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Vitamin B12 deficiency evaluation and treatment in severe dry eye disease with neuropathic ocular pain

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Abstract
Purpose This study aims to understand the effect of vitamin B12 deficiency on neuropathic ocular pain (NOP) and symptoms in patients with dry eye disease (DED).
Methods Patients with severe DED (without receiving topical artificial tears treatment) and ocular pain were enrolled (n = 90). Patients with severe DED and vitamin B12 deficiency (group 1, n = 45) received parenteral vitamin B12 supplement + topical treatment (artificial tears treatment + cyclosporine), and patients with severe DED and normal serum vitamin B12 level (group 2, n = 45) received only topical treatment (artificial tears treatment + cyclosporine). Patients were evaluated by the ocular surface disease index (OSDI) questionnaire, 3rd question (have you experienced painful or sore eyes during last week?) score of OSDI as a pain determiner and pain frequency measure), tear break up time (TBUT), and Schirmer's type 1 test. We compared the groups' OSDI, TBUT, and Schirmer's test recordings at the first visit and after 12 weeks retrospectively.
Results The OSDI score, 3rd OSDI question score, TBUT, and Schirmer's test results improved after 12 weeks ($p < 0.001$ for each group). The mean vitamin B12 level at enrollment was 144.24 ±43.36 pg/ml in group 1 and 417.53 ±87.22 pg/ml in group 2. The mean vitamin B12 level in group 1 reached to 450 ±60.563 pg/ml after 12 weeks of treatment. The mean score changes between the groups were not statistically significant; however, the decrease in the OSDI questionnaire score (-30.80 ±5.24) and 3rd OSDI question score (-2.82 ±0.53) were remarkable in group 1 (Table 2). The mean TBUT increase was +7.98 ±2.90 s and Schirmer's test result increase was +12.16 ±2.01 mm in group 1. The mean TBUT increase was +6.18 ±1.49 s and Schirmer's test result increase was +6.71 ±1.47 mm in group 2.
Conclusions These findings indicate that vitamin B12 deficiency is related with NOP. It may be important to consider measuring the serum vitamin B12 level in patients with severe DED presenting with resistant ocular pain despite taking topical treatment.

Keywords Vitamin B12 · Neuropathic ocular pain · Dry eye disease

Introduction

Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms such as discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface [1]. Blurred vision, irritation, and ocular pain are the main symptoms of dry eye disease (DED). The symptoms associated with DED are chronic and require visits to an ophthalmologist, and their treatment has significant cost implications [2]. Within dry eye-associated ocular pain, some patients report transient pain and others, chronic pain. When ocular pain in DED patients persists for more than 6 months, it is considered chronic ocular pain [3]. Pain in patients with chronic DED show characteristics of chronic neuropathic ocular pain (NOP). In DED's chronic stage, changes occur in the ocular sensory apparatus. If ocular surface damage persists, changes may occur in the central nervous system (CNS),

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causing central sensitization [3]. Chronic inflammation and nerve damage can result in aberrant activation of the sensory fibers of the eye, resulting in neuropathic pain [4]. Unsatisfactory response to tear dysfunction therapies should prompt consideration of neuropathic mechanisms being involved. Symptoms which persist after local anaesthetic instillation are more likely to be neuropathic in origin. Neuropathic symptoms are caused by a lesion or disease of the somatosensory nervous system and can be the result of hypersensitization of peripheral or central corneal and conjunctival somatosensory nerves.

Ocular pain in DED may result from various types of diseases that lead to progressive corneal nerve damage. Vitamin B12 deficiency may be one of them, because B12 has been used as a treatment in pain associated with herpes, diabetic neuropathy, and surgical procedures [5–7]. Furthermore, vitamin B12 deficiency has been associated with pain disorders such as myofascial pain [8]. Vitamin B12 shows antioxidant activity and can improve re-epithelization and corneal reinnervation [9, 10]. Recently, the parenteral and topical forms of vitamin B12 have been used for ocular pain and symptoms in dry eye treatment [13, 14].

In our daily clinical practice, we observed that DED patients continue to suffer from ocular pain which persists after local anaesthetic instillation and dry eye symptoms while on current topical therapies. Pain descriptors are often different in patients with neuropathic vs. nociceptive pain. The patients in our study had eye pain that persisted after the local anesthetic instillation, which lasted more than six months, and reminiscent of neuropathic pain such as burning, tingling or electrical pain. These patients are likely to be resistant to topical therapy directed at optimizing the ocular surface or they may have pain which is in neuropathic origin (dysesthesia, spontaneous pain, allodynia, and hyperalgesia). After consulting with neurology and internal medicine clinics, we recognized vitamin B12 deficiency in this subset of DED patients who did not have spontaneous improvement or "regression to the mean" after 12 weeks of artificial tear and cyclosporine treatment. Detailed neurological examination ruled out any peripheral neuropathy and internal medicine clinics found that the majority of the patients in group 1 had vitamin B12 deficiency because of low dietary intake. Then, we started to measure the vitamin B12 level of every patient with DED and chronic ocular pain which was resistant to topical treatment. Several studies have shown that neurosensory dysfunction can be a component of dry eye symptoms in some patients [11, 12]. Vitamin B12 is essential for healthy neurosensory functioning.

In this study, we aimed to understand the effect of vitamin B12 deficiency and its replacement on symptoms of DED and corneal pain.

Materials and methods

We retrospectively evaluated 90 patients who sought care at the Department of Ophthalmology at Giresun University Hospital from January 2015 to December 2015 with a diagnosis of severe DED. Informed consent was obtained from all participants after the nature of the study was fully explained. The tenets of the Declaration of Helsinki were followed, and the study received approval from the local ethics committee.

Patients who were not on a current topical artificial tears treatment and who had chronic ocular pain which persisted more than 6 moths and after local anesthetic (Alcaine®, Proparacaine hydrochloride 0,5%, Alcon, Turkey) instillation and severe DED according to the ocular surface disease index (OSDI) questionnaire [15], Schirmer's test type 1 (result of <5 mm at 5 min), and tear break up time (TBUT of <5 s) were enrolled. We referred these patients to an internal medicine clinic and measured their serum vitamin B12 level. The serum B12 level measurements of 45 patients were under 220 pg/mL level (reference range, 225–930 pg/mL) (Table 2). Those of others were within normal limits. We started daily artificial tear + cyclosporine drops treatment for all DED patients. The internal medicine clinic started parenteral vitamin B12 treatment. We divided the patients into two groups: group 1, patients treated with parenteral vitamin B12 supplement (DODEX, Cyanocobalamin 1000 mcg/ml IM, Deva Holding. Turkey) + artificial tears (TEARS NATURALE® II dextran 70 + hydroxypropyl methyl cellulose, Alcon, Turkey) + cyclosporine (RESTASİS® % 0.05 0.4 ml Allergan, Turkey; n = 45), and group 2, patients who had normal serum vitamin B12 level and were treated only with artificial tears + cyclosporine (n = 45). Patients who had trigeminal neuralgia, ocular diseases (such as keratitis, glaucoma, corneal scar, ocular traumatic sequels diabetic retinopathy), diabetes mellitus (diabetic neuropathy), rheumatoid arthritis, scleroderma, pemphigoid, SLE, hyperthyroidism, cirrhosis or hepatitis, Stevens–Johnson syndrome, pernicious anemia, atrophic gastritis, Crohn's disease and who were under oncologic treatment or pain relief medication were excluded. According to records, the vast majority of our patients had similar visual acuity (20/25–20/20 as per Snellen tests) and intraocular pressure. In the internal medicine clinic, 1000 mcg of vitamin B12 was administered parenterally (deep intramuscular) daily for 1 week followed by 1000 mcg per month to patients with vitamin B12 deficiency. The patients were evaluated by the same ophthalmologist (S.O.), who looked at their total OSDI questionnaire, TBUT, and Schirmer's test type 1 (without anesthetic) scores at the first visit and after 12 weeks of parenteral B12 treatment and daily artificial tear + cyclosporine drops treatment. We used the score of the third question of the OSDI questionnaire (have you experienced painful or sore eyes during last week?) as a pain

determiner and pain frequency measure, for evaluating changes in chronic ocular pain.

We compare the groups' OSDI, TBUT, and Schirmer's test recordings at the first visit and after 12 weeks retrospectively.

Statistics

A sample size of 90 patients, with 45 patients per group, was sufficient for the statistical analysis. We used SPSS program (16.0, Chicago, IL, USA) for the analysis. We used an independent sample *t* test for age and OSDI, TBUT, and Schirmer's test 1 scores for comparing between groups and the chi square test for gender distribution. The data were reported as mean and standard deviation (SD).

Results

Table 1 shows the characteristics of the groups. Most patients were female, but there was no difference between the two groups in terms of age.

The mean plasma vitamin B12 level was significantly lower (144.24 ±43.36 pg/mL) in group 1 than in group 2 at first enrollment. After consulting, the internal medicine clinic patients (group 1) received vitamin B12 deficiency treatment. After 12 weeks, the mean vitamin B12 level of patients in group 1 reached 450.31 ±60.563 pg/mL (Table 2).

At the first evaluation, the OSDI score, 3rd OSDI question score, TBUT, and Schirmer's test results were similar between the two groups (Table 2).

The patients' OSDI score, 3rd OSDI question score, TBUT, and Schirmer's test results improved after 12 weeks ($p < 0.001$ for each group). The mean score changes between groups were not statistically significant; however, interestingly, the decrease in the OSDI questionnaire score (-30.80 ±5.24) and 3rd OSDI question score (-2.82 ±0.53) were remarkable in group 1 (Table 2). The mean TBUT increase was +7.98 ±2.90 and Schirmer's test increase was +12.16 ±2.01 in group 1. The mean TBUT increase was +6.18 ±1.49 and Schirmer's test increase was +6.71 ±1.47 in group 2.

Table 1 Characteristics of groups

	Group 1^	Group 2*	*p* value
Age, years (mean ±SD)	42.24 ±5.01	43.91 ±5.26	0.90
Gender, male n (%)	17 (37.8)	15 (33.3)	0.66†

SD: standard deviation *p* value calculated by independent samples *t* test

† *p* value calculated by chi-square test

^ received parenteral vitamin B12 and topical artificial tear+cyclosporine treatment for 12 weeks

*received only topical artificial tear+cyclosporine treatment for 12 weeks

Discussion

A literature review of chronic ocular pain demonstrates that tear dysfunction persistence causes ocular sensory nerve injury, leading to chronic pain with neuropathologic changes [16]. Another study was performed to assess dry eye symptoms and patients' response to artificial tears; incomplete improvement in ocular pain with artificial tears is associated with features of NOP [17]. Ocular pain correlates with the symptom severity and persistence [18].

Vitamin B12 has been associated with pain disorders in many studies. In a review, methyl cobalamin (MeCbl), a vitamin B12 analog, was found to have potential analgesic effects on neuropathic pain via its effect on improvement in nerve conduction velocity, injured nerve regeneration, recovery of neuromuscular functions in peripheral hyperalgesia and allodynia, and inhibition of ectopic spontaneous discharges from peripheral primary sensory neurons in neuropathic pain states [19]. Recently, it was reported that NOP in a case was treated with parenteral vitamin B12 supplement [14].

These studies' findings suggest that ocular pain in some patients with severe DED is likely to be a result of neurosensory dysfunction. Ocular pain changes to NOP because of incomplete improvement in pain symptoms despite taking topical treatment. In our study, we evaluated the examination records of 90 patients at the first visit and after 12 weeks. These patients were not under topical artificial tears treatment at first sight. Thus, after starting topical treatment to all, dry eye symptoms and ocular pain were alleviated for each group. A close relationship between dry eye severity and ocular pain has been observed, especially in a subset of patients who also have vitamin B12 deficiency. After restoring the normal serum vitamin B12 level (reference range, 225–930 pg/mL), ocular pain has improved. Especially, amelioration achieved in group 1's OSDI score and third OSDI question score , which we assumed as a pain determiner, was remarkable. By looking at the patients' disability grade, which is based on the OSDI questionnaire, we found a majority of patients in group 1 improved from severe to mild-moderate disability. The mean TBUT increase and Schirmer's test result increase was better in group 1 than group 2. These findings may point out the correlation between NOP and vitamin B12 deficiency.

DED is a major health problem due to its increasing incidence and significant morbidity. Its treatment has significant cost implications. Treatments with topical artificial tears targeting the ocular surface are not sufficient for pain improvement in a certain number of DED patients. A subset of dry eye may be better represented as a chronic neuropathic pain disorder; dry eye exams should include an evaluation of NOP and underlying reasons.

Based on our knowledge, vitamin B12 deficiency alone does not cause ocular surface disease, but it may aggravate ocular surface pathologic changes and neurosensory damage

Table 2 Comparison of dry eye severity and vitamin B12 level at enrollment and after 12 weeks of therapy with parenteral vitamin B12 and topical artificial tear + cyclosporine drops

Patient group (mean ±SD)				
	Group 1 (n = 45) at enrollment	Group 1 (n = 45) after 12 weeks of treatment	Group 2 (n = 45) at enrollment	Group 2 (n = 45) after 12 weeks of treatment
Vitamin B12, pg/ml	144.24 ±43.36	450.31 ±60.563	417.53 ±87.22	–
OSDI, score	67.67 ±4651	37.09 ±3.76	66.71 ±4060	53.08±4.54
3rd question of OSDI, score	3.80 ±0.40	0.98 ±0.39	3.69 ±0.46	2.62 ±0.80
TBUT, s	3.53 ±0.54	11.73 ±2.87	3.56 ±0.52	9.53 ±1.40
Schirmer's test, mm	2.82 ±0.91	14.98 ±1.92	3.11 ±0.61	9.82 ±1.41
Comparison within group and between groups, *p* values and scores				
	Group 1 vs. group 2 before treatment	Group 1 before vs. after treatment	Group 2 before vs. after treatment	Group 1 vs. group 2 after treatment
Vitamin B12	p < 0.001	p<0.001	–	–
OSDI	p:0.3	p<0.001	p<0.001	p<0.001
OSDI change, score		−30.80 ±5.24	−13.24 ±4.86	
3rd question of OSDI	p:0.23	p<0.001	p<0.001	p<0.001
3rd question of OSDI change, score		−2.82 ±0.53	−1.07 ±0.88	
TBUT	*p* = 0.12	*p* < 0.001	*p* < 0.001	*p* < 0.001
TBUT change, s		+7.98 ±2.90	+6.18 ±1.49	
Schirmer's test	*p* = 0.08	*p* < 0.001	*p* < 0.001	*p* < 0.001
Schirmer's test change, mm		+12.16 ±2.01	+6.71 ±1.47	

OSDI: ocular surface disease index, TBUT: tear break-up time, SD: standard deviation

p value calculated by independent samples *t* test

to corneal nerves resulting in abnormal pain persistence in DED patients despite being under topical artificial tears treatment. In this context, we searched for an answer to 'does vitamin B12 deficiency plays a role on NOP development in severe DED patients?' question and we have conducted our study. We have demonstrated the correlation between ocular pain and vitamin B12 deficiency.

Neuropathic pain is more likely to be chronic, difficult to treat, and, therefore, important to distinguish in dry eye patients. In this regard, serum vitamin B12 level measurement should be taken into account for management of ocular symptoms and NOP in DED patients who continue to have dry eye symptoms while on current therapies.

Conclusions

Pain in dry eyes is chronic and may be neuropathic in a subset of patients. We use the term NOP in this sense. We tried to understand the role of vitamin B12 in dry eye symptoms and NOP improvement. It may be important to consider measuring the serum vitamin B12 level in patients with severe DED. Treating the vitamin B12 deficiency in addition to topical treatment may improve ocular pain in this subset of patients with DED and NOP. Recognizing NOP in chronic DED and vitamin B12 deficiency can help in effective management. Further studies examining NOP in DED may help elucidate the reasons and contribute to the development of new potential therapeutic interventional strategies.

Compliance with ethical standards

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Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study, formal consent is not required.

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