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Low Vitamin B12 Syndrome in Trigeminal Neuralgia

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Abstract

Objective: The cause for trigeminal neuralgia is not clearly understood. Multiple theories have been proposed, and some implicate a low vitamin status with trigeminal neuralgia pain however to date there is no conclusive evidence. The treatment of trigeminal neuralgia can be challenging and B vitamins have been found to be a clinically useful for patients with neuropathic pain. The aim of this study was to investigate whether patients with trigeminal neuralgia had lower levels of vitamin B12 compared to patients with other facial pain syndromes and whether increasing the level of vitamin B12 improve pain levels.

Methods: As part of the patient's routine clinical assessment for the management of trigeminal neuralgia, serum vitamin B12 levels were performed. A total of 76 patients took part in this study. 57 patients had trigeminal neuralgia. We also used 19 patients with other types of facial pain and 6 population subjects, as controls.

Results: We did not find any patients with trigeminal neuralgia to be "vitamin B12 deficient", but 23% patient's with trigeminal neuralgia had serum vitamin B12 levels, compared to only 12% of controls, when using the criterion based on the USDA recommendation in 2000 of serum total vitamin B12 of less than 205 pg/mL.

Conclusion: Vitamin B12 deficiency can have serious consequences long before anaemia is evident. The normal serum level of vitamin B12 in Australia ranges between 106 to 665 pg/ml. Researchers now propose that the current standard norms of vitamin B_{12} levels are too low and the criterion for a low vitamin B12 syndrome should be increased at least to 205 pg/mL, if not to 350 pg/mL. It is possible that low vitamin B12 levels fails to sustain the demand of repair to the myelin from a nerve that is continuously being traumatised and may be one of the explanations why trigeminal neuralgia pain is intermittent. Vitamin B12 supplements may therefore have a role in the treatment of trigeminal neuralgia.

Keywords: Vitamin B12; Trigeminal neuralgia

Introduction

Trigeminal neuralgia (tic douloureux) is a disorder of the fifth cranial (trigeminal) nerve that causes episodes of intense, stabbing, electric shock-like pain in the areas of the face where the branches of the nerve are distributed - lips, eyes, nose, scalp, forehead, upper jaw, and lower jaw.

The International Association for the Study of Pain (IASP) defines trigeminal neuralgia as a sudden, usually unilateral, severe, brief, stabbing, recurrent pain in the distribution of one or more branches of the fifth cranial nerve [1]. Typically, brief attacks of pain are triggered by talking, chewing, brushing teeth, and shaving, applying make-up or even a slight breeze. Generally, it is a clinical diagnosis, although imaging may be necessary to exclude other pathology.

The trigeminal nerve has 3 sensory divisions known as V1 (Ophthalmic) which supplies the eye, forehead and nose, V2 (Maxillary) which supplies the upper teeth, gums and lip, the cheek, lower eyelid and the side of the nose and V3 (Mandibular) supplying the lower teeth, gums and lip. Pain can involve one or more branches of the trigeminal nerve.

First line of treatment of trigeminal neuralgia is usually in the form of anticonvulsant drug, especially carbamezepine. When medication does not satisfactorily manage pain, various surgical options are available, including microvascular decompression, radiofrequency ablation and stereotactic radiosurgery, with a gamma knife.

Microvascular decompression is the only procedure that has successfully provided long term pain relief [2]. Devor and Rappaport confirmed from biopsy specimens that demyelination occurred during nerve compression. It is widely believed that the sustained pulsatile of the compression demyelinates sensory axons in the nerve and nerve root. They hypothesized that MVD provides prolonged pain relief due to remyelination after the decompression [3].

The cranial nerves, except for the first and second, are part of the peripheral nervous system. The Schwann cells produce and maintain myelin to the peripheral nerve axons. About one quarter of the axons in the PNS are myelinated.

The cause for trigeminal neuralgia is not clearly understood. Multiple theories have been proposed, and some implicate a low vitamin status with trigeminal neuralgia pain however to date there is no conclusive evidence. Vitamin B12 (cobalamin) is an important water-soluble vitamin. In contrast to other water-soluble vitamins it is not excreted quickly in the urine, but rather accumulates and is stored in the liver, kidney and other body tissues. As a result, vitamin B12 deficiency may not manifest itself until after 5 or 6 years of a diet supplying inadequate amounts.

Cyanocobalamin has been shown to reduce spinal nerve ligation induced alloydnia and tactile allodynia in rats and therefore may have a role in humans [4]. Vitamin B12 functions as a methyl donor and works with folic acid in the synthesis of DNA and red blood cells and is vitally important in maintaining the health of the insulation sheath (myelin sheath) that surrounds nerve cells.

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Methylcobalamin has recently been identified as a form of Vitamin B12 that protects against neurological diseases and aging [5,6]. The liver convert's cyanocobalamin into methylcobalamin within the body but larger amounts of methylcobalamin are necessary to correct neurological defects. Mauro showed that high doses of methylcobalamin are needed to regenerate neurons as well as the myelin sheath that protects nerve axons and the peripheral nerves [7].

Low vitamin B12 levels can have consequences long before anaemia is evident. The normal serum level of vitamin B12 in Australia ranges between 106 to 665 pg/ml. Researchers now propose that the current standard norms of vitamin B_{12} levels are too low. Recent research indicates that B_{12} deficiency is far more widespread than formerly believed. In a cross-sectional, population-based study of 1048 aged subjects, low serum total vitamin B12 (<205 pg/ml) was observed only in 6.1% and borderline vitamin B12 (205-350 pg/ml) in 32% of the subjects [8]. A large study performed at Tufts University by the USDA found that 39 percent of studied group of 3,000 had low values, using a vitamin B_{12} concentration of 350 pg/mL as a criterion of "low level" [9].

The treatment of trigeminal neuralgia can be challenging and in the search for alternatives, vitamin B12 has been found to be a clinically useful pharmacological useful tool for patients with neuropathic pain. Large dose of vitamin B12 were used with good effect in therapy of trigeminal neuralgia in 1953 and 1954 [10,11], but since then clinical studies supporting its use are lacking.

The object of this study was to investigate whether patients with trigeminal neuralgia had lower levels of vitamin B12 compared to patients with other facial pain syndromes and whether increasing the level of vitamin B12 improve pain levels.

Method

As part of patient's routine clinical assessment for the management of trigeminal neuralgia, serum vitamin B12 levels were performed on all patients referred to their treating neurologist. A questionnaire was designed to facilitate details of patient facial pain condition, history, level of pain and if they were taking vitamin B12, folic acid supplements, amount and type used. Participation was on a voluntary basis. Pain patients and their partners were encouraged to have their serum vitamin B12 and folic acid measured in laboratory test.

Recently, holocobalamin assays have become available [12], due to the uncertain clinical significance of the total vitamin B12 level, but these were not widely available when this study was commenced. Patients found to be taking vitamin B12 supplementation were excluded from the study.

This was an observation study performed as part of the patient's conventional medical treatment. It was reviewed by the Sydney South West Area Heath Service Ethics Review Board and granted exemption from a full review. The study was conducted adhering to the Declaration of Helsinki.

Results

A total of 76 patients took part in this study. There were 53 females aged between 37-78 years and 23 males aged between 18 - 82 years. The average age for the group was 63.3 years.

57 patients had trigeminal neuralgia, the 19 patients with other facial pain included 3 with trigeminal deafferentation pain, 8 with trigeminal neuropathic pain, 2 with short lasting, unilateral neuralgiform headache attacks with conjuntival injection and tearing (SUNCT) syndrome, 2 with glossopharyngeal neuralgia, 1 with geniculate neuralgia and 1 with post-herpetic neuralgia.

The average age in the trigeminal neuralgia group was 62.2 years compared to 63.8 in the control group (p>0.05). The male: female ratio was also similar.

Based on the laboratory reference ranges, (106-675 pg/ml), none of our patient group were found to have laboratory vitamin B12 deficiency, as serum vitamin B12 levels ranged from 106 pg/ml to 695 pg/ml [13,14]. Of significance however was that 23% patients with trigeminal neuralgia had serum vitamin B12 levels of less than 205 pg/mL, compared to only 12% of controls (p<0.05), when using the criterion based on the USDA recommendation in 2000 that vitamin B12 deficiency be regarding as a serum total vitamin B12 of less than 205 pg/mL.

Discussion

This study indicates that patients with trigeminal neuralgia have a low vitamin B12 syndrome, as 23% of patients with trigeminal neuralgia, compared to only 12% of patients with other causes of facial pain had serum vitamin B12 levels less than 200 pg/ml. These results are markedly abnormal when compared to a cross-sectional, population-based study of 1048 aged subjects in which low serum total vitamin B12 (<205 pg/ml) was observed in only 6.1% population controls [8].

There is no known toxicity from taking additional vitamin B12. Methylcobalamin may even be protective against neurotoxicity by enhancing brain cell methylation, as it has been shown that methylcobalamin protected against glutamate-aspartate and nitroprusside-induced neurotoxicity in rat cortical neurons [5].

One problem encountered was the different measurement units from different laboratories. Most used picomol (pmo/mL), while others used picogram (pg/mL) and microgram (µg/mL). Reports in Australian are in pmol/L while literature worldwide uses pg/ml. Conversion was made for the purpose of comparisons [15].

Molecular weight of B12 = 1355.38 daltons.

To convert pmol/L to pg/ml-no. pmol x 0.7378 = pg/ml

To convert pg/ml to pmol/L-no. pg/ml x 1.35 = pmol/L

It is possible that low vitamin B12 levels fail to sustain the demand of repair to the myelin from a nerve that is continuously being traumatised. This may be one of the explanations why trigeminal neuralgia pain is intermittent. When vitamin B12 levels are reasonable, myelin sheaths repair quickly, but when vitamin B12 levels are low, the repair rate is slower, as one Schwann cell can only myelinate 0.2-1.8 mm of cytoplasmic membrane along the length of one axon [16].

Causes of Low Vitamin B12

Malabsorption [17]

a. low hydrochloric acid in the stomach

Group	B12 Serum level (pg/mL)	Trigeminal Neuralgia patients	Other or No Facial Pain Controls
1	<106	0 (0%)	0 (0%)
2	106-205	13 (23%)	3 (12%)
3	205 - 300	18 (32%)	14 (56%)
4	301 - 350	14 (24%)	6 (24%)
5	>351	12 (21%)	2 (8%)
Total		**57**	**25**

Table 1: Serum vitamin B12 results.

Low vitamin B12 or B12 deficiency most often results from food – cobalamin malabsorption due to gastric dysfunction and may be exacerbated by the use of acid- lowering agents such as H2 blockers, antacids and proton pump inhibitors. Absorption of vitamin B12 depends on the stomach to produce high concentration of hydrochloric acid and enough intrinsic factor.

Naturally found vitamin B12 is dissociated from proteins in the stomach via the action of acid and the enzyme pepsin. The forms of vitamin B12 released by this process are methylcobalamin and adenosylcobalamin. All forms of vitamin B12 bind to proteins called haptocorrins or R proteins, which are secreted by the salivary glands and the gastric mucosa. This binding occurs in the stomach. Pancreatic proteases partially degrade the B12-haptocorrin complexes in the small intestine where the vitamin B12 that is released then binds to intrinsic factor (IF). Intrinsic factor is a glycoprotein which is secreted by gastric parietal cells. The B12-intrinsic factor complex is absorbed from the terminal ileum into the ileal enterocytes via a process that first requires the complex to bind to a receptor called cubilin. Within the enterocytes, vitamin B12 is released from the B12-IF complex and then binds to another protein called transcobalamin II which delivers it to the portal circulation. The portal circulation transports vitamin B12 to the liver which takes up about 50% of the vitamin; the remainder are transported to the other tissues of the body via the systemic circulation.

Vitamin B12 in the circulation is bound to the plasma proteins transcobalamin I (TCI), transcobalamin II (TCII) and transcobalamin III (TCIII). Approximately 80% of plasma B12 is bound to TCI. TCII is the principal B12 binding protein for the delivery of B12 to cells, vitamin B12 a specific receptors for TCII. This B12 binding protein (TCII) is identical to the one that delivers vitamin B12 from the enterocytes to the portal circulation.

b) Immune System - Intrinsic factor in the stomach.

The most common cause of vitamin B12 deficiency is the stomach being unable to produce enough intrinsic factor. This is frequently caused by an immune system problem where antibodies attack the stomach lining and damage the cells that produce intrinsic factor.

c) Bacterial overgrowth and infestation with tapeworms or other intestinal parasites that can compete for dietary vitamin B12 in the small bowel.

d) Antibiotics: The use of antibiotics may alter the intestinal microflora and may decrease the possible contribution of vitamin B12 by certain inhabitants of the microflora (e.g. Lactobacillus species) to the body's requirement for the vitamin

e) Lack of calcium in the food can also reduce the uptake and so can heavy metals.

f) Megadoses of vitamin C and/or copper can cause vitamin B12 deficiency

Transport [18]

Once absorbed, vitamin B12 binds to transcobalamin II it is transported throughout the body.

Congenital transport-protein deficiencies, including transcobalamin II deficiency, are another rare cause of vitamin B12 deficiency. It has also been suggested that in the presence of heavy metals the cobalt atom is oxidized from CO^{2+} to CO^{3+} (denaturation) at the same time as the heavy metal is reduced. The properties of the cobalamin are hypothetically changed and vitamin B12 has lost its biological properties.

Conclusion

Fortunately, oral supplementation with vitamin B12 is safe, efficient and inexpensive. Most multi-vitamin pills contain 100-200 microgram of the cyanocobalamin form of B12. This must be converted to methylcobalamin before it can be used by the body.

The actual absorption of B12 is also a problem with supplements. Swallowing 500 micrograms of cyanocobalamin can result in absorption of as little as 1.8 microgram so most multivitamins do not provide an adequate daily intake. The best approach is to dissolve a sublingual tablet of methylcobalamin (1000 micrograms) under the tongue every day. That will be sufficient to maintain adequate body stores. Some physicians still maintain that monthly injections of vitamin B12 is required to maintain adequate levels in the elderly and in patients with a diagnosed deficiency. There is however, no scientific evidence supporting the notion that injections are more effective than sublingual supplementation [19].

The serum vitamin B12 results indicate that subjects in this study have a low vitamin B12 syndrome (<205 pg/mL) rather than clinical deficiency. Holocobalamin assays have become available to assess this better, but these were not widely available when this study was performed. A further study to assess the efficacy of vitamin B12 supplementation in the treatment of trigeminal neuralgia pain is planned.

References

1. Merskey H, Bogduk N (1994) A Current List with Definitions and Notes on Usage. IASP Task Force on Taxonomy, IASP Press, Seattle 209-214.
2. Baker FG 2nd, Jannetta PJ, Bissonette DJ, Larkins MV, Jho HD (1996) The Long Term Outcome of Microvascular Decompression for Trigeminal Neuralgia. N Eng J Med 334: 1077-1083.
3. Devor M, Amir, Ron, Rappaport ZH (2002) Pathophysiology of Trigeminal Neuralgia: The Ignition Hypothesis. Pain 18: 4-13.
4. Caram-Salas NL, Reyes-Garcia G, Medina-Santillan R, Granados-Sotos V (2006) Thianimine and Cyanocobalamin relieve neuropathic pain in rats: syergy with dexamethasone. Pharmacology 77: 53-62.
5. Akaike A, Tamura Y, Sato Y, Yokota T (1993) Protective effects of a vitamin B12 analogue, methylcobalamin, against glutamate cytotoxicity in cultured cortical neurons. Eur J Pharmacol 241: 1-6.
6. Ide H, Fujiya S, Asanuma Y, Tsuji M, Sakai H, et al. (1987) Clinical usefulness of intrathecal injection of methylcobalamin in patients with diabetic neuropathy. Clin Ther 9: 183-192.
7. Mauro GL, Martorana U, Cataldo P, Brancato G, Letizia G (2000) Vitamin B12 in low back pain : a randomised, double-blind placebo controlled study. Eur Rev Med Pahrmacol Sci 4: 53-58.
8. Loikas S, Koskinen P, Irjala K, Löppönen M, Isoaho R, et al. (2007) Vitamin B12 deficiency in the aged: a population-based study. Age Ageing 36: 177-183.
9. McBride J (2000) B12 Deficiency May Be More Widespread Than Thought. News from the USDA Agricultural Research Service.
10. Broggi E (1953) Larger doses of Vitamin B12 in therapy of trigeminal neuralgia. Gazz Med Ital 112: 178-180.
11. Surtees SJ, Hughes RR (1954) Treatment of trigeminal neuralgia with vitamin B12. Lancet 266: 439-441.
12. Ulleland M, Eilertsen I, Quadros EV, Rothenberg SP, Fedosov SN, et al. (2002) Direct assay for cobalamin bound to transcobalamin (holo-transcobalamin) in serum. Clin Chem 48: 526-532.
13. Haas JT, Thomas FP, Kinsella LJ (2004) Is the serum cobalamin assay the best predictor of vitamin B12 deficiency? Ann Neurol 56: S34.
14. Chalk CH (2004) Diseases of the peripheral nervous system. In DC Dale, ed., ACP Medicine, section 11, chap. 2. New York: WebMD.
15. Savage DG, Lindenbaum J, Stabler SP, Allen RH (1994) Sensitivity of serum

methylmalonic acid and total homocysteine determinations for diagnosising cobalamin and folate deficiencies. Am J Med 96: 239-246.

16. Jacobs WB, Fehlings MG (2003) The Molecular Basis of Neural Regeneration. Neurosurgery 53: 943-950.
17. Carmel R (1995) 10 Malabsorption of food cobalamin. Baillieres Clin Haematol 8: 639-655.
18. Adcock BB, Mcknight JT (2002) Cobalamin Pseudodeficiency Due to a Transcobalamin I Deficiency. South Med J 95.
19. Dharmarajan TS, Norkus EP (2001) Approaches to Vitamin B12 deficiency: early treatment may prevent devastating complications. Postgrad Med 110: 99-105.