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Original article

Alternating Hemiplegia of Childhood: Pharmacological treatment of 30 Italian patients

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Abstract

Background: Alternating Hemiplegia of Childhood (AHC) is a severe disorder. Several drugs have been administered as prophylaxis for paroxysmal attacks, however, no therapy is completely effective.

Methods: Our aim is to review the pharmacological data related to the prophylactic and acute treatment of a cohort of 30 patients (16 M, 14 F, age range 5–42 years) and to correlate them with the clinical and genetic data collected through the Italian Biobank and Clinical Registry for AHC.

Results: Flunarizine was the most commonly used long-term treatment in the cohort; it reduced duration and frequency of attacks in 50% of patients and decreased intensity in 32.1%. In younger patients, flunarizine seemed significantly more effective in reducing intensity. We found no correlation between the effectiveness of flunarizine and genotype, or between developmental outcome and duration of treatment. In particular, 3 of our patients affected by E815K mutation presented rapid neurological deterioration despite ongoing treatment. Among the other administered prophylactic therapies, few proved to be effective (benzodiazepines, niaprazine, acetazolamide, melatonin, olanzapine, ketogenic diet). No clear rationale exists regarding their use, but these therapies may work by reducing the triggering factors.

Conclusions: The presented data are retrospective, but they are aimed at filling a gap given the rarity of the disease and the lack of randomized and controlled studies. Besides their usefulness in clarifying the pathophysiology of the disease, prospective studies involving larger cohorts of *ATP1A3* mutated AHC patients are needed to provide a rationale for testing other molecules.

Keywords: Alternating Hemiplegia; *ATP1A3*; Flunarizine; Phenotype; Genotype; Treatment

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1. Introduction

Alternating Hemiplegia of Childhood (AHC) is a rare, predominantly sporadic disorder with an incidence of one affected individual in one million births (OMIM 104290, 614820), and it is characterized by the early onset (within 18 months of age) of a combination of paroxysmal attacks and permanent neurological features.

The etiology of the syndrome was unknown until 2012, when heterozygous de novo mutations in the *ATP1A3* gene that codes for the α3 isoform of the Na +/K+ ATPase were detected in more than 75% of AHC patients [1].

Since phenotype variability of AHC is extensive, drug therapy is often difficult and challenging. The main objectives of drug therapy are to prevent paroxysmal attacks by means of prophylactic therapy, and to stop paroxysms by inducing sleep which often blocks a crisis. Other paroxysmal manifestations requiring treatment include epilepsy (which may be associated in approximately 50% of patients) and migraine. Several combinations of movement disorders (such as chorea, myoclonus and dystonia) with various degrees of severity, and psychiatric comorbidities vary from patient to patient and represent other targets for treatment.

Several drugs have been used since AHC was first described, mainly to control the paroxysmal attacks that represent the most disturbing symptoms. Due to the rarity of this disease, prospective, randomized and controlled studies are lacking. Currently, only flunarizine, a calcium entry blocker, has been shown to reduce the severity and/or duration of AHC attacks [2,3].

The aim of this study was to review the pharmacological data regarding the prophylactic and acute treatment of an Italian cohort of patients and to correlate treatment response to clinical, demographic and genetic data.

2. Subjects

The clinical, demographic, genetic and pharmacological data of 30 AHC patients (16 males - 53.3%, 14 females - 46.7%) ranging in age from 5 to 42 years (20.9 ± 10 years) were collected from the I.B.AHC (the Italian Biobank and Clinical Registry for AHC: www.ibahc.org). Data were collected by the patient's referring paediatric neurologist and subsequently validated by the I.B.AHC data managers (MG, EDG and MS). Diagnoses were established by consensus among the members of the Scientific Committee of the Italian Patient Association (A.I.S.EA) on the basis of the 7 specific diagnostic clinical criteria [4] and by analysing video recordings during and between paroxysmal attacks. All patients (or parents acting on their behalf) gave informed consent to participate in the study and each patient underwent molecular analysis of the *ATP1A3* gene.

3. Methods

The following data were analysed: onset of disease; age at last follow-up; gender; clinical manifestations (epilepsy, migraine, cognitive impairment, dystonia, walking disability, language impairment); genotype (presence and type of *ATP1A3* mutation); frequency, severity and duration of each type of paroxysmal attack (tonic/dystonic/plegic) before and after administration of every prophylactic and/or symptomatic therapy; reported side effects.

Drugs were classified as follows: sleep-inducing treatments, benzodiazepines, anti-epileptic drugs (AEDs), drugs for spasticity and movement disorders, antimigraine, antidepressant, anti-psychotic, anti-inflammatory (including non steroidal anti inflammatory drugs), paracetamol, corticosteroids, hormonal therapies, vitamins and supplements, homeopathy and other therapies (ketogenic diet (KD), vagal stimulation, relaxation techniques). A favourable response was empirically defined as a clinically significant reduction in terms of frequency, duration or intensity of the spells according to the referring neurologist, evident and sufficient to warrant continuation of the treatment.

Treatment with flunarizine was specifically analysed. Using the I.B.AHC database, as well as the patients' charts and the interviews with family members and parents, we rated intensity, duration and frequency of the attacks before and after treatment in order to achieve data standardization. A numerical scale ranging from 1 to 10 (1 = low intensity, 10 = high intensity) was used to assess the intensity of the attacks, while duration was measured in hours, and frequency in number of episodes per week. The percentage of positive or negative modifications was calculated for each item in order to measure the effects of flunarizine, while to better define the number of patients in whom there was no or only minimum change in the frequency, intensity, and duration of paroxysmal attacks, we decided to categorize the response rate, considering a minimum cut-off of 30% as a significant decrease.

The Flunarizine Index (FI), defined as the duration of the treatment with flunarizine divided by the patient's age [2], was also calculated.

The hypothesis that the cognitive and neurological outcome of these patients might be correlated with the duration of flunarizine treatment was investigated by comparing the FI to the cognitive profile, the presence and severity of dystonia and any impairment of autonomous walking and speech.

The data in our statistical analysis were described as mean and standard deviation (SD) or median and range