The Patient-Driven Registry for Alternating Hemiplegia of Childhood

evolution, challenges and outcomes

Rosaria Vavassori
A.I.S.EA Past President, ENRAH Past Registry Manager, IAHCRC Data Manager

Tsveta Schyns
ENRAH & ATP1A3 in disease Committee
Summary

- **Background**
  - Alternating Hemiplegia of Childhood AHC
  - Research and Care for AHC

- **The European and International Registry for AHC**
  - Evolution
  - Outcomes and Challenges
  - The IAHCRC-CLOUD Platform
  - Future Developments

- **Conclusions**
Alternating Hemiplegia of Childhood AHC

- Described for the first time by Verret and Steele, 1971

- Until 2012 only clinical criteria for the diagnosis
  (Krageloh e Aicardi 1980, Aicardi 1987, Neville e Ninan, 2007)
  - Onset before 18 months of age
  - Repeated bouts of hemiplegia of either side, lasting few minutes to several days
  - Episodes of bilateral hemiplegia or quadriplegia
  - Other paroxysmal manifestations during hemiplegia or in isolation: abnormal ocular movements, dystonic attacks autonomic disturbances
  - Disappearance of all symptoms with sleep
  - Evidence of developmental delay and neurological abnormalities

- Until 2012, many delayed or incorrect diagnoses
  - Difficult description and characterization of the clinical manifestations, both paroxysmal and non paroxysmal
  - Variability of clinical presentation (30% cases have also epilepsy, ....)
  - Diagnosis “per exclusionem”, no markers
Alternating Hemiplegia of Childhood AHC

- **Epidemiology**
  - Estimated prevalence 1 in a 100,000 (*Hoei-Hansen et al, Eur J Paed Neurology, 2013*)
  - Case reports, mostly sporadic

- **Pathophysiology: no meaningful results from any kind of investigations**
  - neuropathological
  - Neuroimaging: CT, MRI, PET, SPECT (contradictory findings: hypoperfusion and hyperperfusion), angiography
  - Neurophysiology: evoked potentials, blink reflex (*Vollono et al, European Journal of Neurology, 2014*), EEG,
  - Metabolic: skin and muscle biopsy (contradictory findings: small vessel abnormalities in 4 European patients, absence of small vessel abnormalities in 6 Japanese patients)
  - genetic: karyotype, candidate genes (CACNA1A, EAAT1, GLUT1, ATP1A2), exome-sequencing √
Alternating Hemiplegia of Childhood AHC

Gene Identification

- **De novo mutations in ATP1A3** cause alternating hemiplegia of childhood. Heinzen et al. Nature Genetics 44(9):1030-4, July 2012


Alternating Hemiplegia of Childhood AHC

ATP1A3 Gene

- Coding for the α3 sub unit of the sodium pump Na+,K+-ATPase discovered by Jens Skou in 1956

- Other groups of mutations in ATP1A3 cause also Rapid-Onset Dystonia Parkinsonism RDP and the CAPOS Syndrome (Cerebellar ataxia, areflexia, pes cavus, optic atrophy and sensorineural deafness)
  - “AHC and RDP are not distinct clinical entities but are different manifestations along a clinical spectrum” Ozelius L. The Lancet Neurology 2012
  - Phenotypic overlap of alternating hemiplegia of childhood and CAPOS syndrome Rosewich H. Neurology 2014

- Excellent research on ATP1A3 during the past years: structure, functional and in vivo studies, animal models
Alternating Hemiplegia of Childhood AHC

**Prognosis**

- Variable outcomes, generally medium to severe: Persistent neurological symptoms, including poor motor and organizational skills, tremor, ataxia, involuntary abnormal movements and intellectual disability, some paroxysmal manifestations tend to decrease with age (abnormal ocular movements), but some other can appear suddenly (seizures, dystonic attacks, ...)
- Sudden deaths with no certain causes (heart failure during a prolonged and severe episode; convulsions, ...)
- No longitudinal studies

**Pharmacological Treatment**

- Prophylaxis of the hemiplegic attacks: **flunarizine**, acetazolamide, triptophane, topiramate ....
- Antiepileptic drugs
- Acute treatment: benzodiazepine, cloral hydrate, ...
- All drugs are off-label, no therapeutic trials have ever been carried out to determine their real efficacy, and the long-term side-effects
- Other drugs for the behavior disorders, for anxiety and depression .....
Alternating Hemiplegia of Childhood AHC

Management of the disease

- Requires a multi-disciplinary integrated approach:
  - prevention and management of paroxysmal symptoms
  - motor, intellective and behavioral rehabilitation
  - psychological support
  - socio-educational assistance for autonomy, school and work integration, social inclusion ...

- No guidelines and diagnostic, therapeutic and assistance protocols validated at the international level
  - Neville BG e Ninan M, The treatment and management of alternating hemiplegia of childhood. (Dev Med Child Neurol. 2007)
  - T. Granata, F. Vigevano, White Book for Understanding and Managing AHC (A.I.S.EA Onlus and Scientific Institute E. Medea, 2007) (in Italian and in English)
  - National Centre for Rare Diseases and A.I.S.EA Onlus. National Guidelines for the Assistance to the Persons with Alternating Hemiplegia of Childhood and their families (A.I.S.EA Onlus, National Health Institute, Ministry of Health, 2009) (in Italian)
Alternating Hemiplegia of Childhood AHC

Management of the disease

- EurordisCare 3 Survey, on access to health and social services, included AHC among 15 other rare diseases:
  - lack of or difficult access to centres of expertise for AHC
  - Lack of adequate support from the local social services, to integrate and coordinate the different health and social interventions and to inform and counsel the families about how to find and have access to them
  - Lack of information and awareness of the families about their rights to an adequate health and social assistance (empowerment), isolation

- The main source of information for the families is still represented by the patient associations and by Internet
Alternating Hemiplegia of Childhood AHC

Management of the disease

EurordisCare 3 Survey, on access to health and social services, included AHC among 15 other rare diseases

Need for social assistance

Reduction in professional activity to take care of a relative

Overall: 29%

Overall: 30%

Reduction in professional activity to take care of a relative is more frequent with paediatric diseases
Alternating Hemiplegia of Childhood AHC

The research – critical issues

- Very rare and sporadic disease: “due to the low frequency of the disorder and the sporadic cases genetic research will be problematic” (Cephalalgia. 2000)
- Lack of clinically well characterized patients
- Low awareness and acknowledgment even by the scientific and medical professionals and by the advocates for rare diseases in general – neglected disease
- Funded and supported only by the patient associations
Alternating Hemiplegia of Childhood AHC

The research and the care – a Registry is needed!!

- **provide evidences** of the existence of the disease and of its therapeutic, healthcare and social assistance needs

- **systematically collect** the necessary amount of validated data and share them according to common data elements and standard methods for large scale longitudinal studies (natural history, clinical trials, quality of life, ...)

- **establish a coordinated research and healthcare network** including clinical and laboratory centers and integrating the national and international level

- **involve the patients in the research and healthcare**, in an ethic, informed and active way
Alternating Hemiplegia of Childhood AHC

The research and the care – a Registry is needed!!

- establish and manage information flows to quickly transfer the results from the research and the newly acquired knowledge of the disease to the clinical and assistance practice and to the patients and families

- create an international community including all the stakeholders, to raise the awareness of the disease, to support all the patients worldwide, to obtain more funds for the research and an appropriate health and social assistance
  - basic science and clinical researchers
  - physicians and health and social professionals
  - patients and associations
  - public institutions,
  - pharmaceutical companies

- have a positive impact on the quality of life of the patients and their families!!
Alternating Hemiplegia of Childhood AHC

The research and the care - a Registry is needed !!

- In 1998 a Clinical Registry and Biobank was established in the USA at the Utah University, SLC (Dr. Kathryn Swoboda, AHCF)

- In 2004, in Italy the service «I.B.AHC – Biobank and Clinical registry for Alternating Hemiplegia» [www.ibahc.org](http://www.ibahc.org) was activated by A.I.S.EA and its Scientific Committee in collaboration with the Scientific Institute E. Medea, coordinated by the A.I.S.EA Past President and managed by the I.B.AHC Consortium
Alternating Hemiplegia of Childhood AHC

The research and the care - a Registry is needed !!

- In 2003 ENRAH was created, a European network gathering basic research and clinical centers and patients associations for AHC
- EU funded project «ENRAH for SMEs» 2005-2007, coordinated by ENRAH: 9 EU countries, 14 participants (two patient associations, A.I.S.EA and AFHA)
- A European Clinical Registry established with 157 patients included, closed in 2011
- An extensive set of general and follow-up data collected for each included patient
The “ENRAH for SMEs” Project

- (2006) Consensus on a set of common data elements (ENRAH Questionnaire) to be implemented in the European Registry and in the national databases
- (2007) established a network of national reference centers collecting the data in their own databases, many of them with a linked biorepository for the DNA samples
- (2013) network restored and expanded by the IAHCRC Consortium
Alternating Hemiplegia of Childhood AHC

The research and the care - a Registry is needed!!

- EU funded project **nEUroped** 2008-2011 (initiated by ENRAH and coordinated by HCL-FR): 9 EU nations, 13 participants (a patient association, A.I.S.EA)
- A European Clinical Registry established for three neuropediatric rare diseases: AHC, narcolepsy, RSTES with 131 patients, still open
- consolidates the network of the national reference centers
- supports the creation of an international network of AHC patient associations linked to the network of research labs and reference clinical centers: **International Alliance AHCIA** [www.ahcia.org](http://www.ahcia.org)
Alternating Hemiplegia of Childhood AHC

The European Registry for AHC - Outcomes

- **raising awareness and dissemination of information**

  Two scientific publications, about the first longitudinal studies on a large cohort of AHC patients:

  

- **standardization**

  - A validated set of Common Data Elements
  
  - Diagnostic Criteria
  
  - Guidelines for the Management of the Disease
Alternating Hemiplegia of Childhood AHC

The European Registry for AHC - Outcomes

- **networking**
  - More genetic laboratories and clinical centers involved in close collaboration with the patient associations, at the international level
  - the European Consortium for the Genetic Research on AHC created in 2011, to apply the new technique of the Exome Sequencing on the European AHC patients

- **Findings !!!**
  - In early 2012, the European Genetic Consortium joins the US Centers to sequence the exome of more patients: the DNA samples and the clinical data of 105 European and American patients are included in the study
  - the study leads to the identification of a group of mutations in the ATP1A3 gene as primary cause of AHC
### Alternating Hemiplegia of Childhood AHC

#### The ATP1A3 rare diseases

- Until now, more than 50 ATP1A3 mutations reported in the AHC patients
- 10% of the AHC patients is ATP1A3 negative
- Many ATP1A3 positive patients with undefined or mixed AHC-RDP-CAPOS phenotypes
- It is necessary to collect the data at the international level about all the possible ATP1A3 phenotypes and genotypes to determine their correlations (and to provide the correct diagnosis and care to all the patients)
- It is necessary to define common and standard methods to develop the models of the AHC-mutant sodium-potassium pump and to test new compounds as possible candidates for the pharmacological treatment

#### Table 1

<table>
<thead>
<tr>
<th>ATP1A3 modification</th>
<th>Nucleotide change</th>
<th>Number of AHC probands with the mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>S137Y</td>
<td>c.410C&gt;A</td>
<td>2</td>
</tr>
<tr>
<td>S137F</td>
<td>c.410C&gt;T</td>
<td>1</td>
</tr>
<tr>
<td>Q140L</td>
<td>c.419A&gt;T</td>
<td>1</td>
</tr>
<tr>
<td>D220N</td>
<td>c.658G&gt;A</td>
<td>1</td>
</tr>
<tr>
<td>I274N</td>
<td>c.821T&gt;A</td>
<td>1</td>
</tr>
<tr>
<td>C333F</td>
<td>c.998G&gt;T</td>
<td>2</td>
</tr>
<tr>
<td>G755S</td>
<td>c.2263G&gt;A</td>
<td>1</td>
</tr>
<tr>
<td>N773S</td>
<td>c.2318A&gt;G</td>
<td>1</td>
</tr>
<tr>
<td>D801N</td>
<td>c.2401G&gt;A</td>
<td>36</td>
</tr>
<tr>
<td>M806R</td>
<td>c.2417T&gt;G</td>
<td>1</td>
</tr>
<tr>
<td>I810S</td>
<td>c.2429T&gt;G</td>
<td>1</td>
</tr>
<tr>
<td>S811P</td>
<td>c.2431T&gt;C</td>
<td>4</td>
</tr>
<tr>
<td>E815K</td>
<td>c.2443G&gt;A</td>
<td>19</td>
</tr>
<tr>
<td>Splice site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c.2542+1&gt;G&gt;A</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Y919del</td>
<td>c.2756_2757delGTC</td>
<td>1</td>
</tr>
<tr>
<td>G947R</td>
<td>c.2839G&gt;A</td>
<td>5</td>
</tr>
<tr>
<td>G947R</td>
<td>c.2839G&gt;C</td>
<td>2</td>
</tr>
<tr>
<td>A955D</td>
<td>c.2864C&gt;A</td>
<td>1</td>
</tr>
<tr>
<td>D902Y</td>
<td>c.2974G&gt;T</td>
<td>1</td>
</tr>
</tbody>
</table>

*ATP1A3 mutations and encoded protein coordinates are defined on the basis of UniProt ID P13637 (ref. 24) and Consensus CDS ID CCDS12594.1 (ref. 25).*
Alternating Hemiplegia of Childhood AHC

The research and the care
more networking and collaboration

- After the finding of the ATP1A3 gene as primary cause of AHC in 2012, the “ATP1A3 in disease” international community has developed, with some functional sub-nets collaborating for common projects and studies.

- Need of a common repository for all the data and information about these projects: a federated, open Registry.
The International Consortium IAHCR

www.iahcrc.net

Objectives

After the first study that led to the identification of the genetic cause of AHC in 2012, the involved centers launched further collaborative studies at the international level.

The IAHCR International Consortium for the Research on AHC and other ATP1A3 related diseases was created officially on November 2014 with the approval of the IAHRC Charter by 15 founding centers.

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 nEUroped (2008-2011).
The International Consortium IAHCRC

Objectives

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

Its specific objectives are:

• Contribute actively to the collaborative study of the pathogenetic mechanisms of the ATP1A3 diseases and to the development of an effective treatment for all of them;

• 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;

• Define standard formats, protocols and procedures for the production, the assessment, the collection and the sharing of the information and data for the collaborative studies carried out by the members and for the dissemination of the information inside and outside the Consortium;

• Collaborate with the patient associations and any other non-scientific organization in the pursuing of the first three objectives.
IAHCRC Organization

Disease Experiential Knowledge

Logistics

Funds

IAHCRC Organization

Scientific Coordinator
Assembly

Data Manager

Standardization
Workgroups

Questionnaire(s)
and Methods; SCPs....

Management and Standardization

Clinical Centres and Research Labs

Operation

IAHCRC Information System

IAHCRC Public Website

Node Database

Linked Biobank

Node Database

Linked Biobank

Node Database

Linked Biobank

Node Database

Linked Biobank

Node Database

Linked Biobank

Project

Study Database

Study Database

Study Database

Study Database

TREAT-AHC

Study Database

GPC-AHC

Study Database

ECG-AHC

(1) Ordinary activities and equipment; meetings, teleconferences, IT tools

(2, National level) Establishment and sustainability of the Node Databases, data collection

(3) Studies and research projects

(4, National level) Patient inclusion in the Node Databases, information about the studies and communication of the results, translation of the research results and guidelines into medical practice and social and health assistance

The patients as active partners of the IAHCRC Consortium – R. Vavassori, A. Arzimanoglou 07 January 2015
The International Consortium IAHCRC

Standardization

- **Core Data Elements** for the Genotyping and Phenotyping, based on the ENRAH Questionnaire
- **Genetics Protocol** for the ATP1A3 testing and Standard Operating Procedures for the collection of the samples
- **Consensus on a new set of Common Data Elements** for the Paroxysmal Events and Developmental skills
- **Video Library** for the collegial classification of the paroxysmal episodes of AHC and other clinical manifestations (movement disorders, ...)
The International Consortium IAHCRC

Studies and Projects

- **ECG-AHC** (2014 – 2015) – Study of Cardiac Involvement in AHC, 55 patients - published
- **GEN2-AHC** – Search for the secondary gene(s) in AHC , ~30 patients - in progress
- **ECG2-ATP1A3** (2016 – 2017) – Second Study of Cardiac Involvement in ATP1A3 Syndromes, ~120 patients – in progress
- further studies – planned for 2017 - 2018
The International Consortium IAHCRC

IAHCRC-CLOUD Platform

- An **on-line platform** to collect and host the data from the IAHCRC Centers and from external sources and share them for the IAHCRC Studies and Projects
- A **network of interconnected Databases** serving the National Disease Registries and the International Study Registries
- Data management and sharing according to the collaboration and confidentiality rules set forth in the IAHCRC Charter
- All Databases implementing the **IAHCRC Core Data Elements** and additional specific Data Elements validated by the IAHCRC Standardization Workgroups
- **Accessible** by Researchers, Clinicians and Patients
- **Open and flexible architecture** to serve any number of new studies and projects (clinical trials) and growing incrementally as a disease knowledge base
- Evolving into the **International Registry for the ATP1A3 diseases**
The International Registry for the ATP1A3 Diseases

Challenges

- **Sustainability** – Lack of a continuous source of funding; difficulty to involve professional resources

- **Education and Active involvement of the Patients** – Difficulties in keeping their motivation on a long term project like a Registry; difficulty for them to understand and appreciate the connection between the achievement of the research (or the improvement of the health care) and the use of the Registry; cultural and language barriers to the participation to international, long lasting projects; severe impact of the disease on the everyday life; burnout and no turn over of the patient representatives

- **Consensus and Collaboration** – Difficulties to compose the different views of all the stakeholders, private and public, and to mediate between their different interests and expectations

- **Ethics** – Difficult in obtaining the Informed Consent from the Patients; application to all the Ethics Committees of all the Centers participating to an International Study; Application to the Ethics Committee and Consent Form for each Single Study (Broad Consent; Dynamic Consent; ...); anonymization vs duplication vs information
The International Registry for the ATP1A3 Diseases

Conclusions

• A Registry is much more than a Database!!
• A Registry should be open and its data linkable and reusable for as many studies as possible
• A Registry should include different types of data and grow incrementally to become a full knowledge base about all the aspects of a disease
• The patients should be involved in the design, management and governance of a Registry and their experiential knowledge of the disease included
• A Registry supports the development of awareness and involvement of public institutions and private funders for very rare and neglected diseases like AHC and all the ATP1A3 related diseases
The International Registry for the ATP1A3 Diseases

Contacts

• Rosaria Vavassori, IAHCRC Data Manager, vavassori@iahcrc.net
  www.iahcrc.net

• Tsveta Schyns, ENRAH and ATP1A3 in Disease Committee, ts@enrah.net
  www.enrah.net

The international “ATP1A3 in disease” community
at the Third Symposium in Lunerden, NL, 29 – 31 August 2014