

Clinical Improvement in a Case of Alternating Hemiplegia of Childhood After Cerebral Lymphatic Drainage

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Abstract: Alternating hemiplegia of childhood (AHC) is a rare neurological disorder characterized by recurrent episodes of hemiplegia and dystonia, significantly affecting patients' quality of life. This exploratory study evaluated the effects of the Muscular Acoustic Modulator (MAM) on a single patient with AHC treated for one year. The treatment was associated with a notable reduction in the frequency and duration of hemiplegic and dystonic episodes, with partial and total hemiplegic episodes decreasing by 52% and 85%, respectively, and partial dystonic episodes decreasing by 81%. Additionally, improvements in behavioural symptoms such as anger and strength outbursts were observed. We hypothesize that MAM treatment could modulate cerebrospinal fluid dynamics and enhance glymphatic drainage, potentially offering a new therapeutic approach for AHC and other neurodegenerative diseases. However, the study's limitations, including the single-patient design, necessitate further research to confirm these preliminary results and elucidate the underlying mechanisms.

Keywords: alternating hemiplegia of childhood, AHC, glymphatic system

Introduction

Alternating Hemiplegia of Childhood (AHC) (OMIM #614820) is a rare neurological disorder with an onset before 18 months of age and a prevalence of 1:100,000 to 1:1,000,000.¹ It is characterized by paroxysmal manifestations (hemiplegic and/or dystonic attacks, abnormal ocular movements, typically unilateral nystagmus, and autonomic disturbances) and chronic neurological symptoms (movements disorders, such as dystonia, choreoathetosis, parkinsonism, cognitive impairment and psychiatric disorders). Moreover about 50% of AHC patients have epileptic seizures.^{2,3} The paroxysmal manifestations of AHC often occur due to the exposure to the following common triggers: emotional or physical stress, intense light, specific weather conditions (wind, temperature variations), contact with water, and concomitant upper respiratory tract infections.^{2,3}

In over 80% of patients with AHC, de novo heterozygous mutations in the ATP1A3 gene have been identified as the primary cause.^{4,5} ATP1A3 encodes the $\alpha 3$ subunit of the Na⁺/K⁺ ATPase pump, critical for maintaining neuronal ion balance. Several ATP1A3 mutations have been detected, of which the most frequent are p.Asp801Asn, p.Glu815Lys, and p.Gly947Arg, present in almost 60% of all cases. Individuals with the p.Glu815Lys mutation often exhibit a more severe phenotype and an earlier onset of symptoms.^{3,6}

Currently, there is no specific treatment capable to modify the evolution of the disease; the focus of the current drugs is preventing paroxysmal attacks and managing chronic symptoms like dystonia and epilepsy. Commonly prescribed medications include flunarizine (the gold standard), benzodiazepines, carbamazepine, barbiturates, and valproic acid.^{6,7}

The Cerebro-Spinal Fluid (CSF), surrounds the brain and spinal cord, protects them from traumas, nourishes them and enables their proper functioning by draining the waste substances produced by their cells (see [Figure 1](#)). In addition to drainage in the veins, cerebrospinal fluid has a second drainage system known as the lymphatic system, so in 2015, the

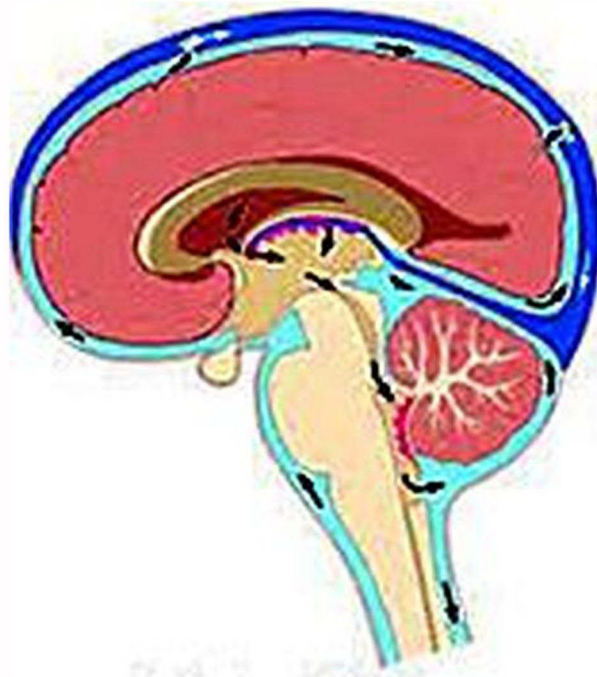


Figure 1 Cerebrospinal fluid circulation.

term of “glymphatic” was coined by Lijf. Recent MRI studies with intrathecal gadobutrol contrast administration showed the drainage of this system into the head and neck lymph nodes.⁸

In 2012, we hypothesized that sometimes the drainage of interstitial fluid in the brain and spinal cord could be hindered or blocked at the level of extracranial and extraspinal lymph nodes. We hypothesized too that lymph nodes, in addition to their immune defence function, might also serve as an additional pump to the lymph propulsion system through the lymphangion pumping mechanisms towards the major supraclavicular venous drainage sites, such as the thoracic duct and the right lymphatic duct. To reactivate this lymph node drainage function, we utilized the Muscular Acoustic Modulator (MAM) device, which has a dual effect on both the lymph nodal and lymphatic vessel muscular system by its mechanical vibration, used synergistically with customized protocols (drenoMAM and acuMAM).

MAM Device

On 2007, the Muscular Acoustic Modulator (MAM) was developed in Rome. It is a patented device for pain treatment that utilizes a special power and frequency-modulated acoustic wave. It is equipped with a probe that is placed over the painful areas to be treated. The emitted wave penetrates the tissues, releasing muscle contractions, the source of pain, and causing them to disappear or reduce within a few seconds. The MAM massager device, Dimasan’s srl Levia model 2017, by a plastic probe, transmits the acoustic MAM waves (modulated in power and frequency 0–2 bar, 0–50 Hertz) for the pain treatment. A painless technique: the method is non-invasive and very rapid. In fact, the MAM treatment allows for the reduction or disappearance of pain with immediate recovery of lost function from the very first session.

In addition to its drainage into the veins, cerebrospinal fluid (CSF) features a second drainage system known as the lymphatic system. In 2012, we postulated that this secondary lymphatic system might experience impaired drainage in certain individuals. Subsequently, we commenced the use of the MAM device to alleviate congestion in these lymph nodes.⁹ Initially, our focus was on treating the pelvic and leg lymph nodes of multiple sclerosis patients, resulting in notable improvements in gait disturbances. This approach is referred to as the DrenoMAM Protocol.

In 2014, we further expanded our protocols by developing another approach specifically targeting the decongestion of lymph nodes in the head and neck. This protocol, known as the head and neck AcuMAM protocol, demonstrated

favourable outcomes not only in addressing chronic fatigue but also in improving aspects such as memory, drowsiness, and overall quality of life.¹⁰

In 2022–2024, seeking to enhance the lymphatic drainage of cerebrospinal fluid, we introduced the intensive outpatient Fluid Dynamic MAM (FD-MAM) protocol. This comprehensive protocol involves one session of acuMAM and one session of drenoMAM per day, five days a week, for two weeks. Clinical results pertaining to the regression of symptoms in patients with progressive multiple sclerosis have shown significant positivity.¹¹

AcuMAM is a message that involves the manual application of the MAM device's probe to predetermined points in a specific sequence and timing. The goal is to decongest the lymph nodes in the total body through targeted stimulation. This sequence and points of application are designed to effectively “soundproof” the areas where the primary lymph nodes responsible for draining the specific area are located (see [Figures 2–7](#) for details).

Objective

The aim of this study is to evaluate the differences in crises characteristics in AHC patient before and after outpatient MAM treatments.

Case Presentation

The patient (EN13) is the thirteen-year-old eldest child of unrelated parents with an unremarkable medical history. Subject was born at the 37th week of an uneventful pregnancy by a Caesarean section due to the rupture of the amniotic sac. The APGAR at 1st and 5th minutes was, respectively, 9 and 10, but shortly after birth, EN13 exhibited respiratory distress. Moreover, mild global neonatal hypotonia was detected and EN13 started physiotherapy at 1 month of age. At 6 months, the first paroxysmal episode of right hemiplegia occurred, it lasted a few minutes, and it was followed by sleep.

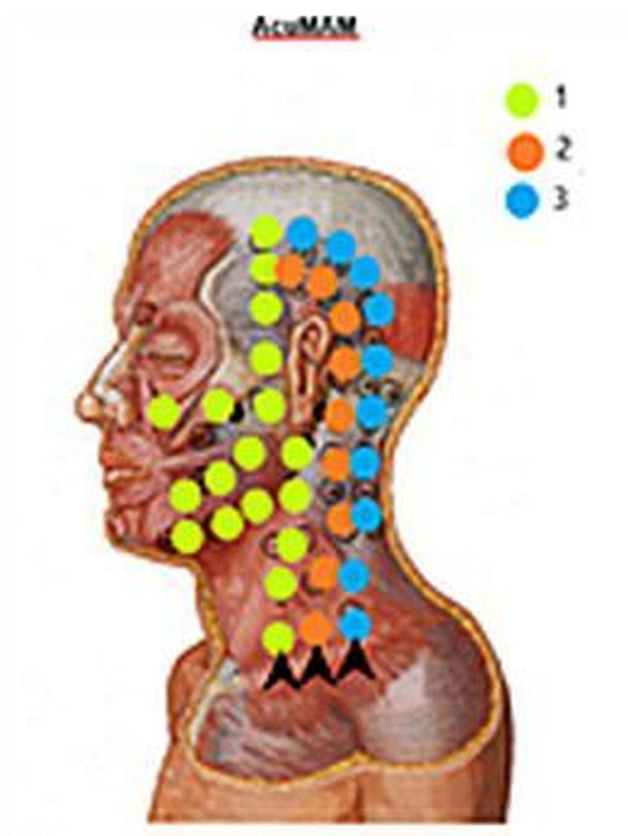


Figure 2 AcuMAM - Neck-Head Area.

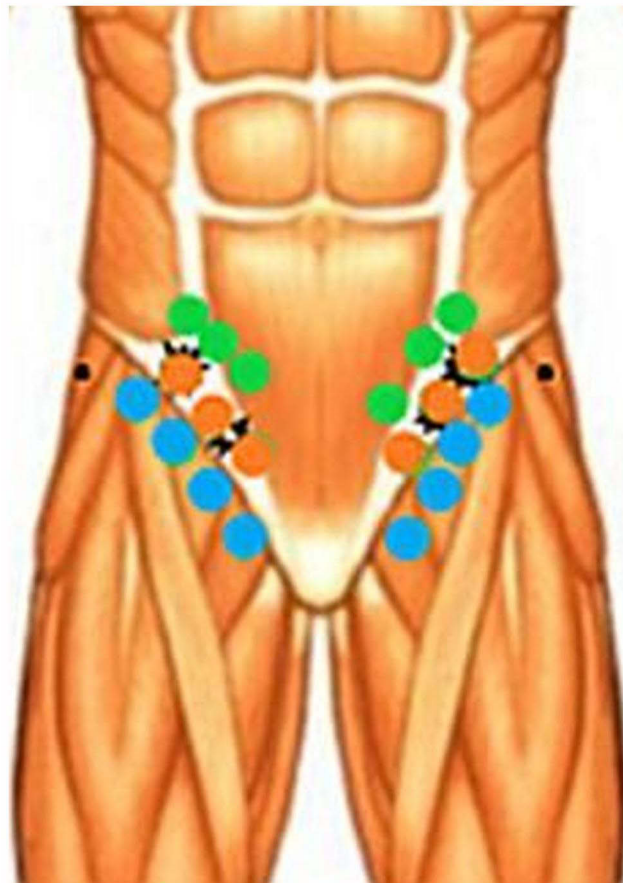


Figure 3 DrenoMAM - Front Area.

Afterwards, similar episodes happened monthly, treated with endorectal administration of diazepam without significant benefit; subsequently, other antiepileptic drugs (AEDs) were tested without complete efficacy.

The psychomotor development was delayed: EN13 reached the walking with bimanual support at 12 months, and EN13 gained the autonomous walking with a widened base at 5 years. In 2010, brain MRI study was performed showing a cerebellar hamartoma; at 9 months EN13 underwent neurosurgical surgery at the Meyer Hospital. During the summer of 2010 the patient experienced several hemiplegic attacks involving alternately both sides of the body and less frequently tetraplegic attacks with dysphagia and dysarthria usually disappearing during sleep. Metabolic investigations (plasma and urinary amino acids, VLCFA, urinary organic acids and acylcarnitine), neurotransmitters analysis on CSF, cardiological exams (ECG and echocardiogram) were negative. Based on clinical criteria, a diagnosis of AHC was made at the age of 24 months. The genetic testing performed at the age of 30 months revealed a de novo D801N mutation of the ATP1A3 gene. Therefore, antiepileptic drugs were discontinued and flunarizine administration was started.

In addition to the plegic and hemiplegic episodes, since 2020 the patient developed short-lasting painful hemi-dystonic events, usually responsive to muscle massage or administration of midazolam hydrochloride.

In 2021 EEG and cerebral PET/CT were performed and showed no pathological results.

The patient developed a mild cognitive disability with a nonhomogeneous cognitive profile and an attention deficit; EN13 attended the school with a support teacher. At the age of 12, EN13 was also diagnosed with an anxiety disorder.

The current pharmacological treatment consists of flunarizine (7,5 mg/day) and topiramate (50 mg/day), together with supplements of aminoamides, vitamins, probiotics, magnesium pidolate, bromelain.

Due to the potential occurrence of hemiplegic attacks caused by fatigue from walking, EN13 began using a wheelchair for support at the age of six.

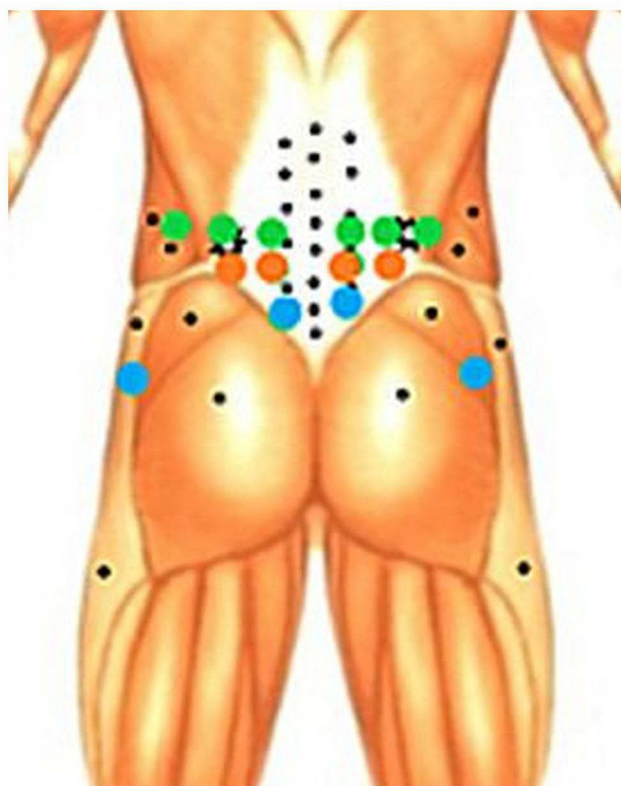


Figure 4 DrenoMAM - Back Area.

MAM Study

The parents provided a signed informed consent to participate to the study. The patient's history was collected, and a clinical assessment was conducted before and after the 12 months of treatment using the AHC – rating Scale (AHC-R Scale). The AHC-R Scale is a specific tool designed to gather information on both paroxysmal and non-paroxysmal manifestations, as well as the adaptive capacities of AHC patients. Four scores are measured: the Paroxysmal Score that is the sum of 5 indexes (the Paroxysmal Dystonia Index – PD index; the Paroxysmal Plegic Index – PP Index; the Paroxysmal Mixed Index – PM Index; the Ocular Abnormalities Index – OA Index; and the Autonomic Abnormalities Index – AA Index), the Epilepsy Score, the Non Paroxysmal Score, and the Adaptive Score.

Approximately every two weeks, the patient underwent a draining massage (AcuMAM) of the neck, head, and lower limbs using the MAM device.

The first treatment was administered on June 6th, 2023, and lasted for 12 months, ending on June 5th, 2024, with a total of 28 sessions. The authors used Echo-Color-Doppler to assess the arterial and venous vessels of the neck and abdomen, they conducted a total body muscular system assessment and utilized a body impedance analysis (BIA).

The parents completed a MAM centre crisis-questionnaire throughout the entire study period to assess potential changes in the frequency, duration, and severity of the paroxysmal attacks. (see [Figures 8–10](#)).

Physiatry Consultations

The patient also received a physiatry evaluation before and after the 12 months of MAM treatments.

On 2022 March 17th physiatry *videat* reports: Hypotonic syndrome, severe prone flat foot, severe walking difficulties. Posture dystonia, tibia tarsus laxity, mainly on the left, lumbar hyperlordosis, pelvis-lumbar rotational imbalance from left to right. In a standing position with stabilising footwear and footplates, EN13 can control alignment in the anterior-posterior plane. More difficult alignment in the sagittal plane is due to lumbar pelvis instability from hypotonia. Adam's test in the absence of structured scoliotic curves. During the quadrupedal test, the patient can control the stability of the

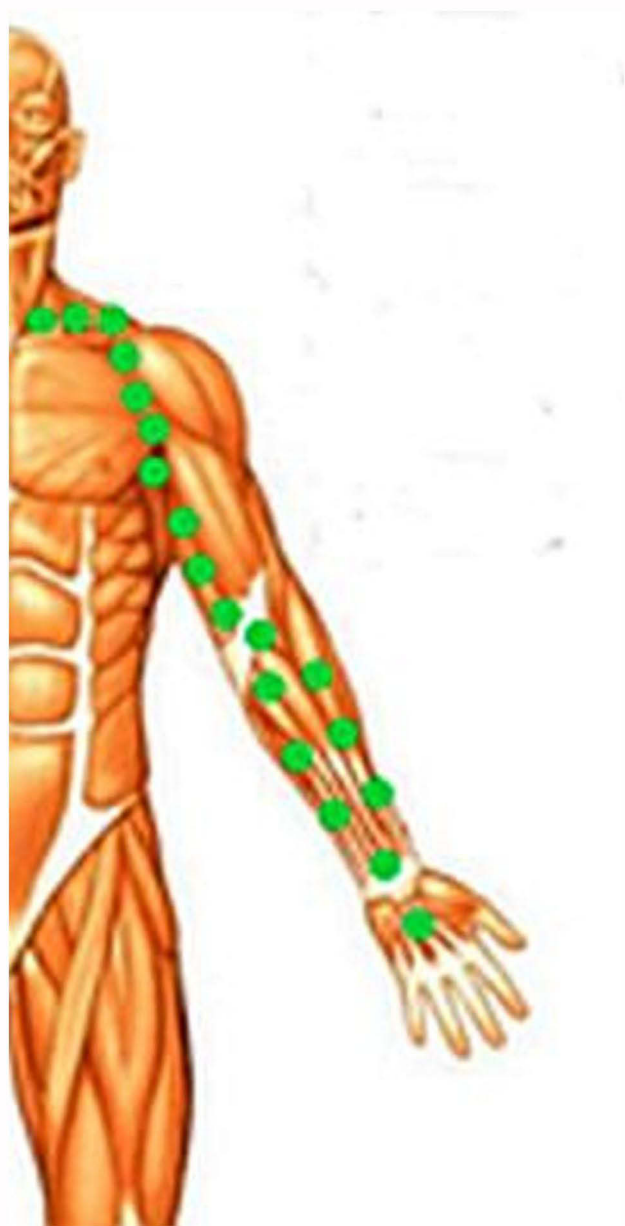


Figure 5 AcuMAM - Arm, Front Area.

scapulae and to lift one limb at a time in isolation in both lower and upper limbs. The patient must be helped to cross-lift the limbs manage to control pelvic-lumbar stability in the cat and camel position. Patient assumes unsuitable seated postures in forced hip intrarotation to be avoided by maintaining more correct postures in extra rotation.

On 2024 November 13th physiatry *videat* reports: “Hypotonic syndrome, alternating hemiplegia less frequent and less intense episodes than in the past being treated with Fluidodynamic MAM and AcuMAM protocols. Improved postural stability, improved muscular endurance and balance, greater harmony in stride dynamics. We note here is plantar arch subsidence in metatarsal flatness-adduction subsidence of the tibiotarsus in varo-supinate, mainly on the left from laxity of the tibio-tarsus and sub-astragalic. manual correction of the tibio-ankle is possible, which cannot be maintained and requires a plantar/shoe and footwear with strong rigidity. Curved back, winged scapulae, thoraco-scapular hypo-validity /lateral-deviation of the trunk to the left, currently in the absence of curves structured pathological curves are in any case improved since the previous visit”.



Figure 6 AcuMAM - Arm, Back Area.

MAM Centre Data Collection Sheet

Figures 8 and 9 show screenshots of the data collection forms used by the subject's relatives to record the number, characteristics, localization and duration of crises during the 24-month observation period (twelve months before to twelve months after the start of MAM treatments).

The specification of the abbreviations used can be found in Figure 10.

Statistical Analysis

Data were collected into a Microsoft Access database (Microsoft 365 MSO Version 2309 Build 16.0.16827.20130–64 bit), and they were analysed by Epi-Info 7 programs (CDC and NIH, 2022 Italian version 7.2.5.0). Statistical analysis estimated descriptive statistics, frequencies, and significance in showed differences. Statistical significance “between” and “within”



Figure 7 AcuMAM - Front Area.

DATE	CET	CET_ORA	CET_ALT	CEP	CEP_DX	CEP_SN	CEP_ORA	CEP_ALT	CEP_TESTA	CEP_ASUP	CEP_MANO	CEP_TRONC	CEP_AINF	CEP_PIEDE
DATE OF THE CRISIS	TOTAL HEMIPLEGIC CRISIS	DURATION	OSCILLATING CRISIS	PARTIAL HEMIPLEGIC CRISIS	RIGHT SIDE	LEFT SIDE	DURATION	OSCILLATING CRISIS	HEAD	UPPER LIMB	HAND	TRUNK	LOWER LIMB	FOOT
dd/mm/yyyy		h:mm					h:mm	h:mm						
07/06/2022	x	12:00												
08/06/2022	x	12:00												
09/06/2022	x	6:00	x											
10/06/2022				x		x	12:00	x		x	x	x	x	x
11/06/2022				x		x	6:00	x		x	x	x	x	x
12/06/2022				x		x	4:00	x		x				
26/06/2022														
28/06/2022														
30/06/2022														
03/07/2022														
04/07/2022				x		x	0:15		x	x	x	x	x	x
10/07/2022														
29/07/2022	x	12:00												

Figure 8 Crisis questionnaire by MAM centre (Total Hemiplegic Crisis). Screenshot from a questionnaire filled in by parents.

groups was calculated on continuous variables. An analysis of variance (ANOVA) was performed to test the equality of means between pre- and post-treatment for continuous variables, including Bonferroni and Newman-Keuls pairwise mean comparison tests. Chi-square Yates corrected test was used for non-continuous variables by Statcalc and Analysis programs. A p level less than 0.05 was considered significant, and 95% confidence intervals were also calculated.

DATE	NOF	NOF_DX	NOF_SN	NOF_ORA	NOF_ALT	NOF_TESTA	NOF_ASUP	NOF_MANO	NOF_TRONC	NOF_AINF	NOF_PIEDE	RAB
DATE OF THE CRISIS	LACK OF STRENGTH	RIGHT SIDE	LEFT SIDE	DURATION	OSCILLATING CRISIS	HEAD	UPPER LIMB	HAND	TRUNK	LOWER LIMB	FOOT	ANGER ATTACK
dd/mm/yyyy												
24/05/2023												
21/06/2023												
09/07/2023	X	X	X	0:10					X			
19/08/2023	X		X	0:05			X					
10/09/2023	X		X	0:05	X		X					
25/10/2023	X	X		0:10			X					
15/11/2023	X	X	X	0:10			X	X	X	X	X	
27/11/2023												
18/12/2023	X	X	X	0:10	X		X	X	X	X	X	
16/01/2024												
30/01/2024												
10/02/2024												
10/02/2024												
28/02/2024	X	X	X	2:00								

Figure 9 Crisis questionnaire by MAM centre (Strength Measurement). Screenshot from a questionnaire filled in by parents.

Ethics and Conflicts of Interest

Italian Law (see D.Lgs. n.211/2003 on Gazzetta Ufficiale of Repubblica Italiana n.184 August 9th, 2003 - supplement to “serie generale”) does not require the authorization of the Ethics Committee in cases of epidemiological and observational studies. Anyway, the authors specify:

To the subject studied was not administered any experimental and/or innovative substance. The therapies approved by the official pharmacopoeia have been used in the context of good clinical practice.

No experimental and/or innovative diagnostic techniques were used on the subject studied. The diagnostic techniques officially accredited in good clinical practice were used for a correct diagnosis.

The subject has issued a suitable release personally or through an agent or legal guardian, after consulting a written information sheet accompanied by further oral explanations by the medical staff.

The subject parents have signed a specific written consent to use their clinical child data for the publication of scientific articles and/or for communication at medical congresses. In full compliance with the European Privacy Regulation, all data are in anonymous format and cannot be traced back to the identity of the subject.

Results

The observation period was extended for a total of 12 months. The characteristics of the 12 months after starting MAM treatment were compared retrospectively with the 12 months before, through anamnestic collection.

Figure 10 shows the number of crises observed with the specified characteristics. In summary, it can be noted the absence of total dystonic crises and multiple daily total dystonic crises, and that hemiplegic crises, partial hemiplegic crises, and partial dystonic crises, decreased in varying percentages until they disappeared after MAM treatment.

Moreover, anger attacks decreased by 100%, or from 8 to 0, after MAM treatments; conversely, the lack of strength after MAM treatment increased markedly compared to the complete absence of the symptom before MAM treatments.

Finally, the use of wheelchair decreased, and now patient does not use it.

In addition to the reduction in the number of crises, the average duration (hh:mm) of the crises was also decreased after MAM treatments:

	abbreviations	PRE-MAM crises number	POST-MAM crises number	difference %
TOTAL HEMIPLEGIC CRISIS	CET	21	10	-52%
DAILY ACCUMULATOR	CET_ALT	7	4	-43%
PARTIAL HEMIPLEGIC CRISIS	CEP	32	5	-85%
RIGHT SIDE	CEP_DX	---	---	---
LEFT SIDE	CEP_SN	32	5	-85%
DAILY ACCUMULATOR	CEP_ALT	14	1	-87%
HEAD	CEP_TESTA	15	2	-87%
UPPER LIMB	CEP_ASUP	30	3	-90%
HAND	CEP_MANO	29	3	-90%
TRUNK	CEP_TRONC	27	3	-89%
LOWER LIMB	CEP_AINF	29	3	-93%
FOOT	CEP_PIEDE	29	2	-93%
TOTAL DYSTONIC CRISIS	CDT	---	2 (*)	+200%
DAILY ACCUMULATOR	CDT_ALT	---	2 (*)	+200%
PARTIAL DYSTONIC CRISIS	CDP	37	7	-81%
RIGHT SIDE	CDP_DX	35	7	-80%
LEFT SIDE	CDP_SN	2	---	-100%
DAILY ACCUMULATOR	CDP_ALT	24	2	0%
HEAD	CDP_TESTA	---	---	---
UPPER LIMB	CDP_ASUP	28	5	-82%
HAND	CDP_MANO	28	4	-86%
TRUNK	CDP_TRONC	4	1	-75%
LOWER LIMB	CDP_AINF	10	5	-50%
FOOT	CDP_PIEDE	28	7	-75%

Figure 10 Percentage changes in symptoms experienced between before and after MAM treatments. (*) The value “1” was used to perform the calculation.

Total Hemiplegic Crisis (CET) from 9:51 to 4:42 (−52%)
 Partial Hemiplegic Crisis (CEP) from 6:15 to 4:52 (−22%)
 Partial Dystonic Crisis (CDP) from 3:49 to 0:24 (−90%)
 Lack of strength (NOF) from 0:00 to 0:24

Discussion

AHC is an extremely complex and rare disorder, and no targeted therapeutic approaches have been developed so far. AHC patients display a composite phenotype including different paroxysmal disturbances (epileptic seizures, tonic and dystonic attacks, plegic episodes, dysautonomia features, abnormal ocular movements, migraine) and chronic neurological features. The outcome of available treatments is completely unsatisfactory in terms of control the most disturbing symptoms: the non-epileptic paroxysmal attacks. Currently, only flunarizine, a calcium entry blocker, has been shown to reduce the severity and/or duration of these attacks.⁷

Here, we report a patient who showed a drastic improvement on number, characteristics, localization and duration of paroxysmal attacks. Both the paroxysmal, and to a lesser extent, the non-paroxysmal score decreased after the treatments.

Both the paroxysmal, and to a lesser extent, the non-paroxysmal score decreased after the treatment. We hypothesize that in our patient, the treatment would act by draining the cerebrospinal fluid, the liquid that surrounds and nourishes the central nervous system, with a mechanism of action that through the drainage of meningeal lymphatics into the lymph nodes of the head and neck would rebalance what is called the glymphatic system. In a recent observation pointed out the possible involvement of the Blood Brain Barrier BBB in the disease mechanisms of ATP1A3 spectrum disorders. Campbell et al described two unrelated cases with AHC phenotype and a mutation of claudin-5.¹² CDLN5 regulates the permeability of the tight junctions of the BBB and has an essential role in maintaining a correct barrier function for the microcirculation of the nervous system.¹³ The mutation found would transform the junctional protein into a selective transport channel for negative particles, thus giving rise to a pathophysiological phenomenon like that found in AHC, increasing neuronal hyperexcitability and diminishing the threshold to develop cortical spreading depression (WWW). Dysfunction in the glymphatic system (GS), a complex network of perivascular space (PVS) surrounding brain vessels and acting as a possible lymphatic circulation, has also been linked to disease mechanism involving Cortical Spreading Depression (CSD). CSD, characterized by a wave of depolarization followed by neuronal suppression, is a hallmark of migraine aura and has been recently described also in ATP1A2 mutated mice, Van den Maagdenberg 2024. It triggers downstream effects, including neuroinflammation and BBB disruption. In AHC, similar depolarization phenomena, stemming from mutations in ion channel genes such as ATP1A3, may underlie the episodic neurological disturbances. These depolarizations could parallel the mechanisms seen in CSD.

Indeed, all these observations point out the possible involvement of the glymphatic system in AHC. Impaired glymphatic function can lead to the accumulation of neurotoxic substances and inflammatory mediators, exacerbating CSD mechanisms and neurological symptoms. In migraines, glymphatic dysfunction is linked to reduced clearance of excitotoxic and inflammatory molecules.¹⁴ In AHC, glymphatic impairment could contribute to prolonged post-episode recovery and neurodevelopmental sequelae.

Conclusion

The Muscular Acoustic Modulator (MAM) treatment has shown more than 80% in reducing the frequency and intensity of hemiplegic and dystonic episodes in a patient with alternating hemiplegia of childhood (AHC).

Follow-up at six months after the end of the first 12 months of MAM treatments showed continued improvement. At present, MAM treatments are continued about every 21 days.

We hypothesize that in our patient, the treatment would act by draining the cerebrospinal fluid, the liquid that surrounds and nourishes the central nervous system, with a mechanism of action through glymphatic system.

However, further large-scale studies are necessary to confirm these preliminary findings and to better understand the mechanisms underlying this therapeutic approach. Particularly, a study focused on the changes in glymphatic system drainage using the DTI-ALPS index¹⁵ and NfL dosage¹⁶ before and after MAM treatment of these patients will be

necessary to validate our hypothesis that the treatment's effect on their quality of life is due to the improvement of glymphatic drainage.

The potential benefit of MAM treatment in a patient with alternating hemiplegia of childhood (AHC) could represent a new frontier in the management of rare neurodegenerative and neurological disorders.

Disclosure

The authors report no conflicts of interest in this work.

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