ALTERNATING HEMIPLEGIA OF CHILDHOOD

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AHC is an essentially neurologic disorder but medical geneticists are often required counselling because of the presence of intellectual disability and physical abnormalities in patients
Table 2  
Diagnostic criteria for alternating hemiplegia of childhood

1. Symptoms before age 18 months

2. Repeated attacks of hemiplegia that alternate in laterality

3. Episodes of quadriplegia as a separate attack or generalization of a hemiplegic attack

4. Relief from symptoms upon sleeping

5. Other paroxysmal symptoms including dystonic spells, oculomotor abnormalities, or autonomic symptoms either concurrent with attacks or independently

6. Evidence of developmental delay or neurologic findings such as choreoathetosis, dystonia, or ataxia
De novo mutations in \textit{ATP1A3} cause alternating hemiplegia of childhood

\textit{Heinzen et al., Nature Genetics, 2012}
De Novo mutations in ATP1A3 in Alternating Hemiplegia of Childhood (Heinzen et al., 2012)

ATP1A3 as a subunit of the neuronal Na⁺ / K⁺ pump

Role of ATP1A3 in neurons:
- Maintenance of Na⁺/K⁺ gradient
- Excitability of neurons
AHC and RDP are allelic disorders
The Italian Cohort

39 AHC patients - 37 families (2 twin sets)

30 patients with ATP1A3 mutations (77%)

9 patients **without** ATP1A3 mutation

3 additional patients with atypical phenotype and no ATP1A3 mutation
DISTRIBUTION OF ATP1A3 MUTATIONS

- E815K: 30%
- D801N: 33%
- G974R: 10%
- Other: 24%
THE RARE MUTATIONS....

E815K (9 patients) 33%
D801N (10 patients) 33%
G947R (3 patients) 10%

S811P (1 patient)
M806R (1 patient)
N773S (1 twin couple)
A955D (1 patient)
919delIV (1 patient)
C333F (1 patient)

(Ex 18-22)
GENOTYPE vs PHENOTYPE

E815K

- Early-onset of seizures
- Developmental delay
- Non ambulant at 6-7 years
- No posture
- No language or very few words
GENOTYPE vs PHENOTYPE

D801N

- Early onset seizures
- Hypotonia
- Poor language
- Still better posture than the previous group
GENOTYPE vs PHENOTYPE

G947R

- Walking at 2 years
- Good language skills
- Good interaction
- Write and read
M806R  •  Walked at 2 years,
  •  Mild developmental delay
  •  Reads and writes
  •  Increasing severity of hemiplegic attacks with age

C333F  •  Walked at 2 years,
  •  Moderate developmental delay
  •  Satisfactory language
  •  Hemiplegic attacks twice a week

A955D  •  Early onset seizures and neurovegetative symptoms
  •  Severe developmental delay
  •  No language, no posture
  •  Sleep disturbance
919delV
• Walked at 3-6 years,
• Mild developmental delay
• Severe myopia
• Frequent hemiplegic attacks

N773S
• Normal language development
• Extremely mild developmental delay
• No seizures
PATIENTS WITH NO MUTATION

All AHC still?
Mild AD-AHC I274N
Acknowledgements

Scientific Committee

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Patients and their families