American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2022; 23: e935349
DOI: 10.12659/AJCR.935349

Received: 2021.11.03
Accepted: 2022.01.09
Available online: 2022.01.29
Published: 2022.03.07

Adrenocorticotropic Hormone (ACTH)-Induced Dyskinesias in Infantile Spasms: A Video Case Report

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1 Ana C.S. Crippa
ABDEF 1 Dafne L. Bayer
ABCDEF 2 Luciana de Paula Souza
ABCDEF 3 Gustavo L. Franklin

1 Neurology Pediatric Unit, Universidade Federal do Paraná, Curitiba, PR, Brazil
2 Paraná Health Department – SESA, Curitiba, PR, Brazil
3 Department of Internal Medicine, Pontifical Catholic University of Paraná, Curitiba, PR, Brazil

Corresponding Author: Gustavo L. Franklin, e-mail: gustavolf_88@hotmail.com
Financial support: None declared
Conflict of interest: None declared

Case series
Patients: Male, 10-month-old • Male, 8-month-old • Male, 5-month-old • Female, 4-month-old
Final Diagnosis: ACTH-induced dyskinesias
Symptoms: ACTH-induced dyskinesias
Medication: —
Clinical Procedure: —
Specialty: Neurology

Objective: Rare disease

Background: Infantile spasms is an age-specific epilepsy syndrome that occurs during infancy and is characterized by tonic and/or flexor-extensor spasms, hypsarrhythmia on electroencephalography (EEG), and neurodevelopmental regression. Adrenocorticotropic hormone (ACTH) is considered one of the main therapies for the treatment of infantile spasms, but despite its great efficacy, it is still associated with potential adverse effects.

Case Reports: Four patients previously diagnosed with infantile spasms were treated with ACTH following the usual treatment regimen. All patients developed asymmetric, involuntary movements, with phenomenology characteristic of dyskinesia. The patients did not manifest loss of consciousness, and the EEG did not show epileptic activity during those episodes. In all cases, involuntary movements disappeared after the completion of the hormonal therapy.

Conclusions: The adverse effect of hormonal therapy in infantile spasms is not well known in the literature and could be mistaken as seizures, leading to inappropriate management.

Keywords: ACTH (1-37) • Dyskinesias • Long Term Adverse Effects • Spasms, Infantile

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/935349

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

Background

Infantile spasms, or West syndrome, is an age-specific epileptic syndrome that occurs during infancy and is characterized by tonic and/or flexor-extensor spasms, neurodevelopmental regression, and an interictal electroencephalographic pattern known as hypsarrhythmia [1]. Infantile spasms may be secondary to a variety of pre- or postnatal brain insults or occur in the absence of demonstrable brain abnormality [2,3].

Adrenocorticotropic hormone (ACTH) is considered one of the first lines of treatment, and although highly effective, it is associated with a number of potential adverse effects, including hypertension, metabolic abnormalities, osteoporosis, congestive heart failure, and cushingoid features [1,4]. It has been described that ACTH can reduce neuronal excitability in infantile spasms by 2 mechanisms of actions: first, by inducing steroid release, and second, by a direct, steroid-independent action on melanocortin receptors, which might give a framework to explain the established clinical effects of ACTH in the therapy of infantile spasms [5]. Movement disorders, such as as dyskinesias, have rarely been described as adverse events associated with ACTH therapy [6,7] and are characterized by movement disorders predominantly in the face, such as repetitive mouth opening and facial grimacing, and limbs contraction and can be difficult to distinguish from spams [6,7].

We describe a series of 4 children diagnosed with West syndrome, treated with ACTH, and presenting with transient manifestations of movement disorders time-locked with the treatment of ACTH.

Case Reports

Case 1

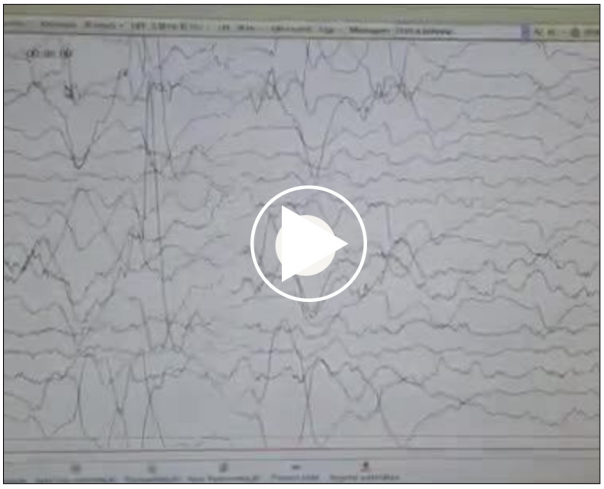
A 10-month-old boy, previously diagnosed with Down syndrome (DS), presented with a 1-month history of tonic spasms that were associated with sleep disturbance, psychomotor agitation, and loss of appetite. The mother reported that the patient had a normal perinatal history but recently lost the ability to smile in response to stimuli. Electroencephalography (EEG) confirmed a pattern of hypsarrhythmia, compatible with the diagnosis of infantile spasms. Brain magnetic resonance imaging (MRI) was unremarkable, as were the inborn errors of metabolism screening. This patient was initially treated with vigabatrin and had a partial response to the treatment. On clinical examination, the patient had periodic epileptic spasms, despite prior treatments (**Video 1**). Thus, ACTH treatment (0.5 IU/kg/day) was started for 3 weeks. After 10 days of hormone administration, the patient developed involuntary, dystonic, asymmetric, and asynchronous movements of the upper and lower extremities and perioral region (**Video 1**). In addition, the patient presented with episodes of upward eye movements that were interrupted by touch. There was no loss of consciousness during these events and they were not associated with any EEG abnormalities. Biperiden was used to control these movements, and the patient responded partially to this treatment. There was a progressive improvement of the spasms and complete resolution of the involuntary movements after 1 month of ACTH withdrawal.

Video 1. ACTH-induced dyskinesia manifested by repetitive tongue protrusion and choreoathetotic movements of the upper and lower limbs.

Case 2

An 8-month-old boy, hypotonic at birth and with neuropsychomotor delay, was diagnosed with malformations of cortical development during the neonatal period, compatible with cortical dysplasia. At 3 months of life, he started presenting clusters of epileptic spasms involving the upper and lower extremities at a frequency of 3 to 4 times a day and lasting approximately 5 min each. His EEG showed a pattern of hypsarrhythmia, and vigabatrin followed by valproate were given. There was a poor response to treatment, and thus, ACTH therapy was administered for 2 weeks at a dose of 0.5 IU/kg/day, which led to a marked clinical improvement and normalization of the EEG. However, the patient developed hypertension, and at approximately 7 days of treatment, dyskinetic movements involving mainly the face and featuring repetitive mouth opening and facial grimacing were seen. These involuntary movements were not associated with loss of consciousness. EEG disclosed no epileptiform discharges during these movements (**Video 2**). The facial dyskinesias responded well to treatment with diphenhydramine, and about 1 week after the discontinuation of ACTH, there was a complete remission of the symptoms.

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]



Video 2. Electroencephalography during events in patient 2, showing no specific epileptic activity.

Video 3. Repetitive cervical torsion and abduction and adduction of the upper limbs.

Case 3

A 5-month-old boy with a history of right focal seizures received treatments of many antiepileptic drugs, including valproate, vigabatrin, and clonazepam, but showed poor response to these treatments. The mother explained that he had regression of the milestones already reached, such as tracking objects with his eyes. In addition, he was having frequent right-sided hemispasms, and the EEG showed a pattern of hemi-hypsarrhythmia. His brain MRI showed a right middle cerebral artery ischemic stroke. Based on these results, ACTH 0.5 IU/kg/day treatment was initiated. After approximately 4 to 5 days, the patient developed facial dyskinetic movements with repetitive mouth opening, facial grimacing, and asymmetrical movements of the upper limbs (**Video 3**). These involuntary movements were not associated with epileptiform discharges on EEG. These movement disorders were also transient, disappearing in less than 1 week after the discontinuation of hormonal therapy.

Case 4

A 4-month-old girl was referred to our service due to an abnormal brain MRI that showed microcephaly and periventricular calcifications, secondary to congenital cytomegalovirus infection. She developed seizures, and phenobarbital (2.5 mg/kg/day) was administered; she had a good response to the treatment. However, during the second month of follow-up, the patient presented with developmental delay, epileptic spasms, and hypsarrhythmia on the EEG, leading to the diagnosis of infantile spasms. Vigabatrin was given, but there was no improvement in her condition. ACTH (0.5 IU/kg/day) was then administered. After 4 days of treatment, she presented with involuntary, asymmetric dyskinetic movements involving the face and upper and lower extremities (**Video 4**), which were controlled with diphenhydramine. Hormone treatment was continued for a total of 3 weeks. Dyskinesias progressively decreased and disappeared completely within 4 weeks.

Video 4. Asymmetric dyskinetic movements involving the face and upper and lower extremities.

Discussion

All patients in this case series presented with dyskinesia that started within 10 days after the start of ACTH treatment and completely resolved within a relatively short time after medication withdrawal. One patient had infantile spasms associated with Down syndrome, while the other 3 patients had infantile spasms due to malformation of cortical development, right middle cerebral artery stroke, and congenital cytomegalovirus infection associated with microcephaly and periventricular calcifications, respectively. Treatment of infantile spasms with ACTH was successful in all patients, despite the dyskinesias.

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

There was a partial response to treatment of these dyskinesias with diphenhydramine in 3 patients and with biperiden in 1 patient, but the symptoms only disappeared after the discontinuation of the hormonal treatment.

The pathophysiology of ACTH-induced dyskinesia is still not clear, and it is speculated that it might share the same mechanisms as the classic tardive dyskinesia [7]. In this case, hyperkinetic movements might arise from a reduced inhibitory outflow of the basal ganglia due to an improper modulation, among other mechanisms [8]. Since there was the primary objective of treating infantile spasms in our cases, we tried at first to not suspend the steroid treatment and attempted to control dyskinesia symptomatically, using empirically medications classically used for the treatment of tardive dyskinesia. The symptomatic improvement described, however, lacks better scientific support.

Prior studies have also reported ACTH-induced movement disorders. Sukhudyan et al [6] described 10 patients receiving steroid treatment who presented with hyperkinetic movements as repetitive mouth opening and facial grimacing, similar to the findings in our cases. Five of them had movements of adduction and abduction of upper and lower limbs, in addition to periodic strabismus. The authors speculated that epileptic spasms play an important role in the development of dyskinesias by activating neuronal circuits that involve the brainstem and putamen, and this activation can facilitate the appearance of movement disorder with the steroid treatment [6]. Arita et al [7] reported 1 patient that had improvement of infantile spasms after the third dose of ACTH but developed dyskinetic movements with arm elevation and tongue protrusion on the seventh day of this treatment. ACTH-induced dyskinesia was suspected, and the clinical picture of movement disorder progressively subsided within 2 months after discontinuation of the hormonal therapy [7]. Likewise, the patients in this report presented with dyskinesias in a time-locked manner when hormonal therapy was initiated and resolved with discontinuation of the treatment.

Although all patients in this study received vigabatrin prior to treatment with ACTH, it is not clear whether there was a synergistic effect with the use of ACTH. However, in the cases described, the onset of dyskinesias had a temporal relationship with the ACTH use but had no chronological relationship with the beginning and suspension of vigabatrin. Vigabatrin is associated with reversible changes in the brain MRI-signal intensity in 22% to 32% of pediatric patients with infantile spasms [9]. Dill et al [10] reported 2 infants with involuntary dystonic limb extension, low-frequency tremors, and athetosis seen after a few months of vigabatrin treatment. These patients had improvement of symptoms after the discontinuation of the medication [10]. In our report, brain MRI was unremarkable in all patients, but unfortunately, it was not possible to perform brain MRI exactly at the beginning of the symptoms, but only after discontinuation of the drug. Both vigabatrin and ACTH could possibly lead to the onset of dyskinesias, and the concomitant use could lead to an interesting synergistic effect; understanding this effect is of extreme clinical importance.

Conclusions

Dyskinesias are rare adverse effects of steroid treatment in patients with infantile spasms. In this case report, we described 4 cases that might help to differentiate these events from spasms. An accurate diagnosis is essential to avoid taking a wrong approach, since the treatments would be carried out in totally opposite directions.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

References:

1. MacKay MT, Weiss S, Adams-Webber T, et al. Practice parameter: Medical treatment of infantile spasms: Report of the American Academy of Neurology and the Child Neurology Society. Neurology. 2004;62:1668-81
2. Paciorkowski AR, Thio LL, Dobyns, WB. A genetic and biologic classification of infantile spasms. Pediatr Neurol. 2011;45(6):355-67
3. Pavone P, Polizzi A, Marino SD, et al. West syndrome: A comprehensive review. Neurol Sci. 2020;41(12):3547-62
4. Antoniuk SA, Bruck I, Spessatto A, et al. West syndrome: Clinical and eletroencephalographic follow up of 70 patients and response to the adrenocorticotropic hormone, prednisone, vigabatrin, nitrazepam and valproate. Arq Neuro-Psiquiatr. 2000;58(3):683-90
5. Brunson KL, Avishai-Eliner S, Baram TZ. ACTH treatment of infantile spasms: Mechanisms of its effects in modulation of neuronal excitability. Int Rev Neurobiol. 2002;49:185-97
6. Sukhudyan GB, Dimova PS, Capuano A, Vigevano F. Dyskinesia as a new adverse effect of hormonal treatment in West syndrome. Epileptic Disord. 2014;16(1):5-12
7. Arita JH, Vale TC, Pedroso JL, et al. ACTH-induced dyskinesia in a child with West syndrome (infantile spasms). Parkinsonism Relat Disord. 2016;24:145-46
8. Waln O, Jankovic J. An update on tardive dyskinesia: From phenomenology to treatment. Tremor Other Hyperkinet Mov. 2013;3:tre-03-161-4138-1
9. Wheless JW, Gibson PA, Rosbeck KL, et al. Infantile spasms (West syndrome): Update and resources for pediatricians and providers to share with parents. BMC Pediatrics. 2012; 12:108
10. Dill P, Datta AN, Weber P, Schneider J. Are vigabatrin induced T2 hyperintensities in cranial MRI associated with acute encephalopathy and extrapyramidal symptoms? Eur J Paediatr Neurol. 2013;17(3):311-15

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]