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Plant-induced seizures: reappearance of an old problem

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Abstract Several plant-derived essential oils have been known for over a century to have epileptogenic properties. We report three healthy patients, two adults and one child, who suffered from an isolated generalized tonic-clonic seizure and a generalized tonic status, respectively, related to the absorption of several of these oils for therapeutic purposes. No other cause of epilepsy was found, and outcome was good in the two adult cases, but the course has been less favorable in the child. A survey of the literature shows essential oils of 11 plants to be powerful convulsants (eucalyptus, fennel, hyssop, pennyroyal, rosemary, sage, savin, tansy, thuja, turpentine, and wormwood) due to their content of highly reactive monoterpene ketones, such as camphor, pinocamphone, thujone, cineole, pulegone, sabinylacetate, and fenchone. Our three cases strongly support the concept of plant-related toxic seizure. Nowadays the wide use of these compounds in certain unconventional medicines makes this severe complication again possible.

Key words Seizure · Epilepsy · Essential (plant, vegetable, volatile) oils · Terpene

Introduction

In the United States and in Europe there is an increasing popularity for unconventional medicines [1], including various herbal treatments known under the generic term of phytotherapy, from which aromatherapy, which uses essential oils (EOs) of plants, is derived. Contrary to their alleged safety, these substances may actually produce many and potentially serious side effects [2], notably on the central nervous system. Although the convulsive properties of several EOs have been known since the second half of the nineteenth century [3], this knowledge frequently escapes the present attention of most physicians and even of epileptologists. Based on three recent cases, we would like to recall the hazards related to the indiscriminate use of these herbal remedies, a problem being poorly recognized and underestimated, as recently suggested by the World Health Organization [4] and a rather alarming report from the United Kingdom's National Poisons Unit [5].

Cases description

Case 1

A healthy 54-year-old woman, without any risk factors for epilepsy, had taken a mouthful of sage EO weekly for several years as a supposed cure for hyperlipidemia. Shortly after each intake, in addition to gastric burning, she experienced a sudden feeling of faintness, profuse sweating, dizziness, and tachypnea. Symptoms receded after 10 min. One day after mistakenly taking a higher but undetermined dose, these adverse effects were particularly prolonged, intense, and associated with involuntary dystonic movements of the tongue. After 30 min she developed a typical generalized tonic-clonic seizure and remained unconscious for 1 h. Upon admission to hospital, neurological examination was normal, as were three electroencephalograms (EEGs) and cerebral computed tomography. Since discontinuing the use of the drug she has remained free of seizures for more than 3 years.

Case 2

A 53-year-old man, whose medical history was unremarkable except for general fatigue for the past several months, received a

dozen drops of sage EO as a stimulant from a coworker. After 20 min, following a short period of poorly defined but profound unease, he suddenly developed a generalized tonic-clonic seizure that was followed by a postictal coma lasting for 15 min. On admission he complained of diffuse muscle ache. Neurological examination was normal, as were two EEGs, cerebral computed tomography, magnetic resonance imaging, and CSF analysis. There was a severe but transient increase in muscle enzymes. Clinical follow-up over 2 years has been uneventful without medication.

Case 3

A 12-month-old healthy girl was given five prolonged baths containing an unknown quantity of EO of eucalyptus, pine, and thyme over a 4-day period for a benign and afebrile upper respiratory tract infection. Shortly after the last bath she became agitated, drowsy and had a tonic convulsion lasting for 1 min, characterized by staring, irregular breathing, and cyanosis, flexion of the arms, extension of the legs, abnormal tongue movements, drooling and a peculiar smile. Two identical episodes occurred the same day. On admission to hospital, neurological examination was normal, as were all blood tests, CSF analysis, brain computed tomography, and magnetic resonance imaging. Viral cultures were negative. EEG showed bursts of spikes at the anterior leads which became occasionally generalized. Over the following days the number of seizures increased dramatically to a maximum of 133 in 24 h, occurring in clusters especially during sleep. Phenobarbital, phenytoin, valproate, carbamazepine, clonazepam, clobazam and nitrazepam were used, either alone or in various combinations, without any improvement. After 4 weeks the seizure activity decreased suddenly and stopped while she was being treated with phenobarbital and phenytoin. After recovery her EEG improved markedly but still showed bilateral temporal spikes, more prominent on the right side.

The child's development was subsequently marked by a temporary delay in her psychomotor and speech abilities. At 21, 28, and 32 months of age she again suffered from a cluster of identical tonic seizures, each time triggered by febrile infections. Repeated EEGs, CSF analysis, and cerebral magnetic resonance imaging were normal. Another afebrile convulsive event occurred at the age of 5 years. She is currently receiving vigabatrin and valproate.

Discussion

During the nineteenth century, attention was given to the convulsive properties of a number of spirits, including absinthe, *vulnéraire*, and *eau d'Arquebuse*, which contained, apart from alcohol, several EOs such as wormwood, sage, rosemary, hyssop, and fennel [3]. The painter Van Gogh was one of the most famous victims of absinthism, a form of alcoholism in which delirium and epilepsy are prominent [6]. Moreover, the use of EOs of pennyroyal, tansy, thuja, and savin in toxic amounts as abortifacients is occasionally complicated by severe epileptic manifestations [7, 8], as noted in the recent review by Anderson et al. [9]. Finally, given their universal use as therapy for colds, intoxication with apparently innocuous herbs such as eucalyptus and pine, from which turpentine derives, can occasionally produce seizures [10, 11].

EOs are usually obtained by steam distillation of plants. Mainly based on terpenes, their composition is complex and highly variable depending on numerous factors such as geographical origin, time of harvesting, chemotype, and even adulteration.

The convulsant EOs contain one or several oxygenated monoterpenes such as camphor, thujone, pulegone, cineole, pinocamphone, fenchone, and sabinylacetate. The majority are bicyclic ketones, all very similar in chemical structure and biosynthesis [12].

The epileptogenic properties of these compounds have been well established and studied in animals both in vivo [3, 13] and in vitro [14]. In fact, it has been shown by electrocorticographic records that Wistar rats, after intraperitoneal injection of 80 mg/kg hyssop EO, develop subclinical generalized sustained high-voltage spikes. Increasing the dose to 1.25 g/kg leads to rhythmic myoclonus, subsequently to one or several tonic, clonic, or tonic-clonic seizures, and eventually lethal convulsive status. Similar results have been obtained with half these doses of pinocamphone, the main component of hyssop [13]. Furthermore it has been demonstrated using the same experimental model that the kindling effect is facilitated by previous exposure to very small doses of sage EO [15]. These experiments clearly suggest that these compounds cannot only induce de novo severe epileptic events in a dose-dependent fashion, but also trigger seizures in predisposed brains.

Pathophysiology of this specific toxicity is unknown. However, EOs share with pentylenetetrazol, another powerful convulsant, the same inhibitory effect on cellular respiration of rat brain slices [14], leading to loss of tissue gradient for Na^+ and K^+ and thus to significant increase in cellular excitability.

Currently more than 40 EOs are sold over the counter without prescription or are included in numerous pharmaceutical products for therapeutic purposes [16]. There is usually little or no mention of their indication, composition, dosage, or adverse effects, and the laws regarding the marketing of herbal remedies vary considerably from one country to another [2]. Compilation of published case reports and experimental data over more than a century results in a list of 11 EOs whose toxicity may be manifested in convulsive events (Table 1). References are scanty in the recent medical literature [9, 13], the majority of cases having been reported before medical data banks became available [3, 7, 8, 10, 11, 17].

Clinically, our cases exemplify what has been reported previously as the main features of this type of toxic epilepsy, including: (a) generalized seizures often preceded by vague faintness (case 1), and frequently accompanied by other symptoms of intoxication; (b) seizures that may occur as an isolated event (cases 1 and 2) or in a repeated manner, which tend to evolve into a refractory convulsive status (case 3); (c) severity of the convulsions is dose dependent, although a cumulative effect with repeated small doses is also possible (case 1); (d) absorption of EOs may be oral (cases 1 and 2), rectal [18], nasal, or cutaneous

Table 1 Convulsant essential oils of plants and their major epileptogenic compounds

Popular name	Botanical name	Epileptogenic compounds[a]	References
Eucalyptus	*Eucalyptus globulus* Labill.	Cineole	7, 10, 16, 19, 20
Fennel	*Foeniculum vulgare* Mill.	Fenchone	3, 20
Hyssop	*Hyssopus officinalis* L.	Pinocamphone, cineole	3, 13, 14, 18
Pennyroyal	*Mentha pulegium* L. or *Hedeoma pulegioides* L	Pulegone	8, 9, 16, 20
Rosemary	*Rosmarinus officinalis* L.	Cineole, camphor	14
Sage	*Salvia officinalis* L.	Thujone, camphor, cineole	2, 13, 17, 20
Savin	*Juniperus sabina* L.	Sabinylacetate, camphor, thujone	7, 21
Tansy	*Tanacetum vulgare* L.	Thujone, camphor, cineole	20
Thuja	*Thuya occidentalis* L.	Thujone, fenchone, camphor	13, 18, 21
Turpentine	Several species of Pinus	Pinenes?[b]	11, 22
Wormwood	*Artemisia absinthium* L.	Thujone	3, 6, 20

[a] Isomers, such as α- and β-thujone, are not specified
[b] Pinenes are important compounds of turpentine, but their convulsant effect remains to be confirmed

(case 3); and (e) adverse effects are not uncommon, as evidenced by reports of long-term neurological sequelae and even death [11, 17].

Despite historical data, the diagnosis of plant intoxication can be difficult as blood screening is not routinely available. It is interesting to note, however, that Anderson et al. [9] have recently identified pulegone and methofuran in serum samples of two cases of pennyroyal toxicity.

Regarding cases 1 and 2, the absence of any epilepsy risk factor, the striking temporal relationship between exposure to EOs and the convulsive event, and the normality of numerous examinations strongly suggest that these seizures were induced by the EOs. In case 3 the subsequent recurrence of seizures despite no further use of EOs and the development of cognitive disturbances suggest in fact that the child had an underlying epileptogenic encephalopathy; it seems likely, however, that exposure to EOs initiated epileptic events that would have evolved into a less dramatic course had these substances not been used.

In conclusion, epileptic seizures are a side effect of certain EOs, and the danger appears to be higher in children [11, 19] and a fortiori in patients with previous epileptic syndromes [18]. Therefore any first seizure of unknown origin or unexplained worsening of a stable epilepsy should suggest the possibility of recent EOs use. Moreover, the present cases add to a growing list of potential hazards related to herbal medicines whose use should not be regarded as "natural" or safe.

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