A STUDY OF THE IAHCRC INTERNATIONAL CONSORTIUM

STUDY OBSERV-AHC

PROSPECTIVE OBSERVATIONAL NATURAL HISTORY AND THERAPY STUDY

Years 2018 - 2020

DESCRIPTION AND PROTOCOL

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Sponsors and Supporting Partners

Association CureAHC, USA (Funds for: Data Analysis, Data Collection from the US-01 Node, IAHCRC-CLOUD Platform Development; support for the recruitment of the patients with their referent clinicians and for the information to the families)

Association AFHA, France (Funds for: Data Monitoring and Analysis, Project Coordination and Management, Data Collection from the FR-01 and IT-01 Nodes; support for the recruitment of the patients with their referent clinicians and for the information to the families)

Associations **AHC Vereninging Nederland**; **AHCUK - United Kingdom**; **AHC Iceland** (Funds for the IAHCRC-CLOUD Platform Development)

DESCRIPTION OF THE STUDY AND PROTOCOL

Alternating Hemiplegia of Childhood (AHC) is a rare and serious disease that is in need of effective, and hopefully even curative, therapies. Afflicted patients suffer from severe paralyzing crises, often excruciatingly painful muscle spasms, severe often life threatening epileptic seizures, and frequently severe developmental and psychiatric/psychological disabilities. Based on the repeated input from family organizations and from professionals, as expressed most recently in the London 2016 ATP1A3 in Disease meeting, there are urgent clinical research needs for AHC that are essential to better understand the disease, evaluate its treatment options and to plan for future controlled clinical trials. We planned this proposal to address these needs as articulated in the following objectives section.

Objectives

Based on the above needs, we designed this study to achieve the following objectives:

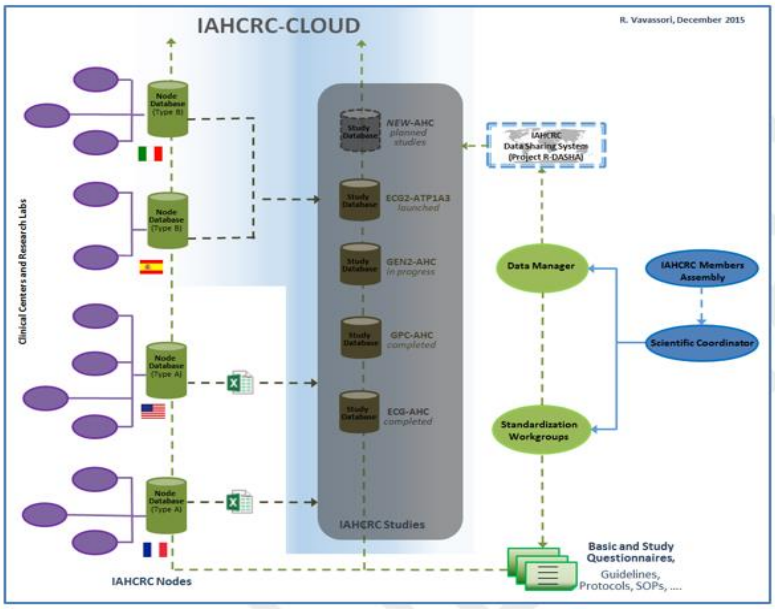
1. Establish an electronic database platform that we will use to efficiently enter, and analyze comprehensive data on AHC patients during the performance of this study and that would also be used in future multicenter prospective studies. Also, establish the validity and reliability of specific procedures to correctly identify and report the different types of spells that occur in AHC patients.
2. Determine the patient variables that can predict long-term outcome. Particular interest here is to determine if flunarizine therapy has an effect on modifying long-term developmental status.
3. Determine the apparent efficacy of various novel therapies introduced, by clinicians (e.g. VNS, Ketogenic Diet, ATP, or Cannabidiol) on an ad-hoc basis and analyze them for possible use of one or more selected agents in future controlled trials.
4. Collect baseline and one year follow up natural history data and determine if AHC paroxysmal and non-paroxysmal manifestations change significantly during that one-year period.

Methodology

Overall design: This study will be a collaborative prospective study over two years conducted by the International AHC Consortium (IAHCRC) on 80 AHC patients. We will collect baseline historical data at baseline. We will also collect specific measures of disease severity (see table below), and data on ongoing therapies at baseline, at follow up visits (performed according clinical needs of each patient) and at a one year follow up (See table below for details). All IAHCRC centers (30 centers) will be eligible to participate, but three of them will be the main ones. These three centers are the study coordinating and data analysis center (Duke, IAHCRC-US Consortium, USA, Node US01), the IAHCRC-CLOUD Platform Develop Center (IEMEST, Italy) and the collaborating center in France (IAHRC French Node FR01; coordinated by University Hospital of Lyon). These three centers will generate in partnership with other IAHCRC centers and with input from family organizations

database collection forms. We have already generated the prototypes of these forms and are pilot testing them in one center (Duke). These three centers will also generate a video library of the various types of events that AHC patients can have and this library will be used to train caretakers to insure consistency and reliability in the identification of different types of spells (work on that library has already started). The initial phase of the study (4 months) will be to insure agreement on the classification system and to demonstrate inter-rater reliability of classifying videos of different types of events. This phase will also include initiation of the IAHCRC cloud platform in the IEMEST center (See diagram below showing the architecture of the IAHCRC-Cloud service and the diagram of the study time line in the "Work Schedule" section below).

Architecture of the IACRC-Cloud Platform



This Platform will not only be used for this study with the option of patients to enter spell frequency data directly through mobile apps (would be verified by provider before being finalized into the database), but also would be used in future prospective studies as well. In the second phase, we will enroll patients from all willing and able IAHCRC centers, and will enter patient data into the IAHCRC cloud platform (18 months, see table below). Finally, in the third phase (2 months) we will analyze the data in the coordinating center with help of the study statistician (at Duke).

Table of Procedures

Variable	Baseline	Follow up visits #	One year follow up
Demographics	x		x
IAHCRC data base form*	x		x
Flunarizine index+	x		x
Paroxysmal disability index*	x	x	x
Non-Paroxysmal disability index*	x	x	x
Paroxysmal event diaries	x	x	x
Medications	x	x	x
VNS parameters (if applicable)	x	x	x
Physical Exam	x	x	x

* Panagiotakaki et al 2010. + Mikati et al 2000.
# Performed according to clinical need as decided on by the treating physician.

Inclusion criteria

Patient who fit the Aicardi AHC clinical criteria, of any age, who are willing to participate and to come for follow up in one year. The Aicardi Criteria are (Heinzen et al 2015) six. (1) Paroxysmal hemiplegia episodes. (2) Bilateral hemiplegia or quadriplegia episodes. (3) Other paroxysmal manifestations, such as abnormal eye movements, nystagmus, strabismus, ataxia, dystonia, choreoathetosis, tonic spells, or autonomic disturbances. (4) Evidence of permanent neurological dysfunction, which can manifest as cognitive impairment, developmental delay, and/or persistent motor deficits such as spastic diplegia/quadriplegia, hypotonia, ataxia, choreoathetosis, or dystonia. (5) Sleep relieves symptoms, although attacks may resume soon after awakening. (6) First signs of dysfunction occur prior to the age of 18 months. Patients having some but not all the above criteria will not be included.

We plan to enroll 80 patients. The IAHCRC Consortium has demonstrated that it can enroll as many as over 150 patients in similar studies. Therefore, we anticipate the ability to recruit the proposed 80 patients. Based on our previous experience with AHC patient investigations and on our power calculations, 80 patients will provide enough statistical power to achieve our objectives. In a previous study, we investigated multiple variables and could determine that age of onset of the disorder and age of onset of the hemiplegia spells correlated with later developmental outcome through the study of 44 AHC patients using a single variable linear regression model (Mikati et al 2000). However, we completed that study well before the identification of ATP1A3 mutations as the main cause of AHC and well before the recognition that the type of gene mutation affects prognosis. Therefore, with the target number of 80 patients we expect that we will be able investigate additional predictors, to achieve higher statistical power, and, to use multivariate statistical analyses.

Statistical analyses in this study to achieve each of the above four goals will consist of the following:

1. Face validity and inter-rater reliability of spell identification. This will require the following steps:

   a) Agreement among experts on the definitions and guidelines provided to professionals and families to correctly identify the various types of spells. We have, completed most of this process during the London ATP1A3 in Disease meeting.

   b) Formation of the video library of events (work has started).

   c) Testing inter-rater reliability of two experts reviewing the same videos (10 videos).

   d) Testing the inter-rater reliability of a sample of caretakers (20) as compared to each other and to expert classification.

   e) The use of Cohen's Kappa to demonstrate high inter-observer agreement (>0.8, Landis et al 1977). In case there is not such high agreement, then we will revise the procedures and then we will repeat the above till we achieve a high level of agreement. Accomplishing this will demonstrate the validity of having the caretakers identify the different types of spells (e.g. dystonia vs epileptic seizure) as compared to the "golden standard" of the experts' opinion as well as inter-rater reliability between experts themselves and between different caretakers viewing the same videos.

2. Predictors of outcome analysis: The independent variables will be relevant variables collected at the time of the first encounter. These will include type of mutation, age of onset (collected as part of the IAHCRC database form), (Pnagiotakaki et al 2015), duration of flunarizine therapy as measured by the flunarizine index (Mikati et al 2000), presence of epilepsy, occurrence of status epilepticus, baseline paroxysmal disability index and baseline non-paroxysmal (developmental) disability index (Panagiotakaki et al 2010). The outcome measures will be three variables obtained at the one-year follow up. These will be the final paroxysmal disability index, the final non-paroxysmal disability index and whether, or not, there was occurrence of a serious or potentially life-threatening event (status epilepticus, apnea requiring intervention, or death). Again, all these variables will be collected through the IAHCRC database form. We chose these variables as measures of disease severity. We will first use the procedure of Single Variable Linear regression followed by Multivariable Linear Regression to investigate potential associations between the independent variables and outcome measures.

3. Prospective efficacy data analysis: The objective here is to answer the following question: what is the apparent efficacy of new therapies that physicians following AHC patients are currently trying on an ad-hoc basis.
   Criteria for inclusion in this analysis are multiple.
   a) Patients whose treating physicians start on a novel therapy after the initial baseline encounter.
   b) Caretakers have recorded at least one month of spell diary data preceding the initiation of such therapy and continue to complete the diaries and come for follow-ups as required by their physicians based on clinical need.
   c) Treating physician keeps background therapies the same for at least one month after initiation.

We will collate and then analyze data regarding response of spells (AHC spells and if applicable epileptic seizures), from patients who were treated with the same agent. We will compare spell frequency during the month preceding the initiation of such therapy with the frequency of the same type of spell during the last month of follow up. If the treating physician had discontinued the medication during follow up then we will use the spell frequency that occurred during the month that preceded the taper. Similarly, if the treating physician had changed a background medication then we will use the spell frequency during the month preceding any such change. We will use a before and after analysis using the Paired t- test or the Wicoxon Rank Sum test as appropriate.

4. Baseline and one year follow up comparisons: We will compare baseline and one year follow up data regarding the paroxysmal and non-paroxysmal disability indices using the Paired t-test or the Wicoxon Rank Sum test as appropriate to investigate for any evidence for progression or improvement during the one-year prospective follow up period.

Expected results

We expect that the above study will provide the following results:

1. Establish a database platform that we use in this study and that others, and we, can use in future investigations. Also, establish a validated and reliable procedure to document spells that occur in AHC in a prospective study. This will be key for the expected future natural history and therapeutic studies.
2. Determine if flunarizine therapy affects long-term developmental outcome (positively or negatively). This will be key in helping guide clinical decisions about initiating this therapy in many patients with AHC in whom spell frequency may not be the only consideration in making decisions about that therapy.
3. Provide preliminary data regarding the apparent efficacy of various therapies that are being tried on an ad-hoc basis by different clinicians (e.g. Ketogenic Diet, Cannabidiol, ATP, VNS, etc.). This could guide the planning of future clinical trials if our study uncovers promising data regarding one or more of these agents.
4. Collect preliminary baseline and prospective follow up data regarding natural history during a one-year follow up period using the above, standardized, methodologies. This then could be the harbinger for future longer-term studies using the same methodologies of our proposed study but for longer periods with even larger numbers of patients.

Perspectives

AHC is a rare usually severe disorder that starts in infancy and persists into adulthood. In the majority of cases, the cause is one of over more than 34 currently reported ATP1A3 mutations. Patients suffer from repeated episodes of hemiplegia and dystonia that often occur several times per day. About half have epilepsy, and in about half of those, the epilepsy is drug resistant. AHC patients also have varying degrees of developmental disabilities ranging from mild to profound. About one-in-50 cases shows regression usually in association with an acute illness or status

epilepticus, and such patients usually have the E815K mutation. Flunarizine (a non-specific calcium channel blocker with neuroprotective properties in animal models of hypoxia) reduces the severity and duration of the hemiplegic spells, but this effect is modest. Some of the patients reported in the literature to have regressed had recently stopped flunarizine. The European Network for Research on Alternating Hemiplegia (ENRAH) and more recently the International Alternating Hemiplegia of Childhood Research Consortium (IAHCRC) have, respectively, reported on the clinical features of 157 patients, in 2010 and on 155 patients in 2015 (Panagiotakaki et al 2010, 2015). Most of the centers that were part of ENRAH are now part of the IAHCRC with additional ones joining. The Panagiotakaki et al 2010 study provided cross sectional data on 157 patients and longitudinal data on 37, and concluded that even though patients show fluctuations in their disability and in their paroxysmal events, there is no evidence for progression. Yet subsequent to that, reports of patients who regressed, as per the above, appeared and not all of these patients had the E815K mutation (Sasaki et al 2014, Panagiotakaki et al 2015). Numerous studies reported, largely in an open label retrospective manner, improvement with flunarizine of the AHC spells, but it is not clear if such therapy affects development. Specifically, Mikati et al (2000) did not find a correlation between the duration of the flunarizine therapy and development. However, since physicians are more likely to start more severely affected patients on this medication, the latter analysis left the possibility open that flunarizine could still have affected long-term outcome. In addition, Mikati et al performed this study before the current knowledge that the type of gene mutation affects the severity of the disease, a discovery that occurred only five years ago. Thus, further studies to investigate the predictors of long-term prognosis taking into consideration the type of gene mutation become necessary. Sweney et al (2009) reported, again in a retrospective manner, the perceived response to different medications used to treat AHC spells. They observed that about 55% reported “positive” response to flunarizine and about 35% to benzodiazepines. Currently, various clinicians taking care of patients with AHC are trying several medications, off label, in individual ad-hoc trials. There is lack of systematic collection of data regarding such individual trials on AHC spells or on seizures. All these factors support the performance of the proposed study, which we geared to leverage the collaboration history of the IAHCRC members and our partnership with family organizations to address the current needs for research on this disease.

Duration

2 years

Work Plan

Timeline

Work package	M 2	M 4	M 6	M 8	M 10	M 12	M 14	M 16	M 18	M 20	M 22	M 24
WP 0	T0.1 – Project Coordination and Management; T0.2 Dissemination											
WP 1	T1.1 – Validation inter-rater reliability and Training		T1.2 – Data Collection									T1.3 – Data Analysis
WP 2	T2.1 – Development		T2.2 – Data Management									

WP1 Observational Study

WP2 Platform Development

WP0 Project Coordination and Management

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