CASE REPORT

Valproate-induced burning mouth syndrome in a male with fibromyalgia and bipolar spectrum disorder

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ABSTRACT

Burning mouth syndrome is a chronic painful condition characterized by a subjective intraoral pain and burning sensations in the absence of an identifiable medical, dental, or psychiatric cause. Although the underlying etiology is currently unclear, an idiopathic (or primary) form and a secondary form to other conditions are formally recognized. However, as several authors have suggested, it might be of clinical utility to consider the existence of a third clinical entity, namely Drug-Induced Burning mouth syndrome, for its therapeutic implications. The latter has been reported with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, antiretrovirals, anticoagulants, chemotherapy, and drugs commonly used in the treatment of neuropsychiatric disorders such as antidepressants, benzodiazepines, and antipsychotics. Regarding anticonvulsants a literature search found a previous case of Topiramate-Induced Burning mouth syndrome but no previous report of valproate-induced Burning mouth syndrome. Our case is, to date, the first case in the literature of Burning mouth syndrome onset following the administration of valproate to a patient suffering from fibromyalgia and bipolar spectrum disorder. Symptoms resolved completely when the drug was stopped, and the association between symptoms and drug was replicated after drug re-administration.

KEYWORDS: Valproate; Burning mouth syndrome; Neuropathic pain; fibromyalgia; bipolar disorder; Stomatodynia

INTRODUCTION

Burning mouth syndrome (BMS) is an idiopathic, chronic pain syndrome, often associated with psychogenic factors and medical conditions, characterized by a subjective burning sensation of the oral mucosa without objective clinical signs or findings and without laboratory abnormalities [1]. Although the underlying etiology remains unclear, in some cases it can be induced by the administration of certain drugs as reported in the literature [2]. This occurrence would represent an adverse drug reaction. This article describes the case of a male patient with fibromyalgia and comorbid bipolar spectrum disorder who developed symptoms of BMS after starting treatment with valproate, a popular anticonvulsant widely used for the treatment of epileptic seizures and bipolar disorders. The symptoms resolved when the drug was stopped and the association between valproate and BMS was replicated on drug rechallenge. To our knowledge, to date, there have been no reports of Valproate-induced BMS.

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CASE PRESENTATION

A 28-year-old man being treated for resistant fibromyalgia came to our attention for mental symptoms that had worsened in the last month, characterized by nervousness, restlessness, impulsivity and marked insomnia. After a careful psychic examination, it was possible to reconstruct that the moodiness episodes arose at the age of 18, when he left home to go to university in another region and in that context, he consumed THC recreationally. The patient mostly reported depressive phases characterized by depressed mood, sense of inadequacy, low self-esteem and hypochondriacal worries probably secondary to vague somatic symptoms such as widespread pain, fatigue, sleep disturbances and decreased libido. Less frequent, however, were the hypomanic phases during which there was a reduction in widespread pain, an increase in energy levels, an increase in libido, optimism, lucidity of thought, euphoric mood, sensations of well-being and a subjective feeling of improved rest. His pathological history was silent for other clinical conditions of interest.

A full range of tests, including blood, hormone, and antibody tests suggestive of rheumatologic disease, yielded

normal results. His drug regimen at the time of the visit was based on duloxetine 60 mg/day, indicated for fibromyalgia. He had been taking it regularly for three months without the slightest clinical benefit. Previous medications included gabapentin, pregabalin, carbamazepine and amitriptyline, all administered with the aim of reducing pain symptoms.

After the diagnosis of "Bipolar Disorde tipe II, mixed episode", duloxetine was gradually reduced and prolonged-release valproate was prescribed in a generic formulation for his psychopathological state and pain symptoms, at a dose of 300 mg/day in a single evening administration. A few hours after administration, the patient described an increasing burning oral pain, "like chewing a hot pepper" involving the tongue and gums in the absence of clinical signs related to the symptoms described. Sodium valproate was then discontinued with gradual reduction of symptoms over 2 weeks. After a 4-week withdrawal period, retreatment with valproate under the brand name "Depakin" at a single dose of 150 mg/day resulted in a recurrence of symptoms, then was stopped again with gradual improvement in oral burning pain until to its complete disappearance.

DISCUSSION

Burning mouth syndrome (BMS) is a chronic intraoral pain condition usually involving several portions of the mouth, most commonly the tongue, in the absence of clinical signs or laboratory findings. Its pathogenesis is uncertain, it is probable that the interaction of genetic and environmental factors together with psychogenic factors and central and peripheral neuropathies may play a role [3].

The symptomatology is described as a subjective burning sensation often associated with a wide range of local symptoms such as numbness, tingling, altered perception of taste, persistence of bitter or metallic tastes, dryness [2]. The prevalence of BMS ranges from 0.7% to 15% in different populations, races, and contexts, and in clinical practice is on average 4%, with a higher prevalence in postmenopausal women [4].

Currently, an idiopathic or primary BMS and a secondary BMS are formally recognized. In secondary BMS the typical symptoms of the syndrome are caused by another condition and are manageable through an adequate etiological treatment [5]. However, as several authors have suggested, it might be of clinical utility to consider the existence of a third clinical entity, namely Drug-Induced BMS, for its therapeutic implications [6,7].

Drug-induced BMS has been reported most frequently with angiotensin-converting enzyme inhibitors, however other cases have been reported with angiotensin receptor blockers, antiretrovirals, anticoagulants, chemotherapy, and drugs commonly used in the treatment of neuropsychiatric disorders such as antidepressants, benzodiazepines, and antipsychotics [8-10]. Regarding anticonvulsants, a literature search found a previous case of topiramate-induced BMS, but no previous report of valproate-induced BMS [11]. Valproate blocks voltage-gated sodium channels and increases brain GABA concentrations [12].

It should be noted that this patient experienced intraoral complaints using both brand name and generic formulations of valproate, suggesting that the active ingredient was involved in the genesis of his symptoms. Furthermore, the excipients that make up the two different formulations of valproate, in addition to being partly different, are not known to trigger BMS. The most probable hypothesis is that the burning mouth syndrome in this patient was an idiosyncratic adverse reaction to valproate that resolved on discontinuation of the drug and recurred on re-challenge.

World Health Organization defines an "adverse reaction" as any "noxious and undesirable reaction occurring at doses normally used for prophylaxis, diagnosis or therapy" [13]. Some adverse reactions are not related to the dose taken; in these cases, we can speak of "idiosyncratic reactions" [14,15].

Although, as already mentioned, psychogenic factors and various medical conditions appear to be frequently associated with BMS in this case it is unlikely that fibromyalgia and bipolar spectrum disorder are the cause of the BMS as the patient had no symptoms of BMS prior to taking valproate.

Although the additive effect of fibromyalgia, bipolar spectrum disorder and valproate seems highly unlikely, given the lack of previous reports of valproate-induced BMS and the widespread use of valproate worldwide, we cannot exclude that these pathological conditions contributed to creating a fertile ground for an adverse drug reaction to Valproate.

CONCLUSION

In conclusion, we present the first case described in the literature of valproate-induced BMS. The fact that the typical symptoms of BMS occurred immediately after valproate administration and resolved after its prompt discontinuation is unequivocal evidence of the drug's responsibility for inducing the syndrome. Furthermore, the recurrence of BMS symptoms following a re-challenge with a different formulation of valproate supports that evidence.

Considering that the symptoms of BMS recurred a second time, with the same modalities, following a re-challenge with a drug dose halved compared to the initial dose, we hypothesize that the mechanism underlying this adverse event is that of an idiosyncratic adverse reaction to valproate.

In fact, idiosyncratic reactions can be defined as adverse reactions that cannot be explained by the mechanism of action of the offending agent and develop independently of the drug dose, duration of administration and route of administration, only in sensitive individuals [14,15].

Fibromyalgia and bipolar disorder are unlikely to be the cause of BMS, as the patient had no symptoms of BMS before taking valproate. Although the additive effect of fibromyalgia, bipolar spectrum disorder and valproate seems highly unlikely, we cannot exclude that these pathological conditions contributed to creating a fertile ground for an adverse reaction to valproate. Fortunately for the patient, it was sufficient to rapidly interrupt the administration of the drug to witness a gradual and complete resolution of the symptoms.

Conflict of interest

The authors declare that they have no competing interests.

Consent for publication

Written informed consent from the patient has been taken and is available for review by Editor in chief of the journal.

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