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The possible contribution of angiitis to the onset of benign paroxysmal positional vertigo (BPPV)

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Abstract

Objective: The aim was to evaluate the oxidative stress and the angiitis in patients with BPPV. **Method:** Patients with benign paroxysmal positional vertigo (BPPV) within 14 days of onset were analyzed. The level of diacron reactive oxygen metabolites (d-ROM) and circulating soluble vascular cell adhesion molecule 1 (VCAM-1), were evaluated. As a treatment the patients were taught to perform the Brandt-Daroff exercise at home by themselves. The prognosis of BPPV, which is measured as the time until the disappearance of positional nystagmus by a physician during the outpatient visit each week, the relation among the level of oxygen metabolites, vascular molecule and the duration until remission were analyzed. **Results:** The patients who required longer time for the disappearance of positional nystagmus showed high d-ROM and VCAM levels, whereas those who required shorter time for remission showed lower d-ROM and VCAM levels. **Conclusion:** There is an increased expression of VCAM-1 and d-ROM confirming the existence of an angiitis and supporting the vascular involvement in BPPV. The identification of the high levels of d-ROM and VCAM-1 can open the way to selective pharmacological treatments able to correct the oxidative stress and activation of endothelial cells.

Keywords: vertigo, VCAM-1, diacron reactive oxygen metabolites.

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INTRODUCTION

Benign paroxysmal positional vertigo (BPPV) is the most common cause of vertigo. Benign paroxysmal vertigo accounts for 26% of all vertigo[1]. The incidence of BPPV increases with each decade of life[2], peaking at the sixth to seventh decade of life[1]. BPPV is a mechanical problem of the inner ear caused by abnormal stimulation of a semicircular canal. Most BPPVs are thought to be caused by otoconia detaching from the otolithic membrane and moving to the lowest point of the inner ear, usually the posterior canal (PC). This is referred as canalithiasis or cupulolithiasis[3]. The vestibule connects to the 3 semicircular canals (posterior canal [PC], horizontal canal [HC], and anterior canal). Each one of the semicircular canal is a candidate of the lesion of BPPV. The diagnosis of BPPV is based on the patient's history and the findings on positional testing. Positional testing is used to identify the canal involved. Once the canal is identified, the patients is treated effectively with an appropriate particle repositioning procedure which is now widely accepted. However. there is so far no suitable pharmacological treatment for this entity. We should understand the basic pathology why either canalolithiasis or cupulolithiasis occur to invent new pharmacological treatment.

The pathogenesis of the benign paroxysmal positional vertigo (BPPV) is a vestibular lesion like canalolithiasis or cupulolithiasis. The prognosis differs among individuals. It may depend on the level of otolith damage. However, it is not known how these vestibular lesion can occur. It is known that oxidative stress play some role in some inner ear diseases.

It is known that oxidative stress play some role in some of inner ear disease like sensorineural hearing loss due to aging. Free radical is produced as a result of oxidative stress. ROS (Reactive Oxygen Species) and NO Nitric oxide are known as free radicals. Radical scavengers and antioxidants play a role protecting the inner ear from oxidative stress. There are some basic data to indicate the relationship between oxidative stress and endolymphatic hydrops. However, there are no clinical data from the patients. In the previous study diacron reactive oxygen metabolites (d-ROM) was measured by the Free Radical Analytical system 4(FRAS4) from the blood of subjects with BPPV. Although there are no statistically significant differences among three groups, the d-ROM value of BPPV and Ménière's disease are higher with respect to control.

We postulated that ischemia of the vestibular organ followed by blood recirculation may provoke oxidative stress. The ischemia due to the angiitis and following reperfusion should be considered. We evaluated vascular cell adhesion molecules (VCAM-1) as an ischemia marker. The elevated oxidative stress can provoke damage in vestibular organ (especially otolith dysfunction). The elevated oxidative stress can cause canalolithiasis, which is one of pathogenesis of BPPV as a result of otolith aberration to the canal organ. Free oxygen radicals are highly reactive molecules playing pivotal roles in the pathophysiology of such different diseases as neurodegenerative disorders, chronic inflammatory disease, and sleep apnea syndrome[4,5]. It is reported that psychological stress is closely related to the onset and course of Ménière's disease[6] and BPPV[7] Oxidative stress and psychological stress are closely related[8, 9]. Based on these considerations, it is hypothesized that BPPV may be linked to increased oxidative stress. The purpose of this study was to evaluate free oxygen radicals by a method providing values of reactive oxygen metabolite (d-ROM) concentration and VCAM-1 in blood samples from patients with BPPV.

MATERIALS AND METHODS

Prospective study was undertaken. Physical examination was performed for the evaluation of vertigo including pure tone audiometry and vestibular examination including positional nystagmus. The diagnosis of BPPV was performed by the typical positional nystagmus evoked by Dix-Hallpike procedure for PC-BPPV. AS for HC-BPPV characteristic direction alternating horizontal nystagmus during right lateral and left lateral position in lying down were examined. Blood samples of BPPV patients who visited our hospital within 14 days of onset of 22 cases of BPPV (age 54.7±15.1:male 5, female 17), PC type 11 and HC type 11 (Table 1). Days until collection of blood from the onset of HC-BPPV (N=11) was 4.4±2.6 days, and of PC-BPPV (N=11) was 4.5±3.2 days.

Table1. Number of subjects according to type of BPPV

	Total	HC-BPPV	PC-BPPV
Males	5	3	2
Females	17	8	9
Total	22	11	11

Blood samples were collected for VCAM-1 and d-ROM evaluation. We evaluated VCAM-1 as an ischemia marker and d-ROM as a marker for oxidative stress. ROMs were measured in blood samples by the Diacron reactive oxygen metabolite (D-ROM) test. This test is based on the ability of transition metals to catalyze in the presence of peroxides, the formation of free radicals, which are trapped by an alchilamine. The alchilamine reacts, forming a colored radical detectable at 505 nm. The utilized reagents are the chromogen (R1, an alchi-

lamine) and a PH 4.8 buffer (R2). Ten μL of hemolyzed blood are added. The sample is mixed and centrifuged. After 1 minute, the sample is read again. The average difference in absorbance (A/min) is multiplied by a k factor and calculated using serum with defined value. The values were expressed as Carratelli Units (U.Carr)[10].

As a treatment for BPPV, the patients were instructed to perform the Brandt - Daroff exercise[11] at home by themselves three times a day. Patients are asked to visit each week for evaluation (positional nystagmus) by a physician to confirm the cure of BPPV.

The prognosis of BPPV was evaluated as the time until the disappearance of positional nystagmus. The average time for remission of PC-BPPV was 19.3±15.1 days and 15.4±9.5 days in HC-BPPV. The relation between these time periods and either initial VCAM-1 or d-ROM levels were evaluated. All data were analyzed by Microcal Origin R ver 6.0 (Microcal Software, Inc. MA USA).

RESULTS:

Patients who required longer time for the disappearance of positional nystagmus showed high VCAM level, whereas those who required shorter time for remission showed low VCAM1 level. There is a correlation between the value of VCAM-1 and time until remission (Figure 1). Patients who required longer time for the disappearance of positional nystagmus showed high VCAM level, whereas those who required shorter time for remission showed low VCAM-1 level.

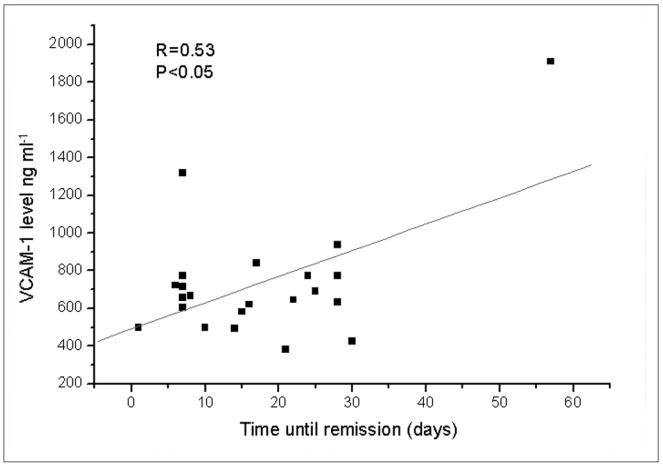

Figure 1. The correlation between value of VCAM-1 and time until remission. There are correlation between value of VCAM-1 and time until remission (R=0.53,P<0.05).

Patients who required longer time for the disappearance of positional nystagmus showed high d-ROM level, whereas those who required shorter time for remission showed low d-ROM level. There is a correlation between the value of d-ROM and time until remission (Figure 2). Patients who required longer time for the disappearance of positional nystagmus showed high d-ROM level, whereas those who required shorter time for remission showed low d-ROM level. There is no correlation between the value of VCAM-1 and d-ROM.

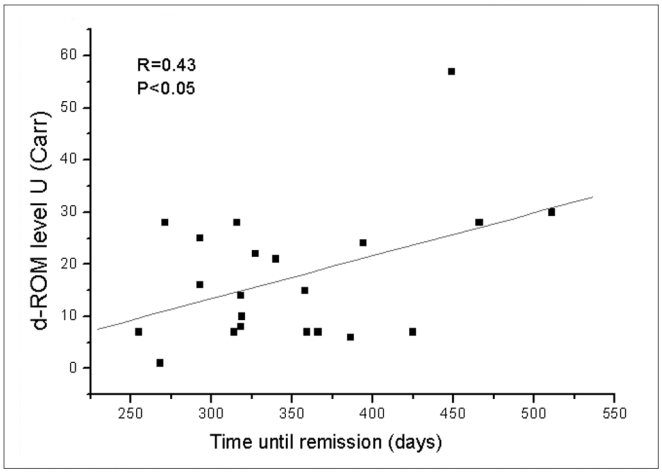

Figure 2. Correlation between value of d-ROM and time until remission There are correlation between value of d-ROM and time until remission (R=0.43,P<0.05).

DISCUSSION

More severe oxidative stress evokes stronger damage in otolith organ. The stronger the damage, the longer the time required for remission. In addition, the stronger the angiitis, the longer the time required for remission. Inflammation is known to play an important role as cause of various angiitis such as atherosclerosis. We postulated that ischemia of the vestibular organ followed by blood recirculation may provoke generation of cytotoxic radicals and produce damage of phospholipids in cytomembrane and result in elevated oxidative stress (Figure 3). Recently it is reported that elevated VCAM is closely related to sudden deafness[12]. The increased expression of circulating adhesion molecules confirmed the existence of an endothelial dysfunction and supports the vascular involvement of the disease.

In the previous report, we presented that free oxygen radicals, as measured in peripheral blood samples by the d-ROM test, were relatively enhanced in BPPV patients[13]. Patients had increase mean value in contrast to healthy adults (between 250 t 300 U.Carr). In this experiment the value of d-ROM was 349.8±68.2 U.Carr, in which 346.54545±67.9 in HC-BPPV and 353.4±72.0 in PC BPPV respectively. These values were comparable to our previous data[13]. Cesarone and colleagues have found that in normal subjects the mean (±SD) levels of free radicals were 312 (±49) U. Carr before antioxidant treatment and 218 (±33) U. Carr after treatment (p<0.05) [10].

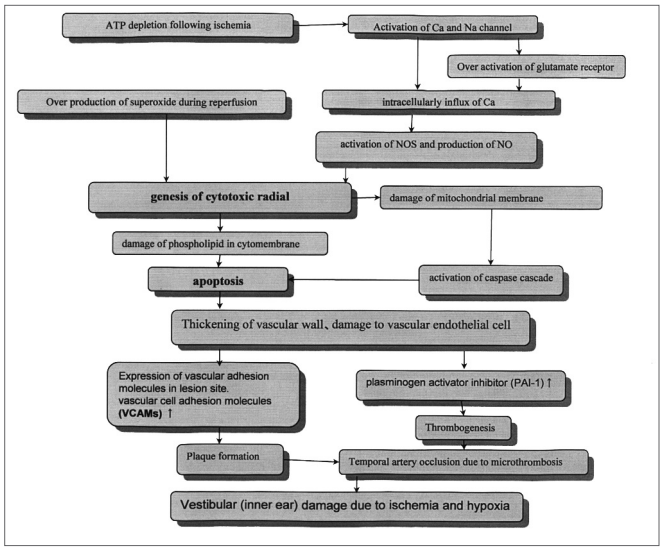

Figure 3. Arteriosclerosis, free radical, ischemic inner ear damage and BPPV (hypothesis)
The ischemia of the vestibular organ followed by blood recirculation may provoke generation of cytotoxic radical and produce damage of phospholipids in cytomembrane and result in elevated oxidative stress.

The d-ROM assay is a new test and future studies must consider its limitations. Some interfering factors must be considered when the D-ROM test is used because several vascular diseases, the use of oral contraceptives, and a state of fatigue after physical exercises have been shown to increase U. Carr levels[10]. It is reported that the D-ROM test is a simple, reliable and inexpensive method for the measurement of endogenous hydroperoxides. There is evidence that the D-ROM assay has both an acceptable stability and an acceptable margin of error[14]. The automatic assay may be regarded as a fast and reproducible method for the quantitative evaluation of oxidative stress. Since it is easily performed, the method is suitable for routine use in clinical laboratories and may provide an estimation of oxidative stress in vivo.

Based on these results, it is reasonable to assume that the angiitis may contribute to the onset of benign paroxysmal positional vertigo (BPPV). It may be useful to control dizziness or vertigo by reducing free radicals as a product of oxidative stress. To treat patients with dizziness due to BPPV to control oxidative stress may be valuable.

In conclusion, the relation between both the values of d-ROMs and of VCAM-1 and the duration of BPPV was found in patients with BPPV. The diagnostic value could be such that enhanced values of oxidative stress would be a marker for BPPV and provide additional information for a diagnosis of BPPV. The hypoxia/reoxygenation phenomenon is the probable underlying mechanism, even though the exact conditions remain to be further elucidated.

In summary, it is reasonable to assume that the severe the angiitis, the longer the time required for the remission of vertigo of BPPV. It is considered that the angiitis and following oxidative stress can be one of the causes of BPPV.

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