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Original Article

The Role of Oxidative Stress and Inflammatory Mediators in Benign Paroxysmal Positional Vertigo

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OBJECTIVE: Benign paroxysmal positional vertigo (BPPV) is the most common peripheral cause of vertigo. It can be defined as transient vertigo induced by rapid changes in head position associated with a characteristic paroxysmal positional nystagmus. The aim of this study was to search for the possible role of oxidative stress and inflammatory mediators in the pathogenesis of BPPV.

MATERIALS and METHODS: Total antioxidant status as well as paraoxonase, tumor necrosis factor alpha, interleukin (IL) 6, and IL-1β levels were evaluated in peripheral venous serum samples of 30 BPPV and 30 control patients.

RESULTS: Total antioxidant status levels were lower in the BPPV group than in the control group (p=0.008). After Epley's repositioning maneuver in the vertigo group, there was a statistically significant decline in IL-1β levels at the first and third month visits (p=0.014 for first month and p=0.013 for third month).

CONCLUSION: Our findings suggested that IL-1β and oxidative stress contributed to the pathogenesis of BPPV.

KEYWORDS: Benign paroxysmal positional vertigo, Inflammation, Oxidative stress

INTRODUCTION

Benign paroxysmal positional vertigo (BPPV) is the most common type of vertigo. Almost 10% of patients admitted to emergency departments with moderate-to-severe vertigo have BPPV [1]. BPPV patients have episodic vertigo provoked by head movements, and they show classical horizontal, vertical, or torsional nystagmus with the characteristics of latency, crescendo and decrescendo pattern, fatigability, transciency, and reversibility [2]. In most cases, the underlying cause is canalolithiasis of the posterior semicircular canal; however, horizontal canal involvement can be greater than expected and may contribute to up to 20% of cases [2]. Although most cases are idiopathic, head trauma (17%), vestibular neuritis (15%), vertebrobasilar ischemia, labyrinthitis, and ear surgery can be the underlying causes [3].

Oxidative stress occurs when the overproduction of reactive oxygen species (ROS) such as hydroxyl radicals, superoxide anions, and hydrogen peroxide occurs [4]. Normally, the harmful effects of oxidation products are balanced by enzymatic and nonenzymatic antioxidation defense mechanisms. Catalase, superoxide dismutase, and glutathione peroxidase are major enzymatic antioxidants, whereas ascorbic acid (Vitamin C), β-carotene (Vitamin A), α-tocopherol (Vitamin E), albumin, and uric acid are the major nonenzymatic antioxidants. Oxidative stress can cause severe tissue injury by provocating enzyme inactivation, lipid peroxidation, and deoxyribonucleic acid (DNA) damage [4].

Total antioxidant capacity (TAC) reflects the overall sum of the main antioxidants in the plasma and body fluids of human beings. Vitamins C, vitamin E, albumin, bilirubin, and uric acid are the main antioxidants contributing to the TAC levels of serum. TAC gives important data about the total status of antioxidation events in the body [5].

Paraoxonase (PON) is an enzyme that hydrolyzes paraoxon, a toxic metabolite of organophosphate molecules. In addition to hydrolyzing organophosphate compounds, thereby reducing their neurotoxic effects, PON decreases lipid peroxidation and initiation as well as the progression of atherosclerosis. There are three forms of the PON gene family: PON 1, 2, and 3. PON 1 is carried by high-density lipoproteins in serum, and it has antioxidant effect [6].

In otolaryngology practice, several diseases have been investigated for their probable relationship with oxidative stress, including otitis media, rhinosinusitis, chronic tonsillitis, nasal polyps, laryngeal cancer, and hearing loss [7].

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Interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α are the main pro-inflammatory cytokines responsible for cascade reactions in inflammation. They are mainly synthesized by monocytes and leukocytes. TNF-α has the ability to induce phospholipase A_2 to provoke the production of other pro-inflammatory mediators, such as prostaglandins, thromboxanes, and leukotrienes, and it is also responsible for the formation of oxygen radicals. TNF-α can be responsible for inflammatory conditions of the inner ear such as hearing loss following bacterial meningitis [8]. The IL-1 family also participates in the cascade reactions of inflammatory conditions of the inner ear. IL-1β may play a role in the pathogenesis of autoimmune inner ear disease because among patients who do not respond to corticosteroid treatment, the IL-1β antagonist Anakinra may be effective [9]. IL-1β, IL-6, and TNF-α have also been shown to be effective in the pathogenesis of cysplatin ototoxicity of the inner ear[10]. Some inflammatory conditions in the body, such as vasculitis, can lead to increased risk of BPPV; this can have possible effects of inflammation in inner ear disease [11]. In this study, we investigated the probable role of oxidative stress and inflammation in BPPV. The evaluated markers were TAC, PON, IL-1β, TNF-α, and IL-6. To the best of our knowledge, this is the first study on the relationship between inflammation, oxidative stress, and BPPV with these markers.

MATERIALS and METHODS

This study was performed in our institution after approval of the local ethical committee with the number of 2009/73. Thirty consecutive BPPV patients were included in the study. All patients experienced posterior canal BPPV. A control group was chosen from sex and age matched healthy volunteers without vertigo complaints or chronic illnesses. For both the patient and control groups, 19 (63%) were female, 11 (37%) were male, and the mean age was 48. Informed consent for the study was acquired from both the patient and control groups.

For the diagnosis of BPPV, the Dix–Hallpike maneuver was applied to patients with vestibular complaints such as vertigo, nausea, vomiting, and imbalance. Worsening of the symptoms with head movements was required on history. Torsional nystagmus with latency, fatigability, and lasting shorter than 60 seconds in the Dix–Hallpike maneuver were considered to indicate BPPV. All patients had geotrophic type nystagmus beating towards the lowermost ear during the Dix–Hallpike maneuver in our study. Routine pure tone audiometry was performed for all patients in the BPPV group. Patients with hearing loss, otologic surgery, neurologic diseases, pregnancy, lactation, hypothyroidism, hypertension, diabetes mellitus, and other inflammatory and infectious conditions were excluded. All patients were treated with Epley's repositioning maneuver. BPPV patients were seen in first and third month control periods. The Dix–Hallpike maneuver was applied in these control periods. All patients were free of symptoms, and nystagmus was not observed during the maneuver in the control visits.

Peripheral serum samples were collected from the BPPV group at the first visit (during vertigo attack) and at the first and third months. Control group serum samples of healthy volunteers were collected during routine medical check-up. To exclude systemic diseases such as renal insufficiency, hepatic illnesses, thyroid disorders, and hyperlipidemias, serum levels of renal, thyroid, and hepatic function tests, serum lipid profiles, and the serum biochemistry of electrolytes such as Na, K, Cl, and Ca were all studied. BPPV and control group patients with normal blood biochemistry were included in the study. Serum samples were stored at -20°C for studying oxidative stress markers, PON, TAC, and inflammatory mediators IL-1β, IL-6, and TNF-α. Measurements of IL-1β, IL-6. and TNF-α levels were obtained by the solid phase enzyme amplified sensitivity immunoassay method with an enzyme linked immunoassay (ELISA) kit (Biosource®; USA). PON and TAC levels were studied by spectrophotometry (Rel Assay Diagnostics®; Gaziantep, Turkey).

Statistical analysis

Statistical was performed using Statistical Package for the Social Sciences version 16.0 (SPSS Inc.; Chicago, IL, USA). The Mann-Whitney U test was used for comparison of the BPPV and control groups at each time point, and the Wilcoxon Signed Rank Test was used for variations over time for the BPPV group. Results were considered to be statistically significant when $p<0.05$.

RESULTS

The mean TAC values in the BPPV group at the first visit (0 months) and at the first and third months were 0.93, 0.93, and 0.88 mmol Trolox equiv/L, respectively. The mean TAC value of the control group was 1.16 mmol Trolox equiv/L. The first visit (0 months) BPPV group values were significantly lower than those of the control group (p=0.008). In the BPPV group, there was a decline in TAC levels in the third month; however, this was not statistically significant (p=0.236). Figure 1 shows the mean values of TAC in the patients.

Mean values of PON of BPPV group in first visit (0 month), first month and third month and control group were 123-127-131-131 U/L respectively. There was no statistically significant difference in PON levels between the groups (p=0.773). After Epley's repositioning maneuver, there was an increase in PON levels at the first and third months; however, this was not statistically significant (first month p=0.274, third month p=0.657).

Regarding the TNF-α results, the mean values were 241.4, 19.6, and 17.2 pg/mL at the first visit (0 months), the first month, and the third month for the BPPV patients, respectively, and 50.7 pg/mL for the

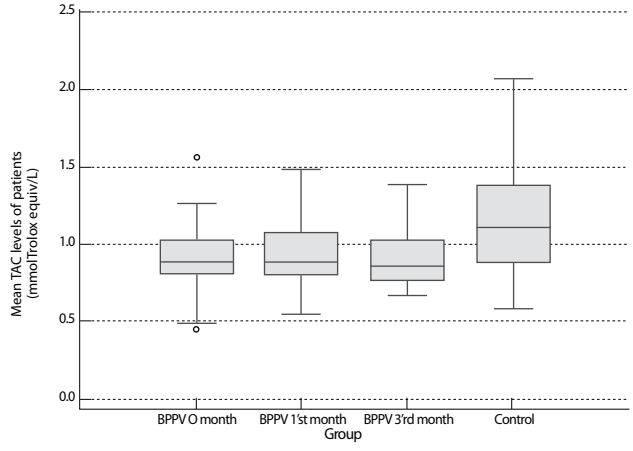

Figure 1. Comparison of serum TAC levels between the study and control groups. (BPPV: benign paroxysmal positional vertigo, TAC: total antioxidant capacity)

control group. In the BPPV group, the 0 month TNF-α values were greater; however, there was no statistically significant difference (p=0.636). There was a decline in TNF-α levels after treatment; however, this was not statistically significant (first month p=0.199, third month p=0.117). Figure 2 shows a comparison of the BPPV and control group TNF-α levels.

The first visit (0 months), first month, and third month mean IL-1β levels for the BPPV group were 92.7, 14.7, and 15.4 pg/mL, respectively; the control group mean IL-1β level was 20.4 pg/mL. The 0 month levels for the BPPV group were greater than those of the control group; however, there was no statistically significant difference (p=0.574). There was a statistically significant decline of serum IL-1β levels between 0 months and after treatment at the first and third months (p=0.014 for the first month, p=0.013 for the third month). The patient and control group IL-1β levels are shown in Figure 3.

The first visit (0 months), first month, and third month mean IL-6 levels of the BPPV group and the mean IL-6 levels of the control group were 436.6, 132.7, 99.5, and 177.5 pg/mL, respectively. The 0 month levels were greater than those of the control group; however, there was no statistically significant difference (p=0.723). There was a statistically significant decline in the levels of serum IL-6 between 0 months and after treatment at the first and third months (p=0.001 for the first month and p=0.018 for the third month). The patient and control group IL-6 levels are shown in Figure 4.

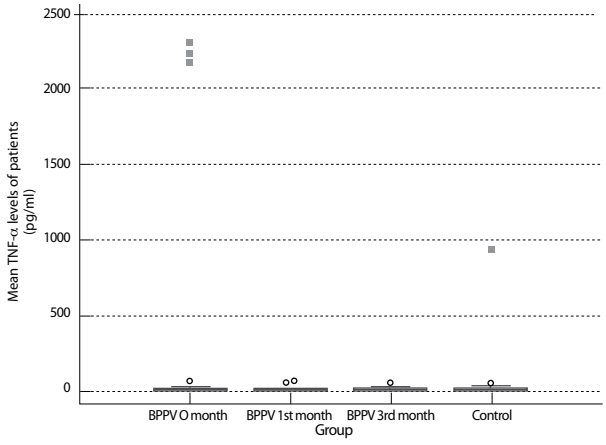

Figure 2. Comparison of TNF-α levels between the study and control groups. (BPPV: benign paroxysmal positional vertigo, TNF-α: tumor necrosis factor α)

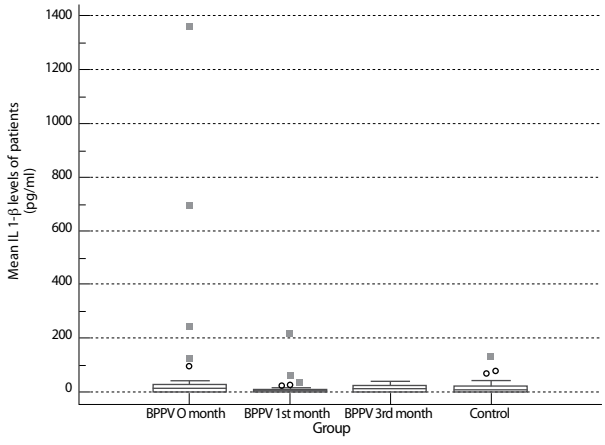

Figure 3. Comparison of serum IL-1β levels between the study and control groups. (BPPV: benign paroxysmal positional vertigo, IL-1β: interleukin 1β)

DISCUSSION

The preliminary results of this study showed that oxidative stress may be connected with the pathogenesis of BPPV. We determined that serum TAC levels in BPPV patients were significantly lower than those of the control group. The PON levels were also lower in the BPPV group, and there was an increase after treatment with Epley's repositioning maneuver; however, this change was not statistically significant. The possible relationship between BPPV and oxidative stress can be explained on an ultrastructural basis. Human otoconia are the sensory detector organs found in the utriculus and sacculus for the detection of linear acceleration and head tilt movements against gravity. They contain more than 90% calcite (crystalized calcium carbonate), and they are the only calcite-based biological structures acting in physiological processes in human beings, whereas other two systems, bone and teeth, contain calcium phosphate [12, 13]. Calcium and carbonate levels in the endolymph are critical for normal otoconial function, which is primarily provided by a calcium channel transport system expressed in the inner ear [14]. When the ultrastructural dysmorphology of human otoconia was investigated by Walther et al. [15], they found that otoconia may have various degrees of degeneration, from minor to major changes. In the major forms, profound morphological alterations, such as fractures with excessive loss of calcium-rich otoconia material, could be observed. Finally, high-grade disintegration in the otoconia caused complete dissolution and fragmentation of calcium-rich material to the endolymph, creating the possible underlying cause of symptoms in BPPV. Vibert et al. [16] also demonstrated that in ovariectomized rats, osteoporosis induction had created a less dense and less calcium-containing otoconia ultrastructure, which can be attributed to the development of BPPV. In addition to the ultrastructural and animal studies, clinical studies have also investigated the probable relationship between BPPV and calcium metabolism. Talaat et al. [13] demonstrated that BPPV may be associated with low bone mineral density and vitamin D deficiency. Calcium metabolism and oxidative stress are closely linked. The endoplasmic reticulum, the major organelle for calcium storage, has the capability to increase the influx of calcium under stress conditions, which in turn triggers the cascade reaction of ROS formation in mitochondria [17].

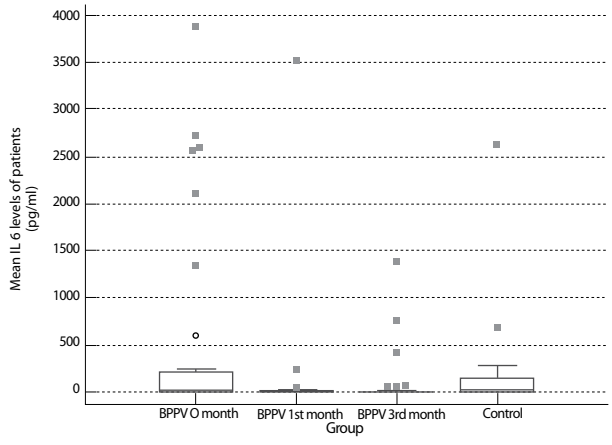

Figure 4. Comparison of serum IL-6 levels between the study and control groups. (BPPV: benign paroxysmal positional vertigo, IL-6: interleukin 6)

Both oxidative stress and calcium influx into the mitochondria cause rupture of the mitochondrial outer membrane and apoptosis under reperfusion injury [18]. When all these studies are considered together, BPPV may have an oxidative stress-based pathogenesis.

In addition to calcium metabolism and its indirect relationship with oxidative stress, there have been also three clinical studies investigating the direct role of oxidative stress in BPPV published in the English literature. Goto et al. [19] studied the probable role of angiitis and diacron reactive oxygen metabolites (d-ROM) in BPPV; they found higher levels of vascular cell adhesion molecule-1 and d-ROM in BPPV with long lasting vertigo attacks, so they concluded that angiitis and ROM can play a role in the pathogenesis of BPPV. Another study investigated the total antioxidant status, the total oxidant status and the oxidative stress index in BPPV patients. The authors found that the total antioxidant status was lower in the BPPV group, similar to the results of our study. There was no significant difference between the BPPV and the control groups regarding total oxidant status and the oxidative stress index. A limitation of this study was that there were no results for markers after the repositioning maneuver or follow-up period [20]. Recently, Tsai et al. [21] found that the serum levels of the oxidative stress marker malondialdehyde were higher in the BPPV group before the repositioning maneuver. The levels of the antioxidant enzyme superoxide dismutase were higher in the post-maneuver group, suggesting the possible role of oxidative stress in BPPV.

In our study, the lower levels of the antioxidant parameters TAC and PON during vertigo attack (first visit) of BPPV patients can be due to two reasons; first, the imbalance between oxidation-antioxidation systems may cause an increase in ROS, which is the probable reason for the formation of otoliths or the transition of otoliths to the semicircular canals; second, vertigo attacks or emotional stress caused by vertigo attacks in BPPV patients may trigger weaker antioxidant defense mechanisms against oxidative stress and decreases in the levels of TAC and PON.

The cascade reactions of inflammation can also be involved in the pathogenesis of inner ear diseases. The inner ear has the ability to initiate an active immune response and inflammatory process, and an increase in these cascade reactions can result in hearing loss. Furthermore, immunosuppressant agents such as steroids can decrease inflammatory reactions and damage the cochlea [22, 23]. After antigen injection into the inner ear, the pro-inflammatory mediators IL-1β, IL-6, and TNF-α increase, causing inflammatory cell accumulation; blocking of TNF-α with etanercept diminishes this inflammatory response [24]. IL-1β can be involved in the pathogenesis of autoimmune inner ear disease, and the IL-1β antagonist Anakinra may have benefits for this disease [9]. The inflammatory mediators IL-1β, IL-6, and TNF-α may also be involved in cysplatin-induced ototoxicity [10].

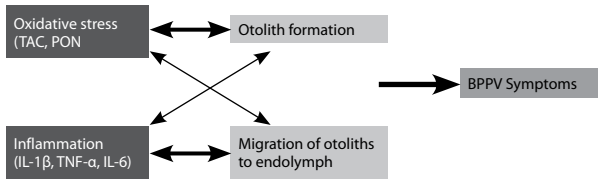

Figure 5. The results of our study. (BPPV: benign positional paroxysmal vertigo, TAC: total antioxidant capacity, TNF-α: tumor necrosis factor α, IL-1β: interleukin 1β, IL-6: interleukin 6)

The inner ear is a unique organ with a blood-labyrinthine barrier like the brain, has connections with cervical lymph nodes, and is capable of cytokine production in the spiral ligament; hence, with cervical lymph node connections, the inner ear is under the control of systemic T- lymphocytes for immune responses [24]. Rheumatoid arthritis, an immune-mediated systemic disorder, can also affect the inner ear and can cause high-frequency hearing loss [25]. A high percentage of BPPV in patients with giant cell arteritis and systemic sclerosis also demonstrates that immune-mediated inflammatory ischemia may play a role in BPPV [3, 26].

In this study, we investigated the possible role of inflammation in BPPV by studying the levels of IL-1β, IL-6, and TNF-α. The levels of all three pro-inflammatory mediators were higher in the BPPV group and decreased with the repositioning maneuver. The decreases in the IL-1β and IL-6 levels were statistically significant after treatment. This may show the probable role of inflammation in the pathogenesis of BPPV. Like oxidative stress, primary elevation of inflammatory mediators may cause otolith formation or otolith migration to the semicircular canals, or, the vertigo attack itself in BPPV may cause an increase in inflammatory mediators.

Although oxidative stress and inflammatory reactions can be discussed separately for damage to the inner ear, they can actually have synergistic effects. In our study, the levels of TAC were lower in the BPPV group than the control group; concomitantly, there was a statistically significant decrease in the levels of IL-1β and IL-6 after the repositioning maneuver. These findings suggested that oxidative stress and inflammation may have a synergistic or complementary role in the pathogenesis of BPPV. The results of our study are shown in Figure 5.

In conclusion, the results of our study revealed that the oxidative stress marker TAC and the inflammatory mediators IL-1β and IL-6 may play roles in the pathogenesis of BPPV, and these two mechanisms may have synergistic or complementary effects. With additional studies, new systemic or intra-tympanic treatment protocols including antioxidant and/or anti-inflammatory medications may be used in the treatment of BPPV patients.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Mersin University Local Ethical Comittee with the number of 2009/73.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - T.G., Z.N.Ü., O.İ., M.B.Y.C., M.Ü.; Design - T.G., Z.N.Ü., O.İ., M.B.Y.C., M.Ü.; Supervision - T.G., Z.N.Ü., O.İ., M.B.Y.C., M.Ü.; Resources - T.G., Z.N.Ü., O.İ., M.B.Y.C., M.Ü.; Materials - T.G., Z.N.Ü., O.İ., M.B.Y.C., M.Ü.; Data Collection and/or Processing - T.G., Z.N.Ü., O.İ., M.B.Y.C., M.Ü.; Analysis and/or Interpretation - T.G., Z.N.Ü., O.İ., M.B.Y.C., M.Ü.; Literature Search - T.G., Z.N.Ü., O.İ., M.B.Y.C., M.Ü.; Writing Manuscript - T.G., Z.N.Ü., O.İ., M.B.Y.C., M.Ü.; Critical Review - T.G., Z.N.Ü., O.İ., M.B.Y.C., M.Ü.

Conflict of Interest: No conflict of interest was declared by the authors.

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