

Alternating Hemiplegia of Childhood

The journey to the gene discovery and effective treatments

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Alternating Hemiplegia of Childhood

First Encounter in 1998:

Described by Verret and Steele, 1971

Only Clinical Diagnostic Criteria

(Krageloh and Aicardi 1980, Aicardi 1987; Aicardi J, Bourgeois M, Goutieres F 1995)

- Onset before 18 months of age
- Repeated bouts of hemiplegia of either side, lasting a few minutes to several days;
- Episodes of bilateral hemiplegia or quadriplegia;
- Other paroxysmal disturbances during hemiplegia or in isolation:
 - abnormal ocular movements, dystonic attacks, autonomic disturbances
- Disappearance of all symptoms with sleep;
- Evidence of developmental delay and neurologic abnormalities.

Frequent misdiagnosis, delay from months to years :
variability in clinical presentation, the complex and evolving phenotype, diagnosis "*per exclusionem*"

Alternating Hemiplegia of Childhood 2.

- **Epidemiology**

Case reports , estimation «1 in a million»

Mostly sporadic

Few familial cases reported :

Autosomal Dominant mode of inheritance suggested by *Mikati et al 1992* ,
Kramer et al 2000

- **Clinical pathophysiology**

EEG, MRI

PET, SPECT : interictal decrease in cerebral metabolism (Sasaki et al 2009)

Contradictory findings

*Small vessel abnormalities in alternating hemiplegia of childhood:
pathophysiologic implications.* Auvin et al. *Neurology*. 2006 Feb 28

Absence of small-vessel abnormalities in alternating hemiplegia of childhood.
Sasaki et al *Brain Dev.* 2011 May

Alternating Hemiplegia of Childhood 3.

- Prognosis

Variable outcomes, generally **POOR**:

Persistent neurological symptoms, including poor motor and organizational skills, tremor, ataxia, involuntary abnormal movements and intellectual disability

Sudden deaths reports

Lack of longitudinal studies

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- **Treatments**

Many

ALL Off label

The most frequently prescribed drug is **flunarizine** :

- reduction in frequency and/or duration and severity of attacks
- International study 1987 (double-blind placebo-controlled withdrawal) with 12 patients failed to demonstrate the initial open-label-study effect of flunarizine in 1984
- Long term/ life long usage, safety not been established

Alternating Hemiplegia of Childhood.5

- Disease Management

- No professional guidelines
- Ranges from telephone consultations and occasional visits to frequent hospitalisation

EurordisCare 3 Survey , on access to health services, included AHC among 15 other rare diseases. The responses indicated:

- lack of (access to) centres of expertise for AHC – personal costs or distance to a centre were not seen as an obstacle

Families often find themselves in isolation due to the lack of an adequate professional and societal support

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What is the first thing most parents do after they have received the diagnosis of Alternating Hemiplegia of Childhood?

❑ **Google** (Sigurður Hólmar Jóhannesson, Siggi)

an AHC Yahoo group set up by parents in France in the late 90's is still a very popular and useful place for parents to share their experience for day-to day management

❑ **PubMed**

✓ **Connect to other parents and identify potential research centres / researchers**

✓ Identify the bottlenecks for research

“due to the low frequency of the disorder and the sporadic cases genetic research will be problematic”
(Cephalalgia. 2000 Oct;20(8):696-70)

➤ need of clinically well characterised patients

“the presented arguments supporting AHC to be a genetic disease are not very convincing”

(Reviewers comments rejecting a grant application
identification of the genetic cause of AHC)

➤ establish a research network including clinical and genetic centres

AHC patient database and bio-bank started in 1998 the US,
University of Utah School of Medicine, SLC



Started in 2003

Advance Research on Alternating Hemiplegia

✓ Generate

Identify areas for research development
design and submit grant applications

✓ Coordinate

Link clinical & research centres , AHC families' org

Facilitate research collaborations : workshops & networking

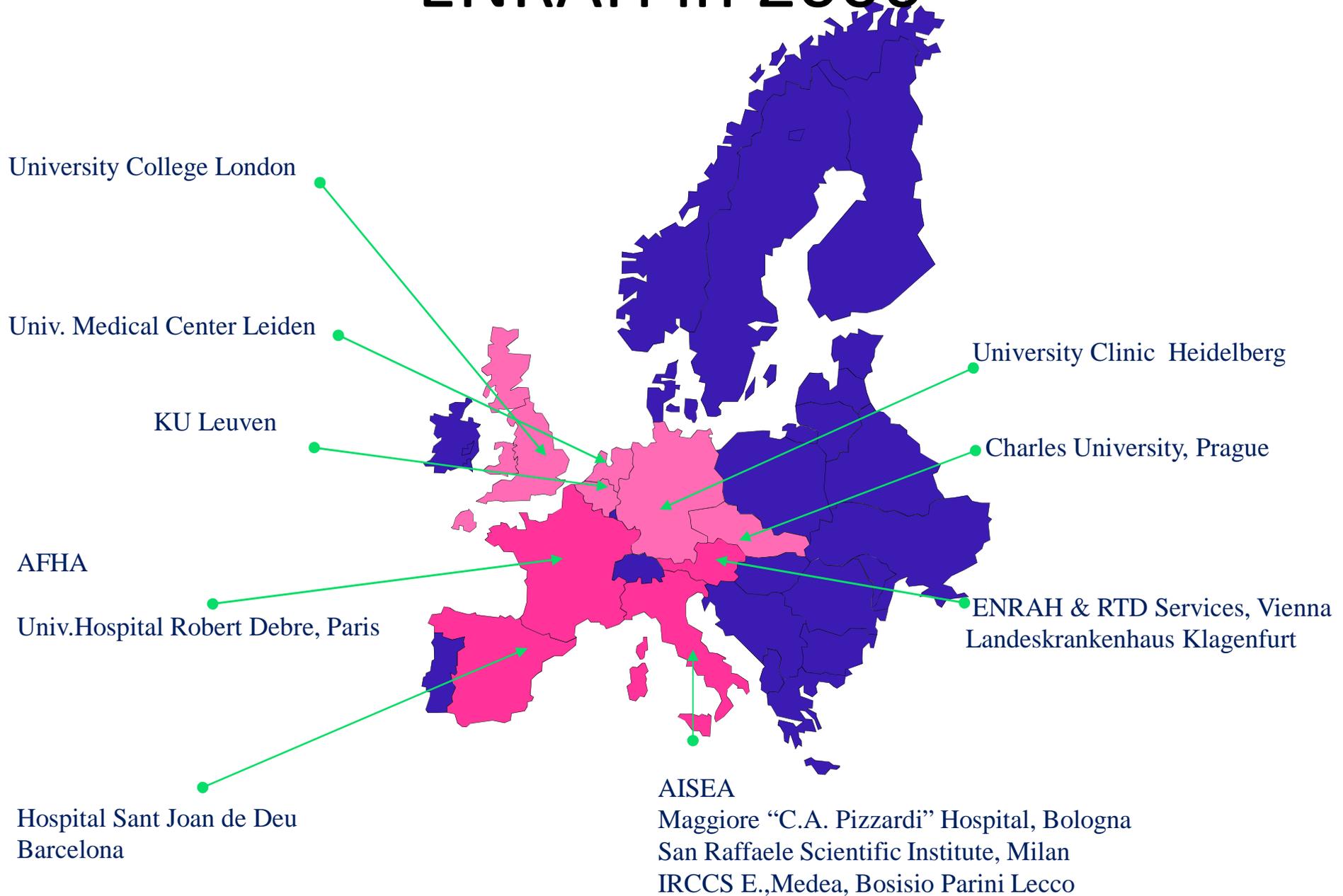
✓ Translate & Disseminate

Guidelines for diagnosis, research and treatment
validated information

ENRAH started with the FP6 grant application

- first attempt in 2003
- **ENRAH for SMEs** in 2004
 - funded by the European Commission Research Framework Program, FP6 from 2005-2007
 - total budget of 380.000, EUR (1/2 of the estimated budget)
 - 14 partners , including 2 families' organisations
 - 9 EU countries
 - **Establish a research Network & Clinical Database of AHC patients and involve SMEs**

ENRAH in 2006



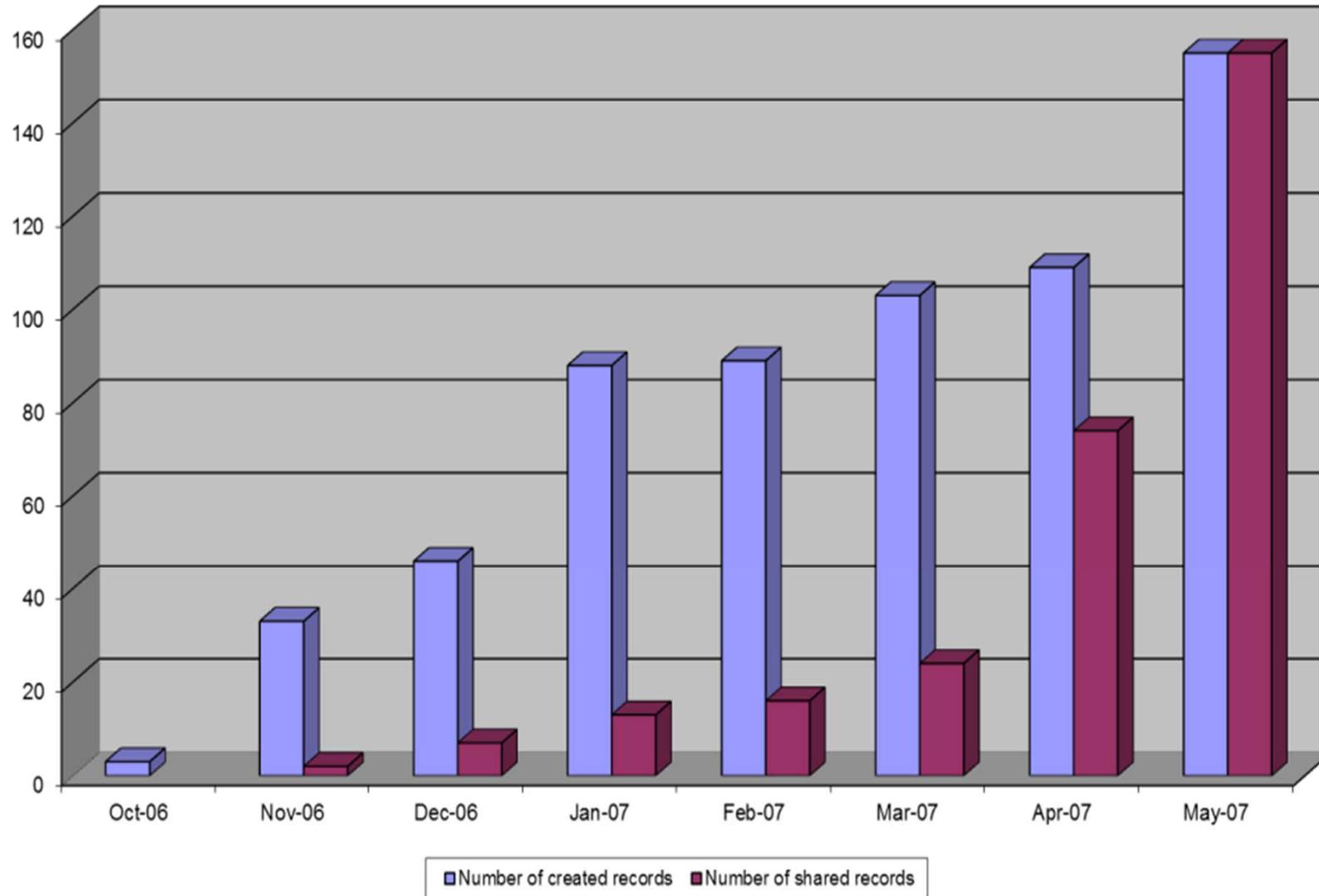


Clinical Registry of AHC patients

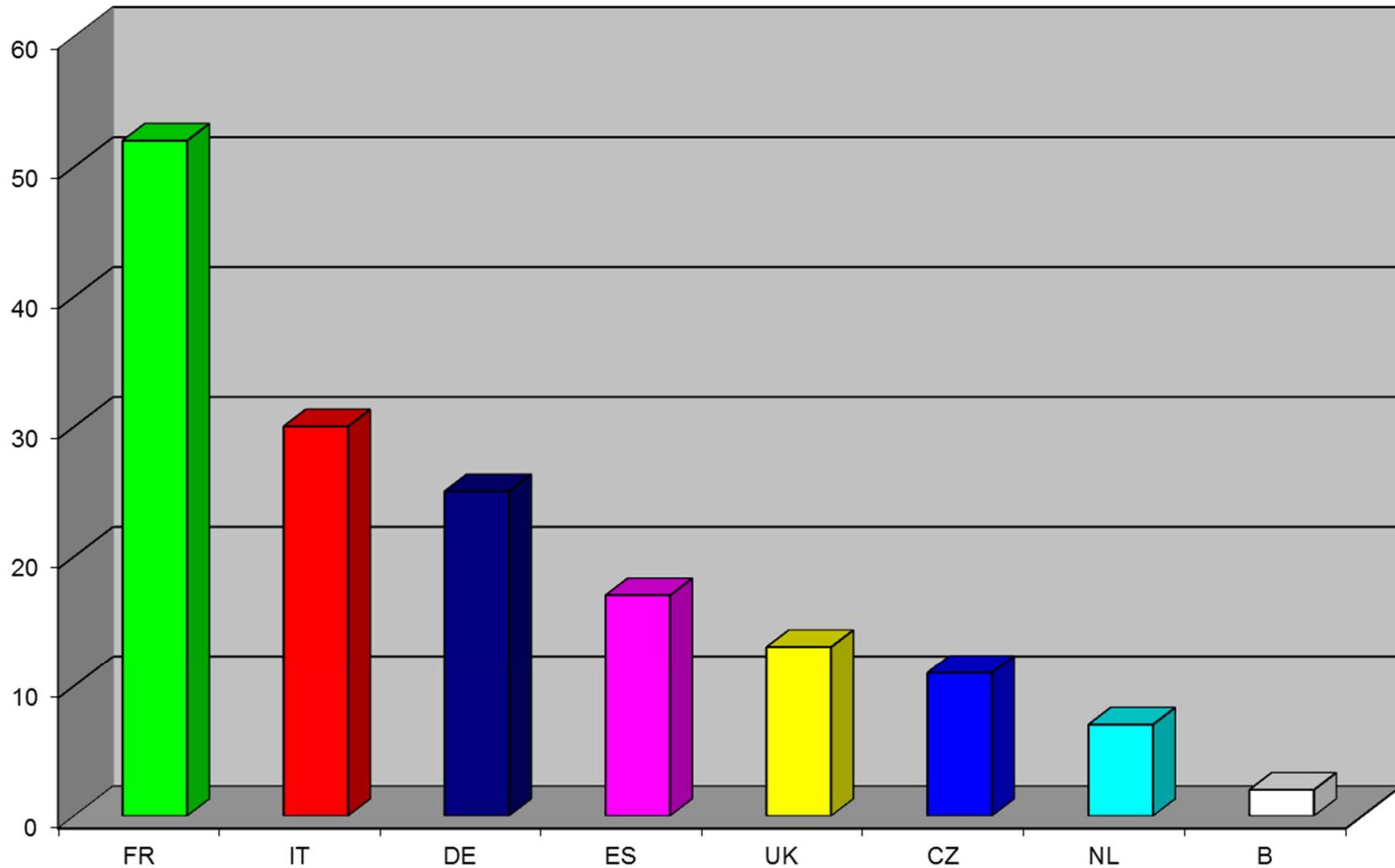
- **One centre** for data collection in each country – dedicated clinician and budget for data collection
- **Extensive clinical data** questionnaire incl retrospective data (not just counting the patients)
- **Informed Consent** (thanks to EuroWilson!)
- **On line European database** in English
 - required a substantial part of the funding
 - shared data files
 - collaborative studies

ENRAH for SMEs Registry

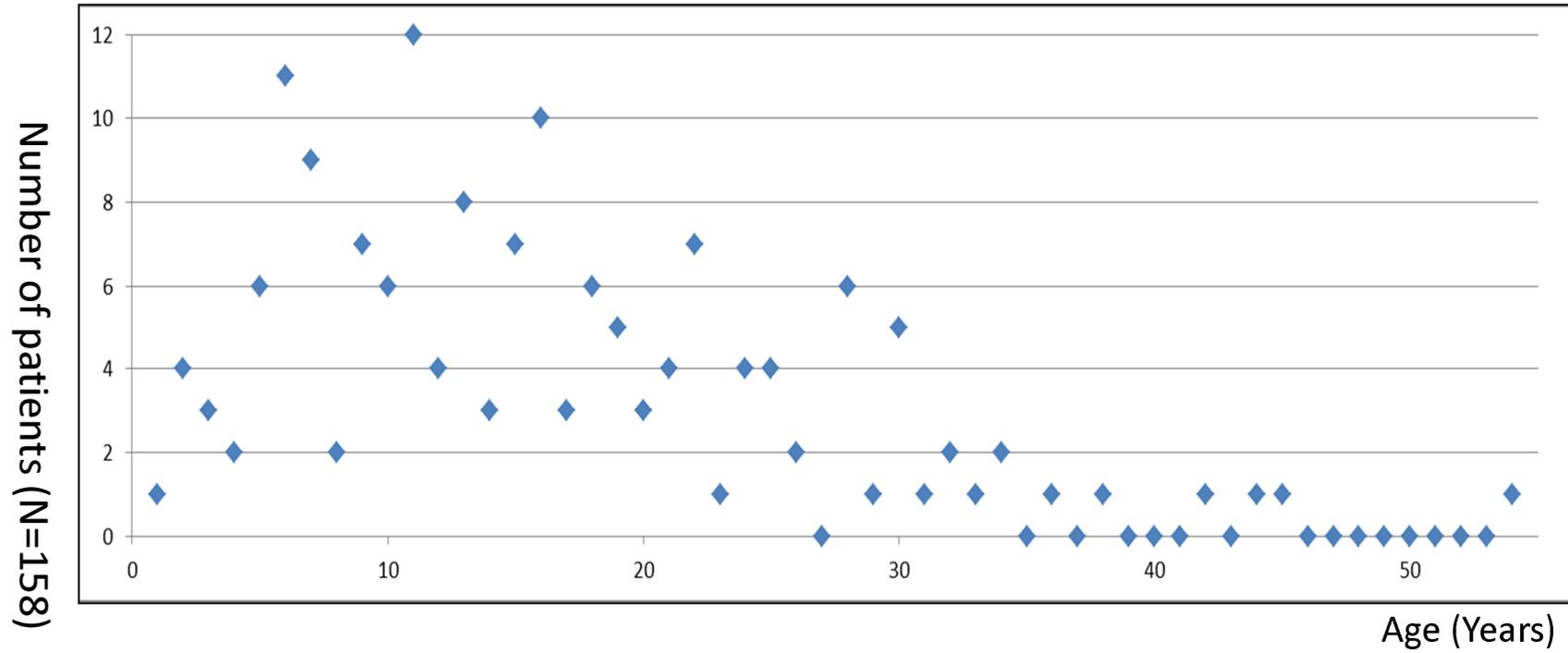
questionnaire finalised summer 2005
on line registry opened September 2006



Source of records (N=158) in the registry



ENRAH for SMEs Registry



ENRAH for SMEs Registry Studies

- *Evidence of a non-progressive course of alternating hemiplegia of childhood: study of a large cohort of children and adults.* Brain2010, 133 (12): 3598-3610.
- *Alternating hemiplegia of childhood: metabolic studies in the largest European series of patients.* Eur J Paediatr Neurol. 2012 Jan;16(1):10-4.

Sustaining the Network and the Registry

- **new and successful grant application nEUroped**
co-funded 60 % in 2008-2011 by the European Commission Health Program
total budget of 1.250.000, EUR
Included AHC, Narcolepsy and “Rare Surgically Treatable Epileptic Syndromes” in children
disease registries, guidelines and network of rare paediatric neurological syndromes with paroxysms , nEUroped
13 partners in 9 EU countries
- **Support new studies and link to the bio-banks at the national centres**

The breakthrough

“a family based exome sequencing approach”

A de novo paradigm for mental retardation. Vissers LE, de Ligt J, Gilissen C, Janssen I, Steehouwer M, de Vries P, van Lier B, Arts P, Wieskamp N, del Rosario M, van Bon BW, Hoischen A, de Vries BB, Brunner HG, Veltman JA. Nat Genet. 2010 Dec;42(12):1109-12.

- Several labs in Europe , the US and Japan have set up in 2011 to do exome-sequencing of AHC trios
- Whole genome sequencing of AHC patients in the US

Alternating Hemiplegia of Childhood

Gene Identification

- **De novo mutations in ATP1A3 cause alternating hemiplegia of childhood.**

Heinzen et al. Nature Genetics 44(9):1030-4, September 2012

- **Heterozygous de-novo mutations in ATP1A3 in patients with alternating hemiplegia of childhood: a whole-exome sequencing gene-identification study.**

Rosewich et al. The Lancet Neurology 11 (9): 764 - 773, September 2012

- **Identification of ATP1A3 mutations by exome sequencing as the cause of alternating hemiplegia of childhood in Japanese patients.**

Ishii A et al. PLoS One. 2013;8(2) February 2013

ATP1A3 Gene

- Coding for the $\alpha 3$ sub unit of the sodium pump Na^+, K^+ -ATPase ($\alpha\beta$ dimer) discovered by Jens Skou in 1956
- a member of a gene family (ATP1A1 , ATP1A2, ATP1A3 and ATP1A4)
- Mutations in *ATP1A3* also cause rapid-onset dystonia with parkinsonism (RDP):

“AHC and RDP are not distinct clinical entities but are different manifestations along a clinical spectrum” Ozelius L. The Lancet Neurology 11 (9): 741 -743.

Excellent research on *ATP1A3* during the past years- Structure, functional and in vivo studies and animal models

First Symposium " **ATP1A3 IN DISEASE:
From Gene Mutations to New Treatments**"
10-11 December 2012 in Brussels, Belgium

- Organised by ENRAH together with Duke University
- 66 participants from 15 Countries
- Clinical and Basic Researchers, Family Associations and Industry
- **A Roadmap of gene discovery to a treatment**
- Second symposium " *ATP1A3 in disease: genotype/phenotype correlations, modeling and identification of potential targets for treatment*"
Catholic University School of Medicine, Rome, Italy,
23- 24 September 2013

- Thanks to
- *The ENRAH for SME Consortium*
 - *The families /parents organizations of AHC in Europe and the US*
 - *The newly established Network on Na, K-ATPase in disease*

International Rare Diseases Research Consortium Conference Dublin, 16-17 April 2013

Alternating Hemiplegia of Childhood : The journey to the gene discovery and effective treatments

THANK YOU for your support!



AHC association of Iceland



AESHA

RTD Services

Bringing science and business together



 **A.I.S.EA** onlus

Associazione Italiana per la Sindrome di Emiplegia Alternante

