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A case-report

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Educational Case Report

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Hypophosphatasia as a plausible cause of vitamin B6 associated mouth pain: a case-report

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Abstract

Background: Mouth pain has been associated with abnormal vitamin B6 levels. Hypophosphatasia is a rare genetic disease, which causes imbalances between B6 vitamers. We report the case of a patient with hypophosphatasia and burning mouth pain.
Case presentation: A 39-year old Caucasian male with chronic burning mouth pain underwent extensive investigations with no cause of the pain being found. During the course of the investigation, an elevated vitamin B6 (pyridoxal phosphate) level was detected, which led to the diagnosis of hypophosphatasia. We hypothesize that the patient's mouth pain stems from hypophosphatasia through a B6 dependent mechanism.
Conclusions: Mouth pain may, in some cases, be a symptom of hypophosphatasia and when investigating B6 in relation to mouth pain, attention should be paid to the exact B6 vitamer measured. The case underlines the importance of low alkaline phosphatase results, especially in patients with unexplained pain, as this should prompt suspicion of hypophosphatasia.

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Introduction

Abnormal vitamin B6 levels have been associated with burning mouth syndrome (BMS). Some studies have found low levels of B6 to be associated with BMS [1–3] while other studies have found high levels of B6 to be associated with BMS [4, 5]. Several possible mechanisms for these associations have been proposed [5].

Hypophosphatasia is a genetic disorder caused by pathogenic variants in the *ALPL* gene that results in low activity of the tissue non-specific alkaline phosphatase (TNSALP), which is involved in vitamin B6 metabolism [6].

We report the case of a 39-year-old male with hypophosphatasia and a burning sensation in his mouth. We hypothesise that his symptoms may be a result of abnormal B6 metabolism due to hypophosphatasia.

Case presentation

A 39-year-old Caucasian male presented at the department of otorhinolaryngology with irritation and white coating on the back of the tongue for two months and a concern that it might be cancer. The patient had a past medical history of paradentosis. He further had an extensive history of chronic pain since he was approximately 30 years old. This included intermittent burning sensations in both legs, pain in hips, sacroiliac joints, thorax, abdomen and head. The patient was a non-smoker and he did not take any medications known to cause mouth pain [7].

Examination of the oral cavity, laryngoscopy and ultrasound of the neck revealed reactive lymph nodes around the sternocleidomastoid muscles and white coating at the back of the tongue. When the patient returned for a follow up two weeks later, the white coating had receded but the irritation had evolved to pain.

In the ensuing 3 years the patient was in contact with the departments of otorhinolaryngology and dermatology

respectively another 13 times, during which time, the pain progressed to burning/smarting, worst on the tip of the tongue and worse when ingesting sour, spicy or salty food.

For treatment of the pain, the patient tried rinsing with chlorhexidine gluconate, benzydamine and local glucocorticoid application. None of the treatments had effect, but were instead reported to worsen the symptoms. The patient also tried to use toothpaste without foaming agent (sodium lauryl sulfate), with no effect.

During the hospital visits, the oral cavity was inspected numerous times, and was on several occasions described as normal. Tonsil stones and fissures of the tongue were seen intermittently. The possibility of lingua geographica with an atypical visual presentation was raised and biopsies were taken to investigate this.

Biopsies were taken on three different occasions and showed inflammation, which was described by the pathologist as milder than what is usually seen in geographic tongue. Repeated swabs for fungi, bacteria and herpes turned out negative and treatment with fluconazole had no effect on symptoms. Patch testing revealed no allergies. Extensive blood work was performed, with the only significant findings being elevated vitamin B6 (PLP) and low alkaline phosphatase. This led to the suspicion of hypophosphatasia, which was confirmed by genetic testing.

We thus had a 39-year old male with B6 disturbances due to hypophosphatasia and a burning sensation in his mouth, for which no specific reason was found. We hypothesize that the patient's mouth symptoms could be a consequence of hypophosphatasia through a B6 dependent mechanism.

Discussion

Vitamin B6 consists of a group of six vitamers (including PLP) [8] and TNSALP is a catalyst of the conversion of PLP to pyridoxal. B6 can only be imported into the cell in the form of pyridoxal, and is then converted back to PLP once inside the cell [8]. Hypophosphatasia causes low activity of TNSALP resulting in accumulation of substrates of the enzyme. PLP thus accumulates in the circulation, while intracellular brain PLP-levels can be low [9], resulting in neuronal PLP-deficiency [9, 10] in spite of high levels of circulating PLP.

Hypophosphatasia can vary in severity and patients experience a wide range of symptoms including skeletal manifestations, muscle weakness and pain, renal, dental and respiratory complications, as well as neurological manifestation such as anxiety, chronic pain and in severe forms B6 dependent seizures [6].

In the 1980s, Lamey et al. found that a high percentage of BMS patients had B1, B2 and/or B6 deficiencies and found that burning mouth symptoms could be abolished by treatment with vitamin B replacement therapy in 30% of these patients [1, 2]. Hugoson et al. later studied 16 patients with BMS and found none with vitamin B6 deficiency [4], but as later noted by Dieb et al. three patients in Hugosons study had elevated B6 levels [5]. Dieb et al. also presented their own investigation of BMS patients finding elevated B6 levels in 16.6% of patients and reporting a decrease in pain severity associated with lowered B6 level in two patients [5]. In 2017, Verenzuela et al. investigated B6 level in 350 BMS patients at the Mayo Clinic and found 6% to be B6 deficient but none with elevated B6 levels [3]. Thus, some studies found high levels and other studies found low levels of B6 to be associated with BMS. Notably, these different studies did not measure the same vitamer. If enzyme defects are present, measuring one vitamer will not accurately represent the B6-status. This complicates interpretation of results and can possibly account, in part, for the diverging conclusions regarding BMS and B6-status.

Although the relevance of B6-levels in BMS patients has not been securely established and a causative effect yet to be proven, the literature indicates a possible association between B6 levels and BMS. We hypothesise that the B6 imbalances induced by hypophosphatasia may be the cause of the mouth pain experienced by this patient and thus may explain the seeming inconsistency between clinical findings and level of pain.

Though enzyme replacement therapy for hypophosphatasia is available, it is still costly and is, in Denmark, not routinely offered to patients with adult onset hypophosphatasia. It has therefore not been possible to normalize the patients B6 levels and our hypothesis thus remains untested.

The patient now attends regular follow-ups, to secure early identification of complications to hypophosphatasia. The patient expressed that he was glad to finally have an explanation for many of his symptoms.

Conclusions

Hypophosphatasia may cause mouth pain through B6 dependent mechanisms and we suggest that attention to specific B6 vitamers is warranted, when evaluating patients with mouth pain. The case further underlines the importance of low alkaline phosphatase results, especially

in patients with unexplained pain, as hypophosphatasia may be the root cause.

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