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Short Communication

Serendipity Can Rule the Day: Remarkable Efficacy of a Mushroom Extract Powder in Childhood Treatment-Resistant Epilepsy

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ABSTRACT

Introduction: The goal of this report is to highlight an unanticipated effect of medicinal mushroom supplement in reducing seizures in a child.
Methods: A detailed case report and literature review.
Results: Medicinal mushroom extract supplementation resulted in a sustained 98% reduction in seizure frequency three years after initiation.
Discussion: This case report provides details of the child's case and reviews the limited literature related to medicinal mushroom therapy for epilepsy with the intent to stimulate interest in more detailed study of medicinal mushroom compounds for the treatment of treatment-resistant epilepsy.

Introduction

It is estimated that one third or more of children with early-onset epilepsy prove to be refractory to pharmacologic therapy.[1] Commonly accepted potential treatments for these individuals include resective surgery, neurostimulation, vagus nerve stimulation, and dietary therapies including ketogenic diet and variations thereof. We present a case of a young child with longstanding treatment-resistant epilepsy and intellectual disability whose parents elected to trial a commercially available mushroom extract to see if it might improve her cognition, communication, and hyperkinetic behavior. Treatment with this produced a dramatic and sustained reduction and near elimination of seizures as detailed in the case description below.

Case

A 10-year-old female was born at term by uneventful vaginal birth to a 35-year-old mother. Parents are not consanguineous with European/Ashkenazy ancestry. Physical and neurological examinations were normal including growth parameters. At age seven weeks she experienced her first seizure described as facial and head twitching to one side followed by bilateral arm twitching with bicycling motions of her legs and impaired responsiveness. Evaluation included a routine electroencephalography (EEG), which showed a left parietal-onset focal seizure on an otherwise normal background. Diagnostic evaluation was unremarkable and unrevealing, including two 3T brain magnetic resonance imaging scans, magnetic resonance spectroscopy, standard blood chemistries, normal plasma amino acids, urine organic acids, plasma acyl carnitine assay, blood lactic acid, cerebrospinal fluid protein, glucose and cell count, cerebrospinal fluid neurotransmitter assay, lactate and pyruvate, chromosome analysis including comparative genomic hybridization oligoarray, POLG1 gene sequencing assay, epilepsy gene panel, and whole exome gene sequencing (including reanalysis three years after the initial whole exome sequencing).

Sequential unsuccessful or transiently beneficial therapies included levetiracetam >100 mg/kg/day, pyridoxine, biotin, topiramate, oxcarbazepine, clobazam, lacosamide, low-glycemic-index diet, cannabidiol, valproate, and lamotrigine (LTG). Vagus nerve stimulation was associated with a dramatic increase in seizures including very frequent total body drop seizures, averaging dozens per day. Vagus nerve stimulation therapy was discontinued after three to four weeks, and her seizure frequency returned to baseline.

In May 2021, at age seven years, a two-day video-EEG study was performed with dose reduction of LTG monotherapy. This study found her to have several electroclinical myoclonic seizures in sleep

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and one electroclinical clonic nonlateralized seizure in sleep. Interictal findings included recurrent generalized 2-4-Hz spike or polyspike-and-wave complexes, rare independent left- or right-sided frontal sharp waves in sleep, and slow posterior dominant rhythm with mixed symmetric or asymmetric delta/theta irregular slowing in the left more than right frontotemporal regions. There was no pattern of slow spike-wave and no generalized paroxysmal fast activity. In addition, there were a few paroxysmal clinical events with abrupt arrest of play behavior, forward trunk flexion with slight jerking motion, smiling with opened mouth, intermittent soft laughter, and variation in response to voice, touch, or gesture lasting two to five minutes, not followed by postictal somnolence. No clear EEG seizure pattern was discerned with these events; however, parents had previously seen these abrupt clinical features progress to bilateral tonic-clonic convulsion. No such progression was seen in that study. These events were judged to be likely a scalp EEG negative epileptic focal aware/unaware seizure phenomenon.

A repeat 3T brain magnetic resonance imaging scan with seizure protocol and focused views of the hypothalamus did not show a hypothalamic hamartoma or any subtle focal cortical dysplasia or other malformation of cortical development.

At age 7.5 years her mother wished to try giving her mushroom extract powder, since she herself noted that this mushroom extract powder (product name: Sacred 7) seemed to help her own alertness, mental processing, and mood. Three months after the above video-EEG study, mother commenced providing her with ½ teaspoon three times daily of a mushroom powder extract. Initially mother added the powder to foods, and later she utilized the same amount of power in capsule form three times daily. This regimen provided to her 429 mg/day of each of the following types of mushroom extracts: chaga (*Inonotus obliquus*), cordyceps (*Cordyceps militaris*), lion's mane (*Hericium erinaceus*), maitake (*Grifola frondosa*), reishi (*Ganoderma lingzhi*), shiitake (*Lentinula edodes*), and Turkey tail (*Trametes versicolor*). (Mushroom fruiting bodies utilized in this preparation marketed as Naturealm Sacred 7 are stated to be tested by a third-party laboratory to verify the content and purity). There was no initial modification of the current antiseizure therapy, which consisted of LTG 625 mg/day with associated random blood level of 14 mg/dL.

In the preceding two years seizures had variable frequency ranging from three to five per day up to 50 per day. The seizure semiologies described included nonconvulsive presumed focal impaired awareness seizures with behavioral arrest and staring, presumed focal unaware seizures with or without left or right tonic or clonic face or limb motor activity, bilateral tonic seizures, or myoclonic seizures. In the few months before having begun mushroom extract supplement, the child was having three to five seizures per day lasting 30-60 seconds with postictal changes including somnolence, fatigue, or cessation of prior play activities for 10-30 minutes. For the first two months no seizures of any type were observed by the family. Subsequently, once when she had a viral illness and missed several doses of the extract, she had a tonic-clonic convulsion, which stopped promptly with intranasal rescue diazepam. Subsequently there have been only brief seizures lasting 5-15 seconds with behavioral arrest and unilateral or bilateral twitching of limbs and face often triggered by pungent odors in her environment. These seizures have occurred at a frequency of one to two seizures approximately every two months. No subsequent video-EEG recording has been judged necessary to assess any electroclinical changes.

Although she did not have symptoms of LTG toxicity, the dosing of LTG was gradually reduced from 625 mg daily to 200 mg twice daily. She continues that dosing regimen now at the time of this report. On this dose of LTG blood levels performed 12, 15, 24, and 40 months after initiation of the mushroom extract ranged from 7-11 mg/dL. She had no insomnia, nausea, vomiting, jaundice, diarrhea, or other concerning systemic symptoms. A complete blood cell count with differential and comprehensive chemistry panel including hepatic function profile was normal when checked 12 and 40 months after commencing mushroom extract supplementation. Her parents emphasized that the medicinal mushrooms compound was completely life changing for the child's condition. Although they hoped that her cognition might improve with the mushroom extract supplement, they had not anticipated it to be associated with such a dramatic reduction in her seizures. This dramatic reduction has persisted now more than three years after supplementation began.

No formal cognitive testing measures were performed at baseline and after supplement began. Her special education teacher remarked to parents one year after the supplement began that they noted substantial improvements in her attention, demeanor in class, and skill acquisition.

Discussion

When epilepsy treatments fail to achieve seizure cessation or major reduction with standard antiseizure medications options to pursue for this purpose included resective epilepsy surgery in appropriate situations, dietary therapy with ketogenic or low-glycemic-index diet, and neuromodulation with vagus nerve stimulation, deep brain stimulation, or responsive neurostimulation. On the horizon are prospects of gene therapy for intractable epilepsies caused by monogenic mutations in a variety of severe childhood-onset epilepsies.[2] When standard therapies have been unsuccessful or not applicable in electroclinical, imaging, and genetic contexts patients and families will often turn to complementary therapies.

A decade ago there was a widespread report of a child with Dravet syndrome who had an SCN1A mutation having a marked reduction in seizure frequency with the use of an artisanal cannabis product.[3] This report prompted further medical and scientific pursuit of detailed exploration of the benefits, pharmacodynamics, and adverse effects of medicinal cannabis for therapy of epilepsy. Several years later toxicologic, pharmacologic, and safety and efficacy human trials in specific epileptic disorders resulted in US Food and Drug Administration approval of cannabidiol for the treatment of epilepsy in patients with Dravet Syndrome, Lennox-Gastaut Syndrome, and Tuberous Sclerosis Complex. Treatment with cannabidiol, either the commercial product or artisanal product, is widely used by physicians and patients today.

For our patient the use of this mixed mushroom extract has produced an enduring similar drastic reduction in seizures with concomitant improvements in parent- and teacher-reported behavior and cognition, without apparent side effects. Which of the seven mushroom extracts listed above has been the most important in this effect is not known. The mechanism of action in reducing neuronal excitability and seizures of each of these extracts has not been clearly delineated, but some data have emerged in this regard.[4]

What is the possible mechanism by which our patient had such a remarkable reduction in seizures with this supplement? Review of the published literature reveals a paucity of studies attempting to answer this question and only one clinical case series of use of one of the extract types in a case series of humans with epilepsy (See Table).

Several of the above mushroom extracts, however, have shown *in vitro* evidence of immunomodulatory properties, antioxidative features, and anti-inflammatory and immune cell effects that may

TABLE.
Published Studies of Antiseizure/Antiepileptogenic Effects of Mushroom Extracts

Mushroom Extract Type, Species Name, Common Name, (Reference #)	Neuroprotective or Antiseizure Effect in Animal Seizure Models	Reduction in Inflammation in Animal Traumatic Brain Injury Model	Seizure Reduction in Human Epilepsy (Case Series)	No Published Animal Model Studies of Neuroprotection, Seizures, or Epileptogenesis	No Published Studies in Humans with Epilepsy
Hericium erinaceus Lion's mane[5]	x				x
Ganoderma lucidum/lingzhi Reishi[6-9]	x		x		
Cordyceps militaris Cordyceps[10]		X			x
Grifolia frondosa Maitake				x	x
Inonotus obliquus Chaga				x	x
Lentinula edodes Shiitake				x	x
Tramites versicolor Turkey tail				x	x

be relevant in mitigating epileptogenesis via immune-mediated processes.[11-15]

At the time the mushroom extract supplements were provided to this girl the only daily antiseizure medication utilized was LTG. LTG blood levels were not increased over the time of administration of the mushroom extract supplement in this child. LTG is metabolized in the liver via UDP-glucuronyl transferase, mostly UGT1A4 and less so via UGT2B7. CYP2A6 and CYP2D6 may play a very minor role in human clearance of LTG. The only extract in the supplement used that theoretically might increase the levels of drugs metabolized by CYP2D6 is the Shiitake extract.

In vitro studies suggest that the shiitake mushroom extract active hexose correlated compound might induce the CYP2D6 enzyme.[16] This effect has not been reported in humans, and no over the counter supplement-drug interactions with any of the mushroom extracts have been reported to impact any antiseizure medications. In our case the blood level measurements of LTG diminished as expected in association with the dose reduction instituted over time.

Thus a pharmacokinetic effect on her maintenance antiseizure medication is unlikely to be the key factor in the resulting beneficial effect on her seizures. We do not know if there is any synergistic pharmacodynamic effect of mushroom extract supplementation with LTG. Such pharmacodynamic effects on antineoplastic chemotherapy agents have been postulated for benefits seen when medicinal mushroom extracts are added to various regimens employed for treating a variety of human cancers.[17]

Unfortunately for this child no specific genetic etiology for her epilepsy and developmental impairment was discovered. Had a specific epilepsy gene mutation been identified such knowledge might assist future efforts to define particular epilepsy etiologies that may be more likely to benefit from the bioactive properties of the mushroom extracts contained in this medicinal mushroom compound.

Past surveys of patients suffering from treatment-resistant epilepsy indicate that up to one fourth of patients will use herbs or supplements, but only 30% of patients will report this to their neurologists.[18] Our patient's family has been forthright about the circumstances through which complementary therapy with commercial mixed mushroom extract product was initiated and which produced a far greater benefit than any other more standard pharmacologic, dietary, or minimally invasive neuromodulatory therapy had in the preceding eight years. We know that standard medical therapies fail to achieve seizure control in up to one third of persons with epilepsy and that adverse effects are common even when seizures are controlled. Despite the robust response to mushroom extract administration our patient experienced no identified adverse effects. Although this therapy worked well in the above case, we do not at this time advocate initiation of medicinal mushroom extracts as the sole therapy for children or adults presenting with epilepsy. We do endorse further study of mixed mushroom extracts or similar bioactive mushroom compounds in an effort to define better (1) what seizure types or epilepsy syndromes or even specific genetic epilepsy subtypes may respond, (2) how often 50% or greater seizure reductions are experienced by patients, and (3) what adverse effects may occur with their use.

The anecdotal reports of the impressive response of some patients with Dravet syndrome to therapy with botanical cannabidiol[3] resulted in evolution to widespread detailed investigation of this agent and ultimately landmark clinical trials of this botanical agent. Since then there has been widespread acceptance of use of both pharmaceutically regulated CBD product and artisanal CBD products by patients and providers. Such stories should compel us to keep an open mind about options pursued by our patients and their families. Maintaining solid physician-family therapeutic alliances can produce clear benefits for our patients and assist in moving neurotherapeutics forward over the coming years. We encourage ongoing systematic exploration into the potential benefits of therapies with what may prove to be relatively safe medicinal mushroom preparations.

CRediT authorship contribution statement

Olivia Kim-McManus: Writing – review & editing. **Sarah Boylan:** Writing – review & editing, Data curation, Conceptualization. **Mark Nespeca:** Writing – review & editing, Writing – original draft, Data curation.

Declaration of competing interest

The authors declare no conflict of interest or financial disclosures concerning the materials or methods used in this study or the findings specified in this article.

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