Epilepsy & Behavior Reports 13 (2020) 100354

Contents lists available at ScienceDirect

Epilepsy & Behavior Reports

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

Case Report

Reduction in seizure frequency with a high-intensity fitness program (CrossFit): A case report

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ARTICLE INFO

Article history:
Received 11 July 2019
Received in revised form 7 December 2019
Accepted 14 December 2019
Available online 20 December 2019

Keywords:
Oligodendroglioma
High-intensity exercise
Focal seizures
Ketosis
Ketogenic diet

ABSTRACT

Few studies have reported the impact of intensive exercise on seizure susceptibility. Here, we present a case in which a patient developed drug-resistant focal epilepsy after craniotomy for a low-grade glioma. She had a marked reduction in seizure frequency after switching from moderate exercise to a high-intensity exercise program. Psychological benefits of exhaustive exercise included decreased suicide ideation, in part mediated by fewer seizures.

1. Introduction

Whether exercise is helpful, harmful, or has no impact on the frequency of seizures has been debated for years. In the last few decades, clinical and animal studies have demonstrated positive effects of aerobic physical exercise on seizure frequency [1,2]. However, few studies have reported the impact of intensive exercise on seizure susceptibility. The ketogenic diet, which is high in fat, low in carbohydrates and adequate in protein, is considered an effective non-pharmacologic treatment for epilepsy [3,4]. It has a long history of use for seizure control in children with drug-resistant epilepsy, and there is evidence that it can reduce seizures in adults as well [5]. Ketone bodies are also produced with exercise [6]. Here, we present a case in which a patient with drug-resistant epilepsy on a low-carbohydrate, high-fat diet had a marked reduction in seizure frequency after switching from moderate exercise to a high-intensity exercise program.

2. Case

A female in her 40s was admitted to the hospital after a generalized tonic–clonic seizure. A computed tomography (CT) scan and magnetic resonance imaging (MRI) revealed a focal lesion within the left frontal lobe, extending to Broca's area and consistent with a glioma. The patient was discharged on levetiracetam 1000 mg/day. She did not have any seizures between the time of diagnosis in March 2016 and prior to her craniotomy for tumor resection in July 2016 (Fig. 1). The approximate tumor volume reduction was 57% (assuming the tumor was spherical) (Fig. 2). Tissue samples from the tumor indicated an oligodendroglioma. Molecular markers were positive for the IDH1 mutation, retention of ATRX expression, and 1p/19q co-deletion.

In the recovery room following craniotomy and resection, the patient experienced several focal seizures. The patient continued to have focal seizures after she was discharged from the hospital, despite incrementally increasing the dosage of levetiracetam to 3000 mg/day. Semiologic features of her seizures include hyperkinetic facial movements, aphasia, production of involuntary sounds, difficulty breathing, and hypersalivation. Seizure duration was between 60 and 90 s. The patient had two electroencephalograms, one done shortly after surgery in August 2016 and one in May 2017. The findings from May 2017 suggested a potential epileptogenic focus over the left mid temporal region.

In August 2016, in addition to the maximum recommended dose of levetiracetam, the patient began taking 200 mg/day of cannabidiol (CBD). The patient developed suicide ideation within a month of her craniotomy but did not meet the criteria for a depressive disorder. She was prescribed clonazepam 0.5 mg/day for anxiety but stopped taking it of her own accord 12 days after her first dose. In January 2017, her

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https://doi.org/10.1016/j.ebr.2019.100354

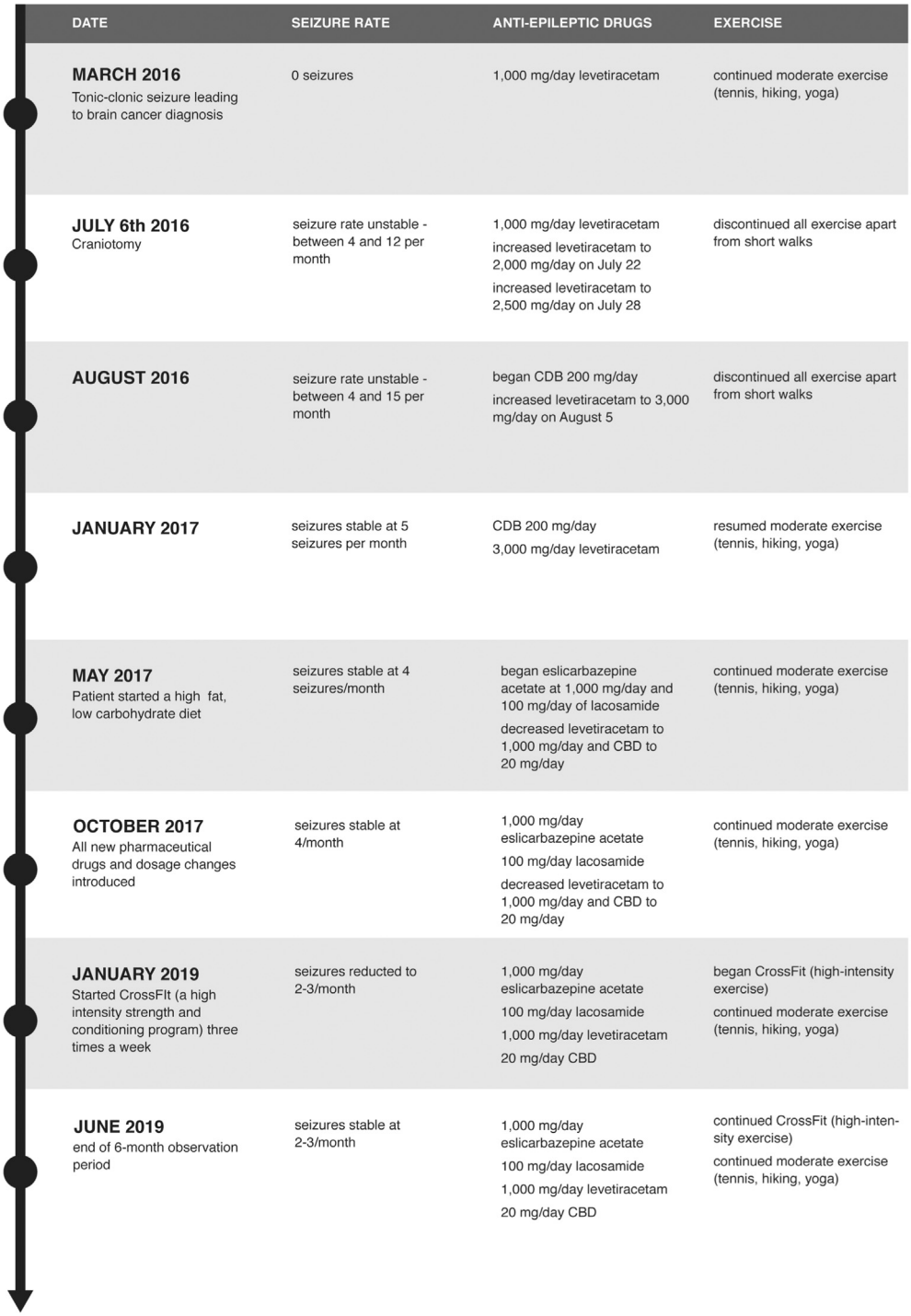

Fig. 1. Seizure frequency, anti-epileptic drugs and exercise regime.

seizure frequency reduced from between six and 14 seizures a month to a stable rate of five per month. Prodromes lasting days, together with exhaustion and severe headaches during the postictal state, forced her to discontinue working after surgery.

In May 2017, concomitant with her antiseizure drugs (ASDs), she began a low-carbohydrate, high-fat diet to induce ketosis, measured by regular urine ketone analysis. Between May 2017 and December 2018, the patient experienced a median of four seizures per month. During this time, she began eslicarbazepine acetate at 1000 mg/day and 100/mg of lacosamide per day. She decreased levetiracetam to 1000 mg/day and CBD to 20 mg/day. All new pharmaceutical drugs and dosage changes were introduced before October 2017 (Fig. 1). None of the drugs taken at the dosage specified had an effect on her seizure frequency. In total, she was taking three ASDs at consistent dosages in addition to CBD for 15 months before she began high-intensity exercise. She continued taking these same ASDs at the same dosages for the 6-month period after initiating high-intensity exercise. Before she began high-intensity exercise, her exercise routine included tennis, hiking, yoga and working out three times a week using at-home fitness videos. She was active before her craniotomy and resumed her level of exercise activity within six months of surgery.

In January 2019, she began attending high-intensity fitness classes known as CrossFit three times a week. CrossFit is a strength and conditioning program consisting of constantly varied, high-intensity,

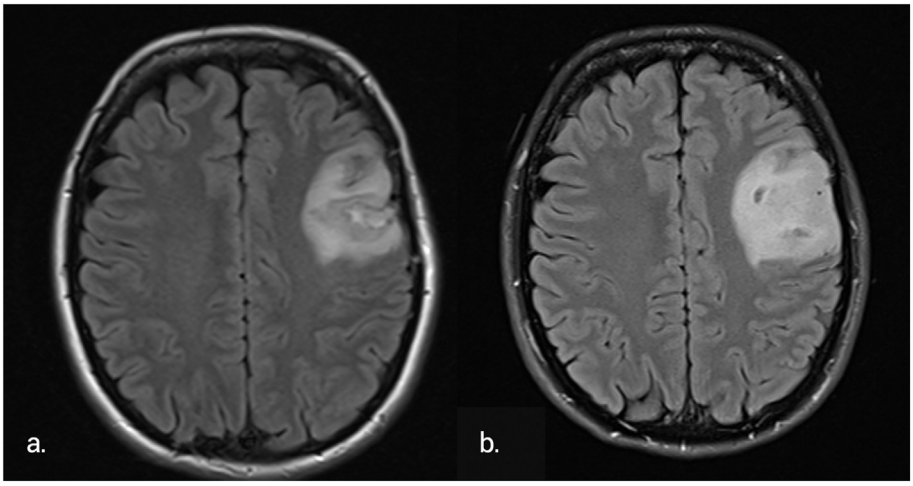

Fig. 2. a. Pre-operative* image of the tumor (May 6th, 2016) and b. post-operative image of the tumor (August 26th, 2016). *date of surgery: July 5, 2016.

functional movements [7]. It draws from aerobic exercise, olympic weightlifting, calisthenics, and gymnastics. Classes are 60 min and vary in their regime, although they are based on foundational movements. Each class consists of a warm-up including stretching, a technical component, and a high-intensity work-out. Table 1 presents examples of CrossFit work-outs (Table 1). The month that she began CrossFit, she had the longest duration between seizures (16 days) since her craniotomy, which was followed by another 16-day interval between seizures. She had 23 seizures in the six months prior to starting CrossFit, that is, during the period of her previous level of exercise activity, and 16 seizures in the six months after starting CrossFit (Fig. 3). Over six months, her seizure frequency decreased by 33%. None of her seizures occurred during CrossFit classes or during the first one to five minutes of the recovery period. Her seizure duration and intensity did not significantly change after she started high-intensity exercise, except that she was able to breathe more easily during a seizure, whereas previously, she had difficulty breathing during most seizures. Hours after a CrossFit class, her urine ketones measured between 4.0 and 8.0 mmoL/L, whereas on a low-carbohydrate, high-fat diet alone, they measured in the range of 0.5–4.0 mmoL/L. With the reduction in seizure frequency, her quality of life improved, suicide ideation decreased, and she felt able to return to work on a flexible, part-time basis. Improvement in her quality of life may in part have been related to exercise-induced increases in beta-endorphins and positive changes in mood [8,9].

3. Discussion

When the patient started a low-carbohydrate, high-fat diet in May 2017, the frequency of her seizures had been stable at five per month for four months. It is unknown whether the decrease in seizure frequency after initiating the diet was likely attributable to the diet or to other factors. Attenuating factors include that she initiated the high fat, low-carbohydrate diet within a year of her craniotomy, a period in which postoperative seizures may decrease with time [10]. She also started a third anti-epileptic drug within four months of starting the diet. Also, the comparison period of consistent monthly seizure frequency was shorter before introduction of the diet (four months) than before the introduction of high-intensity exercise (19 months). Finally, the reduction in seizure frequency during the diet was smaller (20% reduction in monthly seizure frequency) compared to the reduction she experienced after starting high-intensity exercise classes (33%).

Studies on the effect of moderate exercise on seizure frequency in individuals with drug-resistant epilepsy have been mixed. One before-and-after study involving women showed a decrease in seizures during a 3-month exercise program compared to the period before the program [2]. In this report, 60-min exercise classes were conducted twice a week for 15 weeks and included aerobic dancing and strength training [2]. Out of 15 enrolled participants, 13 participants' data were analyzed using a Wilcoxon matched pairs test ($p < .02$) [2]. Participants' seizure frequency increased after they had stopped the exercise program, suggesting the effects of the program were transient [2]. Another before-and-after study and a small randomized controlled trial failed to demonstrate an effect of exercise on seizure frequency [11,12]. Irrespective of whether the studies showed an effect, they all indicated that exercise had psychological and social benefits, such as improvements in mood [2,11,12].

Interestingly, our patient did not experience a reduction in seizure frequency with regular exercise but did with high-intensity exercise, which has been understudied in drug-resistant epilepsy. In Brazil, individuals with temporal lobe epilepsy were evaluated to determine whether intense exercise induced seizures during exercise, but the effect on seizure frequency over time was not examined [13]. Subsequent studies evaluating cardiorespiratory and electroencephagraphic responses to exhaustive exercise in people with temporal lobe epilepsy and juvenile myoclonic epilepsy also did not report seizures during or after physical exertion [14] [15]. One of these studies demonstrated a decrease in the number of epileptiform discharges during the recovery period after acute exhaustive exercise [15]. In animals with epilepsy submitted to a maximum O_2 uptake test, no seizures were detected during the maximum test performed before and after the exercise training period [16]. To our knowledge, no other human studies and very few animal studies have been done on the effect of high-intensity exercise on seizure control. One animal study demonstrated that strength training is protective against seizures in rats over a 30-day period compared to a control group [17]. Strength training is a key component of the CrossFit program.

Table 1
Examples of CrossFit work-outs.

Example 1	Example 2	Example 3
Complete as many rounds in 20 min as you can of: 5 pull-ups[a] 10 push-ups 15 squats	200 single skips 800 m run 45 cal on the rowing machine	4 rounds of: 200 m run 20 dumbbell push presses 20 sit-ups 250 m row on a rowing machine

[a] All exercises can be scaled e.g. the patient was unable to do pull-ups, but modified the exercise using a band for support.

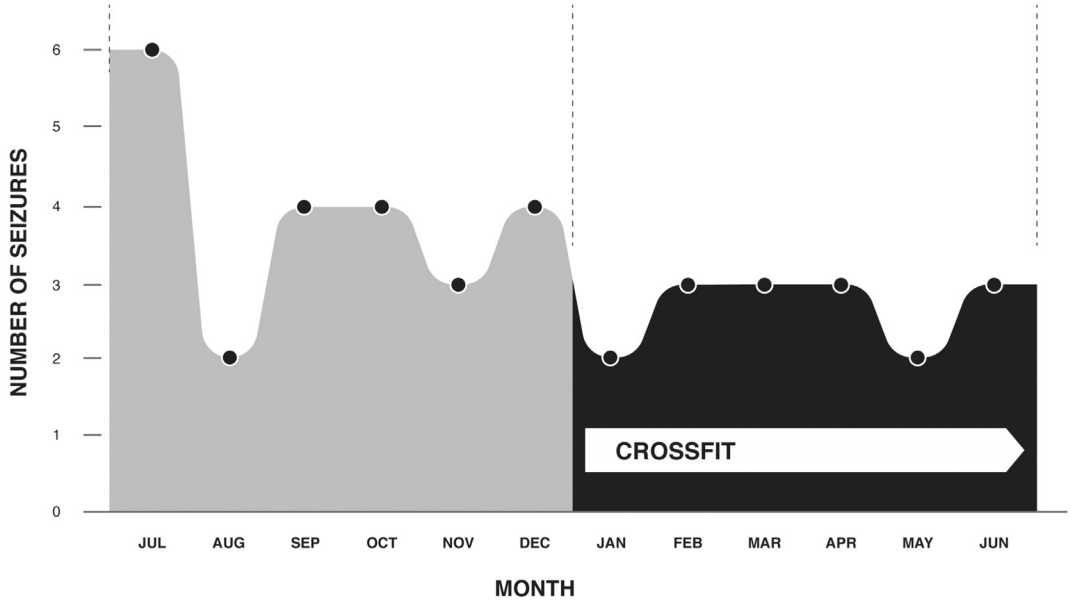

Fig. 3. Seizure frequency in the 6-months before and 6-months after intensive exercise.

Despite the lack of human and animal studies on whether high-intensity exercise has a protective effect against seizures, several biological mechanisms have been proposed. These include decreases in pH of the blood ultimately resulting in increases in gamma-aminobutyric acid (GABA) concentration in the brain; increases in adenosine after intense but not moderate exercise, and changes in the metabolic rates in certain brain structures associated with increased attention and alertness required to do intensive exercise [18].

Numerous studies of the ketogenic diet and its variants as a treatment for drug-resistant epilepsy have been conducted, and several mechanisms of action have been proposed [19]. These include the potential anticonvulsant effects of ketone bodies and the role of chronic ketosis. Ketone bodies are also produced during intense exercise [6]; however, their potential role in seizure control has not been examined within the context of high-intensity exercise. In the case of our patient, her seizure frequency was reduced with a high-fat, low-carbohydrate diet, but she experienced a larger decrease in seizures after she started high-intensity exercise. Although her urine ketones increased on the days that she attended high-intensity exercise classes, it is unknown whether the ketone bodies were responsible for her reduced seizure frequency, or exercise-associated changes in neuronal metabolism, or perhaps another mechanism. A limitation of this case study includes the type of drug-resistant epilepsy the patient developed after craniotomy was a different phenotype from more common lesional epilepsy syndromes. Further limitations include that this study is a single case report with a retrospective bias, and its application may be limited to other non-brain-tumor patients.

4. Conclusion

This case supports a positive effects of diet and high-intensity exercise in patients with drug-resistant epilepsy, including psychological benefits such as decreased suicide ideation. It is the first report of a reduction in seizure frequency associated with high-intensity exercise in a human being and adds to the limited evidence on non-medical treatments for brain tumor patients with drug-resistant focal epilepsies. Whether there is a synergistic effect between a high-fat, low-carbohydrate diet and high-intensity exercise is unknown; the potential beneficial effects of high-intensity exercise in people with epilepsy warrants further study.

Acknowledgements

We would like to acknowledge Dr. Gurdev Parmar for introducing the patient to the ketogenic diet and Dr. Moein-Afshari for his assistance in writing this report.

Declaration of competing interest

The primary author of this manuscript is the patient described in the report. Professors Ekström and Arida have no interests to declare.

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