

Pleasant natural scent with unpleasant effects: Cluster headache-like attacks triggered by *Umbellularia californica*

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Abstract

Umbellularia californica, a shrub or tree indigenous to southwestern Oregon and northern California, is commonly known as headache tree, probably because it is reported that its scent can cause headache. Here, we report the case of a 69-year-old Italian gardener, affected during his young adult age by cluster headache, who, 10 years from his last cluster episode, developed shorter-lasting cluster-like headache attacks after and at any time he was exposed to *U. californica* scent. The present case indicates that, even though endogenous mechanisms causing the cluster headache were no longer present, susceptibility to exogenous triggers remains active in this patient, and suggests that identification of the constituent(s) of *U. californica* responsible for triggering cluster headache-like attacks may help in the understanding of the hitherto elusive mechanism of cluster headache.

Keywords

Cluster headache, trigger factor, *Umbellularia californica*

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Umbellularia californica (*U. californica*) (Hook. & Arn.) Nutt. (Fig. 1), the sole species of the genus *Umbellularia*, is a shrub or tree indigenous to Southwestern Oregon and Northern California (1). The plant is known with a host of common names that make reference not only to the shape and texture of its leaves (California myrtle, California laurel, California bay, myrtlewood, sassafras laurel) or to the strong aromatic properties of the plant (pepperwood, spice tree, cinnamon bush), but also to its alleged headache-inducing properties (headache tree) (2). *Umbellularia californica* has an interesting ethnopharmacology, having been used as a substitute for bay leaves by the early European settlers, as an animal repellent and insecticide (2), and as a spice and natural drug by native Americans (1). Paradoxically for its current reputation, putting the leaves on the forehead, tucking them into and under hats (3), bathing the head with a leaf infusion, or placing a single leaf in the nostril (4) have all been documented as Indian folk remedies for headache. Vapour from the aromatic leaves has been reported to cause sinus irritation, sneezing, headache and even unconsciousness (5,6). The leaves of *U. californica* contain, as major volatile constituent, the monoterpene ketone umbellulone, a compound endowed with a strong, camphor-like odour

that, when extracted from the leaf oil and administered to laboratory animals, affects respiration, heartbeat and blood circulation, eventually causing death (5). The wood-, leaf- and seed-oils have all been used for various purposes, like the treatment of catarrh, rheumatism, meningitis, neuralgia, intestinal colic and dyspepsia (6–8).

Here, we report a case of a 69-year-old man from Northern Italy who, at the age of 22 years in 1961, experienced during his draft his first episode of severe attacks of headache, with pain located to the left fronto-temporal and ocular region, and accompanied by ipsilateral eye reddening, lacrimation, nasal obstruction and rhinorrhoea. Pain attacks with associated symptoms lasted 1–3 h, and recurred for 2 months in the night and early afternoon. The diagnosis of cluster

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Figure 1. *Umbellularia californica*.

headache was not made, and the patient received only common analgesics and carbamazepine. Headache episodes with identical stereotyped symptoms recurred 2 years later for 2 months. Hereafter, every 2 years and for approximately 25 years (the last episode occurred in 1987), the patient experienced 2-month periods of headache. It is of interest that the patient did not experience any either ictal or interictal osmophobia. After a number of medical consultations and prescriptions of ineffective treatments, finally, in the early 1980s, the patient received a diagnosis of episodic cluster headache and was treated with some benefit with a combination of ergotamine tartrate and caffeine. A few prophylactic treatments were attempted with poor or no amelioration.

Approximately 10 years ago and 10 years after the last cluster headache episode, the patient, a professional gardener, while pruning an *U. californica* tree, was exposed to the foliage scent. He experienced an immediate and intense cold sensation into the left nostril, followed, in a few minutes, by a severe pain attack localized to the left eye and the surrounding tissues, accompanied by ipsilateral lacrimation and nasal obstruction. Because symptoms were similar to those of the original cluster headache attacks, the patient seriously feared that his headache could start again. Fortunately, all symptoms faded away in about

10 min without any recurrence. The patient forgot this strange and unexpected episode without considering a possible association between smelling the leaves of *U. californica* and the pain attack. However, a few months later, while working again with the tree, another identical headache episode occurred, inducing him to associate the sniffing of *U. californica* and headache, that again lasted, fortunately, no longer than 10 min. The patient next tried to determine a causal relationship between exposure to the leaves of *U. californica* and headache occurrence. Thus, he purposely sniffed some smashed leaves of *U. californica*. After a first and immediate cold sensation, a 10-min headache episode occurred, characterized by involvement of the left eye and the fronto-temporal region with ipsilateral lacrimation and nasal obstruction. After this confirmatory experience, the patient carefully avoided working in the vicinity of *U. californica*. No episode of headache occurred during the following years. Two months ago we became aware of this unique story and, after having obtained the patient's signed consent, interviewed him with agreement to a second interview within 15 days to better define additional issues. During this time, to furnish a more accurate description of the episode and spurred by the curiosity to assess if the headache could occur again after several years, the patient spontaneously decided again to sniff some leaves of *U. californica*. After 20 years from the last cluster headache episodes, and 10 years from the last episode provoked by exposure to the plant, he experienced a new left-sided headache attack, with all the associated symptoms reported before. We did not have the opportunity to perform any evaluation of the patient's subjective perception of smells. The patient reported that he did not receive such an evaluation from any other physician and did not have any obvious change in smell perception.

A number of exogenous causes have been reported to trigger headache attacks, and volatile agents like perfumes and scents have been reported to cause migraine and other types of headache (9). A number of anecdotal reports but little, if any, scientific evidence are available on the association between *U. californica* and headache. The present case report adds two important findings in support of the view that the leaves of this plant contain compound(s) capable of triggering cluster headache-like attacks. First, although shorter in duration, the symptoms were identical to those of the real attacks. Second, re-challenge was invariably effective in provoking the headache attack. The present case suggests that exposure to *U. californica* can trigger headache by activating mechanism(s) intimately related to the genesis of this type of headache. It is well known that a variety of agents, including alcohol, histamine and trinitrine, can trigger cluster headache attacks,

although their ability to produce such an effect is usually confined to cluster active periods. Thus, it is surprising that in our present case exposure to *U. californica* could repeatedly trigger cluster-like episodes after the resolution (10–20 years after the last cluster headache attack) of the cluster headache. This observation would lead to speculate that *U. californica* acts by a mechanism of action different from those brought about by alcohol, histamine and trinitrine. One common feature of histamine, alcohol and nitrates is their vasodilating effect (10), and it is possible that during the cluster period patients are more susceptible to mechanical vessel wall distension, which results from vasodilation. However, it should be noted that nitroglycerin is a prodrug for nitric oxide, which can activate the trigeminal vascular system (10), and most odorants have the propensity to stimulate both olfactory and trigeminal nerve (11). Finally, alcohol is a powerful stimulus for sensory nerve terminals because it lowers the threshold temperature for activation of the pain-producing capsaicin ‘receptor’ (transient receptor potential vanilloid 1) (12), and by this mechanism alcohol releases neuronal calcitonin gene-related peptide (CGRP), thus causing dilation of meningeal blood vessels (13).

There is no report of any specific vasodilating or sensory neuron-stimulating property of *U. californica* or any of its constituents. However, it should be noted that cluster headache-like attacks in our present case were always preceded by a cold sensation localized to the nostril, ipsilateral to the side of the pain attack. There are two known transducers of cold sensation expressed in primary sensory neurons, both belonging to the TRP superfamily of ion channels, the TRPM8 and the TRPA1 (14). Because TRPM8 is activated by menthol and there is no report that menthol triggers cluster headache, it may be excluded that a menthol-like substance acts in the present case. However, it is possible that *U. californica* contains a hitherto unknown constituent that activates perivascular trigeminal endings by stimulating TRPA1, thus causing an immediate cold sensation associated with the release of CGRP, which may trigger the cluster

headache-like attack. The identification of the constituent(s) of *U. californica* responsible for triggering a cluster headache-like syndrome is currently being pursued.

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