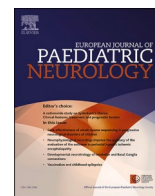




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Original article

Real life retrospective study of cannabidiol therapy in alternating hemiplegia of childhood



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ABSTRACT

Background: Many alternating hemiplegia of childhood (AHC) patients have received Cannabidiol (CBD) but, to our knowledge, there are no published data available.

Goals: Test the hypothesis that CBD has favorable effects on AHC spells.

Methods: Retrospective review of available data of AHC patients who received CBD. Primary analysis: Clinical Global Impression Scale of Improvement (CGI-I) score for response of AHC spells to CBD with calculation of 95% confidence interval (CI) for rejection of the null hypothesis. Secondary analyses, performed to achieve an understanding of the effect of CBD as compared to flunarizine, were CGI-I scores of 1) epileptic seizures to CBD, 2) AHC spells to flunarizine, 3) epileptic seizures to flunarizine. Also, Mann-Whitney test was done for comparison of CGI-I scores of CBD and flunarizine to both AHC spells and seizures.

Results: We studied 16 AHC patients seen at Duke University and University of Lyon. CI of CGI-I scores for AHC spells in response to CBD and to flunarizine, each separately, indicated a positive response to each of these two medications: neither overlapped with the null hypothesis score, 4, indicating significant positive responses with $p < 0.05$ for both. These two scores also did not differ ($p = 0.84$) suggesting similar efficacy of both: CBD score was 2 ± 1.1 with a 95% CI of 1.5–2.6 and flunarizine score was 2.3 ± 1.3 with a 95% CI of 1.7–3.1. In patients who had seizures, CI calculations indicated a positive effect of CBD on seizure CGI scores but not of flunarizine on seizure scores. CBD was well tolerated with no patients discontinuing it due to side effects and with some reporting positive behavioral changes.

Conclusion: Our study indicates a real-life positive effect of CBD on AHC type spells.

1. Background

Alternating hemiplegia of childhood (AHC) is a rare and serious neurodevelopmental disorder that is characterized by paroxysmal spells and non-paroxysmal symptoms including, progressive neurological impairments [1–3]. This disease is known to have complex clinical manifestations which include repeated episodes of unilateral hemiplegia, quadriplegia, dystonia, epileptic seizures and abnormal eye movements, each alone or in combination. Episodes can last minutes, hours, or, much

longer and often occur several days per week [4–7]. Most cases are caused by *ATP1A3* gene mutations [1,8]. About half of the patients have drug resistant epileptic seizures and many have status epilepticus that can lead to regression [1,8–10]. There is an urgent need for improved treatment of this disease due to severe morbidity that results from the paroxysmal AHC spells in all AHC patients and due to the epileptic seizures in those who have epilepsy.

Cannabidiol (CBD) is an oral form of cannabinoids, a phytocannabinoid, derived from the cannabis species. It has been approved for use as

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an antiseizure medication for Dravet and Lennox-Gastaut syndrome [11–13]. There is also evidence that it can help certain movement disorders [14–16]. However, we are not aware of any published data on its potential efficacy in AHC. In our AHC Multidisciplinary Clinic at Duke University Medical Center, we initially started using it in AHC patients with drug resistant epilepsy and some of our patients started to use it as part of “over the counter” preparations that can be ordered without physician prescription. Due to the favorable feedback, we used it in additional patients at our Duke Center. AHC patients in other centers such as the one in the Lyon University Hospital (HCL) have received CBD too. The goal of our study was to analyze and report on our experience with CBD, regarding its effects on AHC spells and its safety and tolerability. Our goal was to test the hypothesis that CBD helps not only epileptic seizures but also AHC type spells (including hemiplegia, dystonia).

Double blind placebo-controlled drug trials are the golden standard to assess the effects of medications in any disease. Short of the controlled trials, real life observational studies do offer insights into therapy of various disorders and can help guide future controlled studies [17,18]. Our goal was to report on the real-life experience of the use of CBD in AHC by testing one main hypothesis and addressing, statistically, a number of related and corroborating sub-hypotheses on data obtained from our retrospective patient files’ review.

2. Methods

2.1. Overview (Fig. 1)

This was a retrospective analysis of the records of consecutive patients who fulfilled the following inclusion criteria from two centers that are part of the International Alternating Hemiplegia of Childhood Research Consortium (IAHCRC). These two centers are Duke University and University Hospital of Lyon: 1) Patient has the diagnosis of AHC according to the Aicardi criteria [2,8]. 2) Patient received CBD with no change of background AHC type or anti-seizure medications for at least 4 weeks before any medication was added (to allow for minimum period on CBD to compare with the one-month baseline) and 3) Chart review allowed determination of the response of the patient’s AHC spells and of seizures to CBD and to flunarizine. 4) Informed consent and IRB approval. Data obtained from chart review were analyzed to determine the response of AHC spells and seizures to CBD, using the Clinical Global Impression Scale of Improvement (CGI-I, see below in methods), as compared to the one month preceding the start of CBD [19]. We included patients who received brand name CBD, Epidiolex (twelve patients) and those who received over the counter preparations (four patients). In patients who received Epidiolex, we followed the initiation and dose titration recommended by the FDA package insert for Epidiolex usage for seizure therapy with dose adjustments performed according to clinical response.

2.2. Primary outcome analysis

The response of the AHC type spells to CBD in the total group of 16 patients from Duke University and University of Lyon was the primary outcome. It was assessed by the CGI-I on the final tolerated dose of CBD before any medication was added as compared to the one-month baseline before CBD was added with 4 indicating no response, 1 and 2 indicating very much, much and 3 minimally improved and 5,6 and 7 indicating minimally, much and very much worse [19].

The CGI-I was determined by review of the patients’ chart by investigators not initially involved in the care of the patient. In addition, whenever needed, phone calls to the caregivers were used to clarify the information and refine the determination of the CGI-I. We evaluated patients’ responses with respect to all types of AHC spells combined. We did not attempt to collect spell-type specific data such as distinguishing between dystonia or hemiplegia events since so many, if not most, of the

spells have combinations of these manifestations [20]. This methodology was reviewed and coordinated between the investigators at both centers to ensure similarity across both centers.

The average and standard deviation of the CGI-I was calculated using Excel. A 95% confidence interval (CI) was calculated using 0.05 as our alpha, standard deviation and number of samples in the cohort. A 95% CI that is lower than and does not cross the score of 4 was considered as evidence for benefit, as 4 indicates no response on the CGI-I scale. If the 95% CI crossed the score of 4, then this was considered as failure to reject the null hypothesis.

2.3. Secondary outcome analyses

Flunarizine and AHC spells: This consisted of determining, using the CGI-I scores, the effect of flunarizine on AHC type spells. This was done in the thirteen of the 16 patients who also had received flunarizine previously, at least six months before starting CBD (given that flunarizine has a long half-life and the relatively wide range of potentially effective dosing and concentrations in AHC) [21,22]. Fig. 1 gives the overview of the study secondary analyses subgroups; this was necessary because not all 16 patients in the primary analysis had received flunarizine or had seizures. Similar to the primary analysis regarding CBD, here we compared the response of AHC spells at the final dose of flunarizine to the one month before starting flunarizine to determine the flunarizine CGI-I.

CBD and seizures: We also used the procedure described above to determine the CGI-I score of the seizure responses to CBD at the final CBD dose as compared to baseline.

Flunarizine and seizures: We used the same procedure (described in detail for flunarizine and AHC spells) to determine the CGI-I score of the responses of seizures to flunarizine.

Comparison of effects of CBD and of flunarizine on AHC type spells and on seizures: We performed secondary analyses, using the Mann-Whitney *U* test, to compare the CGI-I scores of the responses to CBD and of flunarizine on AHC type spells (one analysis) and on seizures (another analysis): After calculating the confidence interval for the CGI-I scores for each of the two drugs’ effects, CBD and flunarizine, we used the Mann-Whitney *U* test to determine if these scores differed between the two medications. We chose the Mann-Whitney *U* test because it is a nonparametric test of the null hypothesis and the CGI-I scores are non-parametric variables. This test allowed us to calculate the *p* value to test for any differences in the effects of these two medications.

2.3.1. Other effects

We also reviewed the records for any adverse or favorable side effects and documented those whenever they occurred.

3. Results

3.1. Patient characteristics

We had 16 patients who fulfilled the inclusion criteria in the both the USA and French site (see Table 1). The mean age at onset of AHC spells was 6.77 months (range: 2 weeks up to 30 months). Fourteen of the 16 had *ATPIA3* mutations, one had an *ATPIA2* mutation, and one was gene mutation negative. The baseline AHC spell frequency 1.33 AHC spells a day, standard deviation 1.3 spells a day (range of 1x/week up to 4.5x/day). Twelve of the 16 patients received brand name Epidiolex. The average dosage was 12.7 mg/kg/day \pm standard deviation 5.1 mg/kg/day (range of 4.3 mg/kg/day up to 20 mg/kg/day). The other 4 patients received “over the counter” CBD preparations that had variable amounts of CBD concentrations that could not be as well documented as the medicinal preparation and, thus, the dosing calculations were based on the pharmaceutical Epidiolex preparation doses. Most patients had an average of three other medications being given for AHC symptoms and or for seizures. These were not changed during the one-month baseline

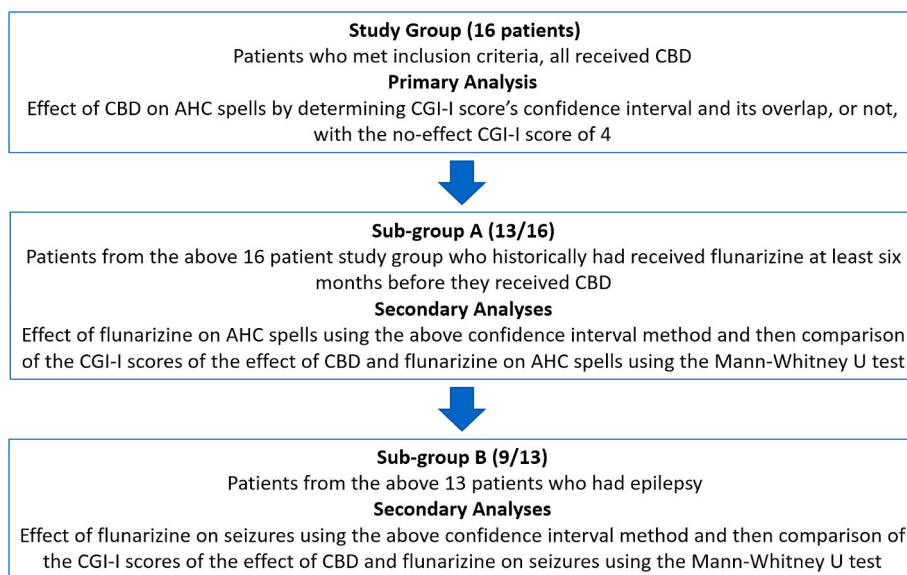


Fig. 1. Overview of the study subgroups and analyses.

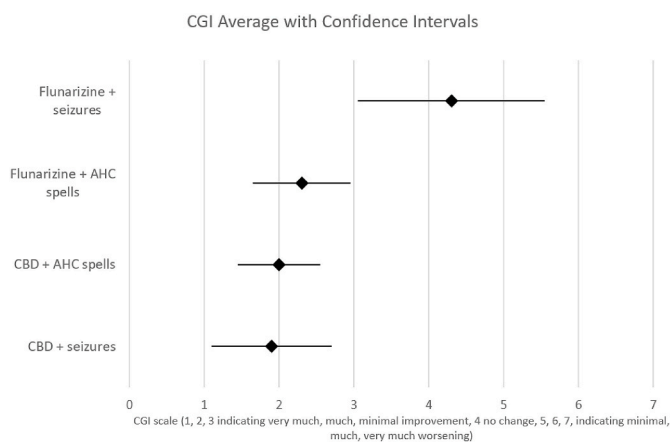


Fig. 2. Plot of the mean CGI-I and 95% CI for the primary (CBD + AHC spells) and secondary outcome analyses (all three other analyses). If the mean and its confidence interval crossed over 4, it indicates that the medication was not effective for the given type of event. In this graph, we see that flunarizine and seizures crossed over 4, consistent with lack of its efficacy on seizures. The other three categories of comparison all supported effectiveness, with our primary outcome of CBD effect on AHC spells and secondary outcomes of CBD effect on seizures and flunarizines effect on AHC spells.

period and during the minimum period of four weeks after starting CBD, otherwise the patient would not have qualified for the study as per the inclusion criteria.

For 9 patients of the 16 above patients who had epilepsy and also received flunarizine, their baseline seizure characteristics were as follows: age of onset of seizures was 24.12 months (range of day of life 1 up to 154 months) and baseline seizure frequency was 0.90 seizures per day, standard deviation 1.1 seizures per day (range of 2.5 per years up to 2.5 per day). Seizure types included focal, generalized tonic and generalized tonic-clonic seizures.

3.2. Primary outcome analysis (Fig. 2)

3.2.1. CBD and AHC spells (Fig. 2)

CBD and AHC Spells: The mean and SD of the CGI-I score for the entire cohort of 16 patients (12 patients from Duke and 4 from HCL Lyon) was 2 ± 1.1 with a 95% CI of 1.5–2.6 which does not overlap 4,

Table 1

Patient characteristics.

Gender (n, %)	
Male	9 (56.3%)
Female	7 (43.7%)
Genetic changes (n, %)	
ATP1A3	14 (87.5%)
ATP1A2	1 (6.25%)
Gene mutation negative	1 (6.25%)
Age of Onset of AHC spells (mean, standard deviation, range)	6.77 months, standard deviation 7.6 months (range: 2 weeks up to 30 months)
Age of Onset of Seizures^a(average, standard deviation, range)	24.12 months, standard deviation 48.16 months (range of day of life 1 up to 154 months)
CBD Usage (n, %)	
Epidiolex	12 (75%)
CBD Preparations	4 (25%)
Optimized dose of Epidiolex	12.7 mg/kg/day, standard deviation 5.1 mg/kg/day (range of 4.3 mg/kg/day up to 20 mg/kg/day)
AHC spells frequency baseline (mean, standard deviation, range)	1.33 AHC spells a day, standard deviation 1.3 spells a day (range of 1 per week up to 4.5 per day)
Seizure frequency baseline^a(mean, standard deviation, range)	0.90 seizures per day, standard deviation 1.1 seizures per day (range of 2.5 per year up to 2.5 per day)

^a The age of onset of seizures and seizure frequency baseline was calculated in the patients that had epilepsy and had exposure to both CBD and flunarizine (9 patients).

hence supporting efficacy of CBD on AHC type spells.

The mean CGI-I for the Epidiolex patients (12 out of 16 who were on the medicinal CBD) was 2.3, with a standard deviation of 1.1, and a 95% confidence interval ranging from 1.6 to 3.0 which does not cross over 4,

hence also indicating efficacy of medicinal CBD in AHC spells.

3.3. Secondary outcome analyses (Fig. 2)

Flunarizine and AHC Spells: The mean and SD of the CGI-I score for the subgroup of 13 patients (10 from Duke, 3 from HCL Lyon) was $2.3 + 1.3$ with a 95% CI of 1.7–3.1, which does not overlap 4, hence supporting efficacy of flunarizine on AHC spells.

To investigate if there is an additive effect of CBD over and above that of flunarizine we calculated the CGI-I scores for patients on CBD with concurrent flunarizine and the scores of those without concurrent flunarizine and found similar efficacy whether the patients were on concurrent flunarizine or not. CBD + flunarizine group (8 patients): Average CGI-I $2.5 + 1.3$, confidence interval 1.6–3.4. CBD without concurrent flunarizine group (8 patients): Average CGI $1.6 + 0.7$, confidence interval 1.1–2.1. Both confidence intervals did not cross 4, and comparison using the Mann-Whitney *U* test provided a *p*-value of 0.18, indicating no difference between the two groups.

CBD and Seizures: The mean and SD of the CGI-I score for the subgroup of 9 patients (6 from Duke, 3 from HCL Lyon) was $1.9 + 1.2$ with a 95% CI of 1.1–2.7 which does not overlap 4, hence supporting efficacy of CBD on seizures.

Flunarizine and Seizures: The mean and SD of the CGI-I score for the subgroup of 9 patients (6 from Duke, 3 from HCL Lyon) was $4.3 + 1.9$ with a 95% CI of 3.1–5.6, which does overlap 4, thus supporting lack of efficacy of flunarizine on seizures.

Comparison of CBD and flunarizine effects on AHC type spells: We found there was no statistically significant difference between the effect of flunarizine or CBD on AHC spells in the combined cohort (CGI-I scores comparison: $p = 0.54$).

Comparison of CBD and flunarizine, effect on seizures: We found a statistically significant difference between the effect of the two medications with lower score (indicating response) to CBD (CGI-I scores comparison: $p = 0.01$).

3.4. Other effects

No significant adverse effects to CBD were reported in our patients. To the contrary, in 9 of the 16 patients the caregivers reported observing positive effects including improved sleep, attention, communication, behavior, reduced levels of irritability and developmental gains. Examples of specific quotations included: “improved communication and development”, “increased vocalization”, “less anger outbursts” and “improved sleep”.

One patient (23 months old) discontinued the treatment after one month because of vomiting, but a gastrointestinal infection was also considered possible during the medical evaluation.

4. Discussion

More effective therapies to prevent paroxysmal spells in AHC are needed. We observed, in a real-life retrospective study, positive responses during the use of CBD in AHC patients. Our study indicates that CBD is a potentially effective medication for not only seizures but also for AHC spells.

Flunarizine is a non-selective calcium channel blocker that has been considered, also mainly based on retrospective open label data, to be the only medication so far that can, at least partially, ameliorate AHC type spells [4,23–25]. Our observations are consistent with such an effect of flunarizine and add another potential option for AHC non-epileptic spells, namely CBD. Similar to prior experience in a study of flunarizine in a non-AHC patient population with drug resistant epilepsy [22], we did not observe any anti-seizure effect of flunarizine in our patient population.

The potential mechanism by which CBD may help AHC type spells remains to be studied. However, even though CBD is approved as an

anti-seizure medication it has other effects that could contribute to its potential positive effects in AHC. It has been noted to palliate the effects of dyskinesia and dystonia in Parkinson’s Disease and Huntington’s Disease and to ameliorate spasticity in multiple sclerosis [14–16,26]. Several pre-clinical studies have looked into its mechanisms of action in seizures and movements disorders. It reduces neuroinflammation and excitotoxicity (by reducing pro-inflammatory cytokines and reactive oxygen species and increasing anti-inflammatory cytokines), and also acts as agonist/antagonist for some receptors (especially serotonin receptor 1A, cannabinoid receptor type 1, cannabinoid receptor type 2, peroxisome proliferator-activated receptor gamma and transient receptor potential vanilloid type 1) [11].

Given that there are many medications that can exacerbate behavioral problems in AHC, and given the concerns about flunarizine induced Parkinsonism, our observation of positive behavioral and developmental effects of CBD is pointing to a potentially attractive therapeutic alternative for AHC type spells that has other potential favorable effects [27,28].

We point out several limitations of our study. As AHC is a heterogeneous disease, our patient population reflects the ranges of AHC spell and seizure frequencies that were documented at baseline. The retrospective nature of the study and the dependence on chart extracted data are sources of potential bias. Our potential bias and limitation caution also apply to the suggestion by our data of an apparent additive effect of CBD on AHC spells over and above the effect of background flunarizine therapy as well as to the inability to fully investigate any potential differences between medicinal and non-medicinal CBD in our study. We observed while performing the study that the primary clinicians in both centers, all of whom were experienced in the care of AHC patients, as a rule, had detailed clinic notes which not only documented seizure frequency and AHC spell frequency, but also non-seizure outcomes and side effects, which helped us calculate our CGI-I scores. We also used phone calls to the families for clarification whenever needed. Nevertheless, we do understand the limitations of this methodology and fully acknowledge that it is inferior to prospective controlled studies. At this point in time, this was the methodology that was useful to use to report on the real-life experience with CBD in AHC. This study brought out the apparent advantage of ameliorating both seizures and AHC type spells which may potentially prove important given the frequent occurrence of epilepsy in AHC and the recently described association of seizures in AHC with apneas [9,29,30]. Further prospective controlled studies addressing the efficacy of CBD and of other agents in AHC are needed and can benefit from the recently described approaches for prospective multicenter studies of AHC and other similar rare diseases [31,32]. We also note that while studying CBD, we were limited because we could not ascertain the amount in the OTC CBD preparations. We did perform an analysis on the patients with only Epidiolex usage, 12 of the 16, which showed similar results. Nevertheless, our study does provide unique and much needed data about the experience of using a potentially alternative medication in AHC.

Our observations support that CBD may be of benefit in the management of paroxysmal spells in AHC with a favorable side effect profile. However, further confirmation is needed in prospective controlled trials. Our current observations lay the groundwork for the performance of such prospective, controlled studies evaluating the use of CBD in AHC.

Declaration of competing interest

All conflicts of interest by any author have been disclosed as noted below.

One of the authors (MAM) has intellectual property interest in gene therapy of ATP1A3 related disease. There are no other conflicts of interest.

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