Seizure: European Journal of Epilepsy 67 (2019) 38–39

Contents lists available at ScienceDirect

Seizure: European Journal of Epilepsy

journal homepage: www.elsevier.com/locate/seizure

Clinical letter

Improving post-hypoxic myoclonus using cannabidiol

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ARTICLE INFO

Keywords:
Cannabis
Dronabinol
Lance-Adams syndrome
Seizure
Epilepsy

1. Case report

A 60-year-old male patient presented to our hospital with treatment-resistant post-hypoxic myoclonus secondary to cerebral anoxia. He had experienced a myocardial infarction complicated by cardiac arrest at the age of 54 years. Spontaneous return of circulation was achieved after 35 min of cardiopulmonary resuscitation. Subsequently, he developed bilateral myoclonic seizures and generalised tonic-clonic seizures supporting a diagnosis of Lance-Adams syndrome (LAS).

Our patient's neurological status was characterised by disorientation in time and place as well as psychomotor retardation. He showed intermittent myoclonus of the extremities aggravated by action and intentional movements. Non-invasive long-term video electroencephalographic (EEG) monitoring showed generalised spikes and poly-spike discharges, with a central maximum located at electrode Cz (10–20 system). While jerk-locked EEG back-averaging was not performed, the myoclonic seizures were hence considered to be of a cortical origin. Initial treatment of LAS with valproate (VPA) produced considerable improvement of the patient's myoclonus. However, VPA had to be discontinued due to the development of VPA-induced parkinsonism with dystonia. Gabapentin and clonazepam were then introduced. Clonazepam (up to 1.5 mg/d) had a certain antimyoclonic effect but dose escalation was associated with intolerable fatigue. Seizure freedom could not be achieved with a multitude of anticonvulsants, including levetiracetam (maximum daily dose [MDD] 1500 mg), brivaracetam (MDD 150 mg), zonisamide, lamotrigine, topiramate, pregabalin and eslicarbazepine. Gabapentin worsened the patient's expressive speech and caused hypersalivation. Topiramate was intolerable due to nausea and vomiting. Lamotrigine and zonisamide were intolerable because of skin rashes. Piracetam (MDD 2400 mg) did not exhibit a noticeable antimyoclonic effect. Pregabalin and eslicarbazepine had little effect on seizures. According to the patient's wife, Brivaracetam worsened the myoclonus. Perampanel was used with a MDD of 8 mg with good antimyoclonic effect; however, ultimately the drug was not tolerated at this dose due to the patient's aggressive behaviour. Dronabinol (delta-9 tetrahydrocannabinol [delta-9 THC]) was administered (up to 30 drops/d, equivalent to 26.3 mg/d), but with little therapeutic success.

On admission, the patient presented with bilateral central facial paresis and tetraparesis of the extremities as well as marked dysarthria, cerebellar ataxia, and dystonic movements of the extremities. Current anticonvulsant polytherapy consisted of levetiracetam 500 mg/d, piracetam 2400 mg/d, perampanel 2 mg/d or 4 mg/d on alternate days and clonazepam 2 mg/d. In addition, he received 20 drops/d (equivalent to 17.5 mg/d) of dronabinol (delta-9 THC). We discontinued dronabinol and started cannabidiol (CBD), which was increased over four days to 750 mg daily, corresponding to 12.5 mg kg of bodyweight per day. Perampanel was reduced to 2 mg/d further to ameliorate the aggression present at admission. Upon uptitration of CBD, the myoclonic jerks improved substantially. The patient did not show any adverse effects during dose increase or maintenance of CBD. A follow-up with the patient's primary caregiver three weeks later revealed sustained improvement of myoclonus, and the patient was able to resume his regular physiotherapy.

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https://doi.org/10.1016/j.seizure.2019.03.003
Received 7 September 2018; Received in revised form 3 March 2019; Accepted 5 March 2019

2. Discussion

Chronic post-hypoxic myoclonus or LAS is a common consequence of transient cerebral anoxia. It is characterised by myoclonic jerks that are movement- and stimulus-induced and often medically intractable [1]. James W. Lance and Raymond D. Adams first described LAS in "The Syndrome of Intention or Action Myoclonus as a Sequel to Hypoxic Encephalopathy." in *Brain* (1963;86:111-136). At times, it must be differentiated from acute post-hypoxic myoclonus (cortical myoclonic status epilepticus or subcortical status myoclonus), which may be seen in comatose patients. LAS usually presents when patients regain consciousness but can also appear within hours after cerebral hypoxia, making a distinction from acute post-hypoxic myoclonus difficult in usually patients treated with sedatives and analgesics in the intensive care unit. The pathophysiological basis of LAS is not well-understood: LAS can either be of cortical or subcortical origin and is characterised by chronic myoclonic jerks and cerebellar dysfunction, while other neurologic functions may remain intact [2]. It is frequently hard to control with anticonvulsive medication. Due to the rarity of LAS, no evidence-based treatment guidelines exist for the use of anticonvulsant drugs in patients with this condition [2]. Several anticonvulsants—including levetiracetam, VPA, zonisamide, and benzodiazepines such as clonazepam—have been shown to reduce myoclonic jerks, and new AEDs such as lacosamide, perampanel, and brivaracetam have been described in case reports as effective. Other medications such as piracetam or agomelatine have also been associated with a favourable effect.

CBD is a cannabinoid that occurs naturally in cannabis plants. While the exact mechanism of action of CBD in epilepsy is unclear, it is unlikely that CBD has a meaningful effect on the CB_1 and CB_2 cannabinoid receptors. Suggested modes of action include an antagonist function on the orphan G-protein-coupled receptor (GPR 55) in the thalamus [3]. Effects in voltage-gated sodium and calcium channels have also been suggested as a mode of action in epilepsy [3]. CBD restored the pathological excitability of hippocampal neurons in a rat kainate model of epilepsy [4]. CBD also acts as an agonist on the serotonin ($5\text{-}HT_{1A}$) receptors [3]. Interestingly, a positive effect of serotonin agonists has been described in a rat model of post-hypoxic myoclonus. CBD is currently approved by the US Food and Drug Administration for the treatment of Lennox-Gastaut syndrome and Dravet syndrome. The exact mechanism of action is unclear, and there is a substantial interaction that may occur with clobazam, topiramate, rufinamide, zonisamide, and eslicarbazepine. The interaction with clobazam may account for some of its action in patients treated with these drugs when introducing CBD.

Conflicts of interest

J.P. Zöllner received speaker's fees from Eisai.

A.H. Noda has no conflict of interest to disclose.

F. Rosenow reports personal fees from Eisai, UCB, Desitin Arzneimittel, Novartis, Medtronic, Cerbomed, Sandoz, GW-Pharma, BayerVital and Shire, grants from the European Union, Deutsche Forschungsgemeinschaft and the Detlev-Wrobel-Fonds for Epilepsy research.

A. Strzelczyk reports personal fees and grants from Desitin Arzneimittel, Eisai, GW pharma, LivaNova, Medtronic, Sage Therapeutics, UCB Pharma and Zogenix.

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