Role of vitamin B6 in idiopathic burning mouth syndrome: some clinical observations

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Abstract – Introduction: Idiopathic burning mouth syndrome (iBMS) is a chronic oral pain syndrome mainly characterized by a burning sensation in the oral mucosa and an etiopathogenesis that remains unclear, with therapeutic options that are disappointing. Any clinical observation providing insight into the disorder can therefore be of interest. Among metabolic factors, deficiencies of vitamins have been pointed out, but only a few studies have focused on the role of vitamin B6 (vitB6) in this syndrome. In this report, we aimed to highlight the involvement of increased but not decreased vitB6 serum levels in a subgroup of BMS Patients.

Patients and Methods: Medical files of patients who attended the chronic orofacial pain consultation, in the dental department of the Groupe Hospitalier Pitié-Salpêtrière (GHPS) in Paris (France) between 09/03/2008 and 12/19/2015 were retrieved from the hospital database and analyzed. This retrospective study was approved by the board of the dental department and authorization for use of patient data was obtained from the National Personal Data Protection Committee (Commission Nationale de l’Informatique et des Libertés (CNIL)) (#1913570).

Results: Seven per- or postmenopausal female patients out of 42 diagnosed with iBMS (17%) displayed an increase in their serum levels of vitB6, one to six times the upper normal limits. There was a statistically significant correlation between pain and vitB6 levels. Moreover, in two patients, the reversal of vitB6 levels to normal values resulted in significant decreases in pain severity.

Conclusion: These clinical observations report for the first time a potential implication of elevated vitB6 serum levels in the burning sensation which might be specific to a subgroup of iBMS patients.

Key words: pyridoxine / pyridoxal 5'-phosphate (PLP) / pain

Mots clés : pyridoxine / pyridoxal 5'-phosphate (PLP) / douleur

Résumé – Rôle de la vitamine B6 dans la stomatodynie idiopathique: à propos de quelques observations cliniques. Introduction: La stomatodynie idiopathique (iBMS, ou idiopathic burning mouth syndrome, en anglais) est une affection douloureuse chronique principalement caractérisée par une sensation de brûlure dans les muqueuses buccales sans cause identifiée. Son étiopathogénie reste obscure et les options thérapeutiques décevantes. Les carences vitaminiques font partie des facteurs métaboliques potentiellement contributifs habituellement recherchés mais peu d’études ont porté sur le rôle de la vitamine B6 (vitB6). Le but de cette étude rétrospective était d’évaluer les taux sériques de vitB6 dans un échantillon de patients iBMS. Patients et Méthodes : Parmi les dossiers médicaux des patients venus consulter pour douleur orofaciale chronique dans le service d’odontologie du Groupe Hospitalier Pitié-Salpêtrière à Paris (France) entre 09/03/2008 et 19/12/2015, ceux diagnostiqués iBMS ont été analysés. L’étude a été approuvée par le conseil de service d’odontologie et a reçu l’autorisation de la Commission Nationale de l’Informatique et des Libertés (CNIL) (#1913570) pour l’utilisation des données des patients. Résultats : Parmi les 42 patients diagnostiqués iBMS, sept (17%) présentaient des taux sériques de vitB6 sérique plus élevés, jusqu’à 6 fois les valeurs normales. Une corrélation statistiquement significative entre la douleur, évaluée par une échelle numérique simple, et les niveaux vitB6 a été observée. En outre, chez deux patients, le retour à des valeurs normales des taux sériques de vitB6 a donné lieu à une diminution significative de l’intensité douloureuse. Conclusion : Ces observations cliniques rapportent pour la première fois l’implication potentielle de taux sériques élevés de vitB6 dans les sensations de brûlure buccale qui pourraient être spécifiques d’un sous groupe de patients stomatodyniens.

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Introduction

Idiopathic burning mouth syndrome (iBMS), also called primary BMS or idiopathic stomatodynia, is mainly characterized by a spontaneous continuous burning pain felt in the tongue or in the oral mucosa in the absence of clinically apparent mucosal alterations, often accompanied by taste dysfunction and xerostomia [1]. It is opposed to secondary BMS (sBMS) for which a local or systemic cause can be identified [2] with clinical examination and routine tests, including cell count, candida identification, dosage of thyroid-stimulating hormone (TSH), iron, vitamins, etc. [2, 3]. The prevalence of iBMS in the general population is relatively low (<1%) but increases with age, and there is a strongly unbalanced sex ratio with more affected women than men around or after menopause, often with anxiodepressive backgrounds. The disorder seems multifactorial and the mechanisms so far remain unclear, although insights into the pathophysiology have recently been achieved. Some histological, psychophysical, pharmacological, electrophysiological, and imaging data suggest neuropathic mechanisms, including both peripheral and central changes and autonomic system alterations. The main clinical characteristics [1, 2], pathophysiological mechanisms [4–7] and therapeutic options [8] of BMS have been reviewed [7].

Despite these interesting advances, treatment options remain limited and often unsatisfactory. In this context, any clinical observation providing insight into the disorder can be of interest. Our clinical experience in a secondary/tertiary pain consultation led us, first, to fortuitously observe vitB6 serum elevation in two BMS patients. One was a male patient treated for prostate cancer with anti-aromatase medications and was referred because of oral symptoms; he complained of bitter taste and burning sensations on the tongue; blood tests revealed elevated vitB6 serum levels (twice normal values), but the patient wanted neither further exploration, nor a medical appointment. The other case was a woman (31 y.o.), also complaining of bitterness and burning sensations on the tip of the tongue. Medical history revealed stressful life events, and blood tests displayed elevated vitB6 serum levels. She also did not want any further testing.

Since these observations, we began to take interest in this particular vitamin and examined the available literature. Among possible causes of BMS, metabolic factors (such as iron, vitamins, copper, zinc, etc.) were extensively studied to find an explanation, and vitamins of the B group, because of their involvement in nervous system functioning, were especially targeted for investigation [2]. Indeed, some BMS patients exhibited low serum levels of vitamin B1, B2, B6, B9, and B12 and it is commonly assumed that vitamin deficiency is a risk factor for BMS, especially for B12. Although frequently cited, we found surprisingly very few reports supporting the involvement of vitB6 deficiency in BMS. Actually, only two seriously document this assertion [9, 10] and interestingly, with contradictory results.

The present study reports 7 clinical cases with elevated vitB6 serum levels. These cases are discussed in relation to the medical history of the patients and to the available current literature related to the biological role, effects, metabolic pathways and toxicity of vitB6. Hypotheses are made regarding a possible role in the pathogenesis of BMS.

Patients and Methods

Medical files of patients who attended the chronic orofacial pain consultation, in the dental department of the Groupe Hospitalier Pitie-Salpêtrière (GHPS) in Paris, France within a secondary/tertiary referral center, between 09/03/2008 and 12/19/2015 were retrieved from the hospital database and analyzed. This retrospective study was approved by the board of the dental department and authorization for use of patient data was obtained from the National Personal Data Protection Committee (Commission Nationale de l’Informatique et des Libertés (CNIL)) (#1913570).

Only patients with a diagnosis of iBMS according to the criteria of Bergdahl et al. [3] and Scala et al. [2] were selected, i.e. patients complaining of a painful or unpleasant sensation in the mouth in the absence of alterations in the appearance of the oral mucosa, or any local or systemic detectable diseases. Pain severity was assessed as the pain felt during the last week on a 0-10 numeric rating [NRS] (0 was defined as the absence of pain and 10 the maximal pain imaginable). All patients had a thorough clinical examination, laboratory investigations (cell count, candida, ferritin, TSH, vitB6, B9, B12) and allergy investigations when clinically suspected, in order to discard secondary BMS. Some patients had additional investigations according to their medical background (for example human serum albumin, creatinine, glycemia, hemoglobin, hepatic enzymes alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, alkaline phosphatase, triglycerides, and cholesterol, zinc, vit D, etc.). Regarding vitB6, serum levels of vitB6 (pyridoxine) or its metabolically active vitamer, pyridoxal-5'-phosphate (PLP) were measured by HPLC by the laboratory where it was ordered, and compared to normal values; these normal values were 35-110 nmol/L for PLP, and 15-75 nmol/L and 35-110 nmol/L for pyridoxine assayed in serum and blood, respectively (http://www.lab-cerba.com/pdf/0525F.pdf). For each patient, the ratio of the “value of vitB6 / upper limit of normal value” was calculated, and the correlation between this ratio and the NRS pain value was calculated with the Spearman test, with a significance set at $p<0.05$. 

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Results

Among the 42 patients diagnosed with iBMS, seven (16.6%) had elevated vitB6 levels. The main characteristics of these patients are summarized in Table II, including pain intensity and location, taste alterations, xerostomia, self-reported chronic stress and/or anxiodepressive background, menopausal status, migraine history, and perimenopausal symptoms such as hot flashes and night-sweats. Two patients had a surgical procedure for sterilization by fallopian tubes ligation. Pyridoxine or PLP levels were markedly elevated but the origin of this elevation was unknown. Only in one patient we identified two medications containing VitB6 (Piascledine® 300 mg (avocado/soybean unsaponifiable) given for arthrosis and Berocca® given as a nutritional supplementation (cocktail of group B vitamins including pyridoxine hydrochloride 107mg, vit C and mineral salts). In this patient, the discontinuation of these treatments led to an alleviation of the burning sensation (see Table I, patient CB).

Levels of vitB6 are given in Table II with the associated NRS pain value. For patient CB, since the level of pain was fluctuating, an assay was performed at several months interval (V1, V2, V3). For patient NP, two measurements were done (V1, V2). When considering all these values, there was a significant positive correlation between the pain NRS value and the level of vitB6 \( R=0.79; p=0.009 (**) \) (Fig. 1).

Discussion

Although several studies have looked at the putative role of group B vitamins in BMS and tongue dysesthesias, they focused mainly on B1, B2, B9 and B12 [2]. Reports looking at the role of vitB6 are in fact limited to two studies [9] and [10], and some anecdotal reports [11]. Interestingly, these two studies showed contradictory results. Lamey PJ et al. [9] reported a deficiency of B1, B2 and/or B6 in some BMS patients and encouraging therapeutic results using vitamin replacement therapy. However, a proper control for assessment of a placebo effect was missing in their investigation. The study carried out by Hugoson A. et al. [10] was intended to control this flaw and used a placebo control to explore possible involvement of vitamin B1, B2 and B6 deficiency in the development of BMS. Besides the absence of efficacy of proper vitamin replacement therapy in patients suffering a vitB1 and B2 deficiency, no vitB6 deficiency was found in their samples. However, 3 patients out of 16 (18.75%) had, on the other hand, an increase in vitB6 serum levels, which was not discussed. Our results are consistent with this observation, since out of 42 BMS patients, 7 patients (16.6%) had increased vitB6 serum levels. Interestingly, in one patient (CB), the advice of removing all medications containing vitB6 led to both a decrease in vitB6 serum levels and in pain severity (from 8/10 to 1/10). In another patient (NP), the decrease in the pain score (from 6/10 to 2/10) was associated with a decrease in vitB6 levels.

VitB6 consists of three related pyrimidine vitamer derivatives: pyridoxine, pyridoxal, and pyridoxamine, and their phosphate esters. The metabolically active coenzyme of vitB6 is pyridoxal 5'-phosphate (PLP) which is synthesized in the liver from inactive dietary precursors [12]. PLP acts as a cofactor for hundreds of different enzymes serving essential roles in living organisms and catalyzing many diverse chemical reactions, such as racemization, and carbon-carbon bond cleavage and formation. For example, PLP dependant enzymes are involved in transamination and decarboxylation of amino acids to amines, such as gamma-aminobutyric acid (GABA), histamine, noradrenaline, adrenaline, serotonin and dopamine, making this compound a major modulator of neurotransmitter synthesis, lipid metabolism, gluconeogenesis, and immune function [12]. Other than serving as a cofactor, vitB6 is also a source of epigenetic modifications, involved in DNA methylation by regulating levels of the universal methyl donor S-adenosyl methionine and methyl transferase inhibitor S-adenosyl homocysteine, likely, then, to regulate gene expression [13]. It is also an important physiological mediator of steroid hormone action, acting on the steroid hormone receptors and transcription factors [14]. Considering the role of both amino acids and steroids in pain, this pivotal biological action of PLP might be of particular importance in the etiopathogenesis of BMS.

Our findings suggest a role for VitB6 in iBMS which is now largely recognized as having neuropathic mechanisms [5]. VitB6 is assumed to have negligible toxicity when administered as a nutritional supplement; however, administration of high doses is neurotoxic, eliciting stomatal lesions in large dorsal root ganglia neurons and axonal degeneration of myelinated nerve fibers [15]. Nonetheless, the doses necessary to develop these neuropathic clinical manifestations are very high (67 – 105 times the upper normal limits) [16] and only one study, without neurological examination, suggests that relatively low doses of vitamin B6 may cause sensory nerve damage [17]. In our patients, vitB6 serum levels did not exceed 4 times the normal limit. These relatively minor increases compared to the massive increases previously reported may likely not be sufficient to develop any motor or sensory symptoms in healthy subjects. However, in patients with impaired metabolic function, these changes might be of importance. All the iBMS patients of our sample with high vitB6 had a background of anxiety/depressions/stress, i.e. neuroamine dysfunction and/or steroid hormonal dysfunction, suggesting a synergistic misbalance leading to BMS symptoms.
Among the many possible hypotheses linking elevated vitB6 and BMS pain, several can be taken into account.

**Neurosteroids**

Woda et al. [4] proposed that adrenal and gonadal steroids play an important role in BMS pathogenesis through intracrinology. Briefly, the gonads and medullo-adrenal glands provide precursors for neurosteroid synthesis which are needed in peripheral tissues and especially in oral tissues for nerve protection. According to this hypothesis, a decrease in these precursors because of stress and/or menopause favors the onset of iBMS. Importantly, vitB6 plays an essential role in steroid hormone action (and other nuclear-acting hormones) [18]. In cultured cells, moderate variations in the intracellular concentrations of PLP can have pronounced modulatory effects on steroid-induced gene expression. Specifically, elevation of

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**Table I.** Main characteristics of the BMS patients with elevated vitB6 levels.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Pain</th>
<th>Menopausal (MP) status and associated manifestations</th>
<th>Psychosocial background</th>
<th>Medical history</th>
<th>Clinical oral manifestations</th>
<th>Concomitant medications</th>
<th>Laboratory analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>CB</td>
<td>43</td>
<td>8</td>
<td>Non MP</td>
<td>Chronic stress</td>
<td>Depression, - Arthrosis, - GI dysfunction - Menstrual irregularity - Migraine - Tubal ligation - Sleep disorder</td>
<td>Burning sensation (whole mouth) - Dysgeusia - Xerostomia</td>
<td>Prazepam - Zopiclone - Vitamin D - Clonazepam topical - Avocado and soy unsaponifiable - Nutriment supplement (vitamins and mineral salts)</td>
<td>Subnormal ferritin level - Decreased vit D level</td>
</tr>
<tr>
<td>RG</td>
<td>46</td>
<td>5</td>
<td>Non MP</td>
<td>Chronic stress</td>
<td>Depression - GI dysfunction - Uterine fibroma</td>
<td>Burning sensation (whole mouth) - Dysgeusia</td>
<td>Pantoprazole</td>
<td>Subnormal ferritin level</td>
</tr>
<tr>
<td>NP</td>
<td>54</td>
<td>6</td>
<td>Non MP</td>
<td>Chronic stress</td>
<td>Depression - GI dysfunction - Migraine - Ovarian cyst - Hypothyroidism</td>
<td>Burning sensation (whole mouth) - Xerostomia</td>
<td>Zolmitriptan - Tramadol - Acetaminophen - Zolpidem - Clonazepam - Ketoprofen - Omeprazole - Levothyroxin</td>
<td>Leukopenia</td>
</tr>
<tr>
<td>ML</td>
<td>63</td>
<td>6</td>
<td>MP</td>
<td>Chronic stress</td>
<td>Depression - Sleep disorders</td>
<td>Burning sensation (tongue) - Dysgeusia - Xerostomia</td>
<td>Clomipramine - Zolpidem - Pregabaline - Clonazepam - Tramadol</td>
<td>Normal</td>
</tr>
<tr>
<td>DC</td>
<td>47</td>
<td>6</td>
<td>Non MP</td>
<td>Chronic stress</td>
<td>Depression - Musculo-skeletal pain - Cervicalgia</td>
<td>Burning sensation (tongue)</td>
<td>Acetaminophen</td>
<td>Increased hepatic GT - Decreased polynuclear</td>
</tr>
<tr>
<td>MG</td>
<td>79</td>
<td>8</td>
<td>MP</td>
<td>Chronic stress</td>
<td>Depression - Arterial hypertension - Hepatitis C - Sleep disorder</td>
<td>Burning sensation - Xerostomia (whole mouth)</td>
<td>Fluidione - Zolpidem - Candesartan cilexetil - Dextropropoxyphene - Clonazepam - Maprotiline hydrochloride - Anetholtrithion - Xylocaine cream - Amitriptyline</td>
<td>Normal</td>
</tr>
<tr>
<td>SM</td>
<td>66</td>
<td>9</td>
<td>MP</td>
<td>Chronic stress</td>
<td>Depression - Arthritis - Rheumatoid arthritis</td>
<td>Burning sensation (tongue tip and palate)</td>
<td>Rosuvastatin</td>
<td>Elevated cholesterol</td>
</tr>
</tbody>
</table>
intracellular PLP levels leads to decreased transcriptional responses to glucocorticoid, progesterone, androgen, or estrogen hormones, suggesting that vitB6 acts as an inhibitor of estrogen action [12, 19]. Steroid hormones can accumulate in the nucleus of target tissues for a longer time in case of vitB6 deficiency, leading to enhanced gene expression [18, 20]. Moreover, vitB6 plays an important protective role against prostate cancer [21], through vitB6 attenuation of steroid hormone responsiveness of target tissues [18]. As a consequence, and supporting the hypothesis of the involvement of steroids in BMS [4], we suppose that minor increases in vitB6 levels may be sufficient for onset of BMS in some subgroups of patients. This can also explain the symptoms of the male patient treated with anti-aromatase and who developed iBMS-like symptoms reported in the introduction.

**Serine racemase – ATP**

VitB6 plays an important role as a cofactor of amino acid racemases [18]. For example L-serine is directly converted to D-serine by the enzyme serine racemase, which uses vitB6 as a key cofactor [22]. Several lines of evidence implicate D-serine as a pronociceptive molecule, especially for neuropathic pain in both neurons and glial cells [23]. Increased vitB6 serum levels may therefore catalyze the serine racemase reaction, resulting in high D-serine synthesis, and therefore pain development.

Another action of interest of vitB6 is related to its purinergic function. ATP receptors are involved in neuronal and glial function in nociceptive pathways; for example ATP showed excitatory effects in a tongue preparation [24]. As PLP is an efficient blocker of the P2X ATP receptors [25], changes in vitB6 levels might impact nociceptive processing. How elevated vitB6 can translate to pain sensation is difficult to determine, but it should be kept in mind that inhibitory inputs can lead to increases in pain sensations [7, 26]. It should also be mentioned that, besides their role in pain transmission, ATP receptors are present on taste bud cells and play a role in the genesis of taste messages [27], alterations of vitB6 levels may then participate in dysgeusia, often accompanying iBMS.

**Dopaminergic controls**

Many studies suggest a link between alteration of dopaminergic controls and orofacial pain including BMS and atypical facial pain [6, 28, 29], and recent clinical studies showed a significant therapeutic response to dopaminergic drugs [30]. Since ATP modulates firing activities in the rat nigrostriatal dopaminergic neurons, possibly via P2X2, P2X2/6, and/or P2X4 receptors [31], and since vitB6 is an antagonist
of P2X ATP receptors, we can hypothesize that increased vitB6 serum levels may inhibit firing activities in the nigrostriatal dopaminergic neurons, whose implication in BMS is well documented [29].

Homocysteine

Homocysteine (Hcy) is an amino acid and several observational studies have shown that Hcy is a risk factor for cardiovascular disease and idiopathic pain, like migraine [32]. Recently, glutamatergic sensitization of trigeminal neurons and satellite glial cells (SGC) by Hcy through NMDA and mGluR5 receptors with a selectivity of effect according to the considered cell has been demonstrated [32]. Furthermore, Hcy leads to production of metabolites (homocysteic acid and cysteine sulfenic acid), acting as NMDA receptors with neurotoxic effects on dopaminergic neurons [33]. Other studies suggest that genetic singularities may alter the link between serum levels of Hcy, vitB6, catecholamine and non-catecholamine neurotransmitter metabolism, leading to depression [34, 35]. The role of Hcy in BMS has recently been investigated, focusing on vitB12, but not on vitB6, suggesting a possible role for Hcy in buccal pain [36]. Altogether, these observations suggest the involvement of vitB6 in clinical trigeminal pain and anxiodepressive disorders.

Further investigations are needed in order to understand the implication of vitB6 serum increase in BMS and among the many questions, the origin of the increase and how to reverse it, are of particular importance. Reactional feedback mechanisms can be evoked since vitB6 deficiency was first reported in women taking high-dose contraceptives [37], and several other studies showing abnormal vitB6 levels in women taking both oral contraceptives and menopausal hormone replacement therapy have been interpreted as indicating estrogen-induced vitB6 deficiency or depletion [38]. It should also be kept in mind that BMS is not a homogeneous entity and several lines of evidence suggest the existence of different subgroups [5, 39, 40]. VitB6 level changes might then be involved only in a specific subgroup of BMS patients.

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References