.org

IAHCRC Cloud Platform Project

* Coordinated by the IAHCRC Data Manager Dr. Rosaria Vavassori and directed by the IEMEST Head of the IT Department Prof. Giosuè Lo Bosco.

The IAHCRC Cloud Platform www.iahcrc-cloud.net is a service developed using the RedCap© software tool and hosted by the IEMEST Institute, a IAHCRC member center.

The Platform is a network of homogeneous databases containing clinical data that can be linked and efficiently reused for any study carried out by the IAHCRC Consortium.

Clinicians, patients and researchers worldwide can enter and safely keep their own data in the Platform through a web browser or a mobile app. They can share their data for any IAHCRC Study conducted by them.

The data collected and shared in the IAHCRC Cloud Platform are managed in full observance of the confidentiality and ethics rules set forth in the IAHCRC Charter, for the development of an effective collaboration among all the stakeholders involved in the study and the care of the ATP1A3 diseases.

Through the Platform, large-scale studies can be carried out using the data of a large number of patients; such amount of data would be otherwise very difficult to collect and include in a study, as AHC and all the ATP1A3 diseases are very rare and the affected patients are scattered among many centers in different countries worldwide.

IAHCRC International Consortium Provinciale Vereniging van Nederlandse AHCIAIAH

(1) Euro-Mediterranean Institute of Science and Technology (IEMEST), Palermo, Italy
(2) Epilepsy, Sleep and Pediatric Neurophysiology Unit, University Hospitals of Lyon, France;
(3) Division of Pediatric Neurology, Department of Neurobiology, Duke University, School of Medicine, Durham, NC, USA;
(4) Department of Human Genetics, Leiden University Medical Center, Leiden, Netherlands
(5) Institute for Genomic Medicine, I-DM, Columbia University, New York City, NY, USA
(6) Institute of Neurology, University College London, London, UK;
(7) www.iahcrc.net/consortium/members.html

娱乐城提现 www.iahcrc.net