有害事象の観察[a]		←											→
重心動揺検査		●	●		●		●		●		●		●

a:有害事象は、副作用など好ましくない全ての事象のことで、GVS 刺激との因果関係は問わない。

○印は試験開始前に行う項目、●印は試験開始後に行う項目

スケジュール表（30 分刺激）

項　目	GVS 刺激直前	GVS 刺激			GVS 刺激終了後			GVS 刺激直前	GVS 刺激		GVS 刺激終了後			
時　期	1 分前	0	30 分	30 分	1 時間	2 時間	効果消失まで 1 時間ごと	1 分前	0	30 分	30 分	1 時間	2 時間	効果消失まで 1 時間ごと
自覚症状・他覚所見	○	●	●	●	●	●	●	●	●	●	●	●	●	●
有害事象の観察[a]		←												→
VAS		●	●	●	●	●	●	●	●	●	●	●	●	●
重心動揺検査	○	●	●	●	●	●	●			●	●	●	●	●

a:有害事象は、副作用など好ましくない全ての事象のことで、GVS 刺激との因果関係は問わない。

スケジュール表（3 時間刺激）

項　目	GVS 刺激直前	GVS 刺激				GVS 刺激終了後				
時　期	1 分前	0	1 時間	2 時間	3 時間	30 分	1 時間	2 時間	3 時間	4 時間
自覚症状・他覚所見	○	●	●	●	●	●	●	●	●	●
有害事象の観察[a]		←								→
VAS		●	●	●	●	●	●	●	●	●
重心動揺検査	○	●	●	●	●	●	●	●	●	●

a:有害事象は、副作用など好ましくない全ての事象のことで、GVS 刺激との因果関係は問わない。

９．中止基準

試験担当医師は何らかの理由で試験継続が不可能と判断した場合には、試験機器の使用を中止し、中止・脱落の日付・時期、中止・脱落の理由、経過を明記するとともに、中止・脱落時点で必要な検査を行い有効性・安全性の評価を行う。

１）被験者から試験参加の辞退の申し出や同意の撤回があった場合

２）登録後に適格性を満足しないことが判明した場合

３）有害事象により試験の継続が困難な場合

４）その他の理由により、医師が試験を中止することが適当と判断した場合

- 有害事象発生により中止した場合は、可能な限り原状に回復するまで治療を行う。

１０．有害事象発生時の取り扱い

（１）有害事象及び不具合発生時の被験者への対応

試験責任医師または試験分担医師は、有害事象を認めたときは，直ちに適切な処置を行うとともに、症例報告書に齟齬なく記載する。また試験機器の使用を中止した場合や、有害事象に対する治療が必要となった場合には、被験者にその旨を伝える。

- GVS 刺激により不快等の症状が生じた場合は、直ちに検査を中止する。
- 転倒により負傷した場合、被験者は東京大学医学部附属病院にて診療を行う。診療費は、障害 1～14 級の場合には臨床研究保険で負担し、それ以外の場合は健康保険で対処する。

（２）重篤な有害事象及び不具合の報告

重篤な有害事象の定義（薬事法施行規則第274条の2に準じて定義する）

１）死亡または死亡につながるおそれ

２）治療のための入院または入院期間の延長

３）障害または障害につながるおそれ

４）１)－３)に準じて重篤

５）後世代または先天性の疾病または異常

試験期間中の全ての重篤な有害事象及び不具合、試験終了（中止）後に試験機器との関連性が疑われる重篤な有害事象及び不具合について報告する。

試験責任医師は、重篤な有害事象及び不具合の発生を認めたときは、速やかに病院長（臨床試験審査委員会）に報告する。報告は第一報（緊急報告）および第二報（詳細報告）とする。

試験責任医師は、侵襲性を有するものにおいて、臨床研究に関連する予期しない重篤な有害事象及び不具合等が発生した場合には、速やかに病院長（臨床試験審査委員会）に報告するとともに、

病院長による厚生労働大臣への報告ならびに公表について協力する。

（３）その他の有害事象

その他の有害事象については、「８．観察および検査項目（５）有害事象と副作用の確認」に記載した手順により、症例報告書に記載する。

１１．実施計画書からの逸脱の取扱い

- 試験責任医師または試験分担医師は、臨床試験審査委員会の事前の審査に基づく病院長の承認を得る前に、試験実施計画書からの逸脱あるいは変更を行わない。
- 試験責任医師または試験分担医師は、緊急回避等のやむを得ない理由により、臨床試験審査委員会の事前の承認を得る前に、試験実施計画書からの逸脱あるいは変更を行う場合は、試験責任医師または試験分担医師は、逸脱または変更の内容および理由ならびに試験実施計画書等の改訂が必要であればその案を速やかに、臨床試験審査委員会に提出し、臨床試験審査委員会および病院長の承認を得るものとする。
- 試験責任医師または試験分担医師は、試験実施計画書からの逸脱があった場合は、逸脱事項をその理由とともに全て記録しなければならない。
- 試験責任医師または試験分担医師は、当該臨床研究において、臨床研究に関する倫理指針に適合してないこと（適合してない程度が重大である場合に限る。）を知った場合には、速やかに病院長（臨床検査審査委員会）に報告し、必要な対応をした上で、その対応の状況・結果についての病院長による厚生労働大臣への報告・公表に協力しなければならない。

１２．試験の終了、中止、中断

（１）試験の終了

試験の終了時には、試験責任医師は、速やかに試験終了報告書を病院長に提出する。

（２）試験の中止、中断

- 試験責任医師は、以下の事項に該当する場合は試験実施継続の可否を検討する。
  1）携帯型前庭電流刺激装置の安全性に関する重大な情報が得られたとき。
  2）被験者のリクルートが困難で予定症例を達成することが到底困難であると判断されたとき。
  3）臨床試験審査委員会により、実施計画等の変更の指示があり、これを受入れることが困難と判断されたとき。
- 臨床試験審査委員会により、中止の勧告あるいは指示があった場合は、試験を中止する。
- 試験の中止または中断を決定した時は、速やかに病院長にその理由ととも

に文書で報告する。

１３．試験実施期間

本申請が承認された日より2015年3月31日までとする。

（症例エントリー最終期限　2015年3月24日）

１４．データの集計および統計解析方法

原資料である重心動揺計に関するデータは重心動揺計解析用コンピュータから抽出される。重心動揺計のデータ、VASスケールや試験期間中の評価項目をCRFで収集する。

（１）主要な解析

30分刺激の残存効果時間に対する3時間刺激の残存効果時間をCox比例ハザードモデルにより評価し、ハザード比を推定する。残存効果が消失した被験者をイベントあり、刺激4時間後の測定においても残存効果が見られる被験者を打ち切りとして扱う。

なお、クロスオーバー試験により各刺激時間の残存効果に相関が生じるため、相関を考慮した下でCox回帰モデルを適用する。

（２）副次的な解析

- 最終評価時点のVAS値と刺激直後のVAS値の差を個人ごとに算出し、対応のあるt検定により30分刺激と3時間刺激の間に差があるか評価する。
- 反復効果を検討することを目的に、30分刺激の1回目と2回目の残存効果消失までの時間を、相関を考慮した下でCox回帰モデルにより評価する。

１５．目標症例数および設定根拠

被験者30名。

30分刺激、3時間刺激の残存効果消失までの時間の中央値をそれぞれ1時間、3時間と仮定する。各刺激の追跡時間を4時間とすると、片側α水準0.05の設定の下で、被験者数が30症例だとすると検出力は約84%となる。仮に、最適刺激がない症例が5例存在し、25症例のみが登録された場合でも約75%の検出力が確保される。

１６．被験者の人権および安全性・不利益に対する配慮

（１）人権への配慮（個人情報の保護）

試験実施に係る生データ類および同意文書等を取扱う際は、被験者の秘密保護に十分配慮する。データは連結可能匿名化して研究者が保存する。

病院外に提出する報告書等では、被験者識別コード等を用いて行う。試験の結果を公表する際は、被験者を特定できる情報を含まないようにする。必要があれば、倫理申請を経て、個人情報を除くデータの二次利用を行う可能性がある。

（２）安全性・不利益への配慮

- 有害事象発生時には速やかに適切な診察と処置を行う。
- 本研究を安全に実施するうえで必要な情報を収集し、検討する。また、必要に応じて研究計画を変更する。

１７．患者の費用負担

本研究に参加することで、発生する被験者の費用負担は無い。
研究参加者に対する謝金は１日 10,000 円（ただし検査のみを受け試験に参加しなかった場合は 5,000 円）とする。

１８．健康被害の補償および保険への加入

（１）健康被害の補償

重篤な健康被害についての補償責任に備え、試験責任医師および試験分担医師は臨床研究保険に加入する。健康被害が生じた場合の診療費は、障害 1～14 級の場合には臨床研究保険で負担し、それ以外の場合は健康保険で対処する。

（２）賠償保険への加入

賠償責任に備え、試験責任医師および試験分担医師は賠償責任保険に加入する。

１９．GCP及びヘルシンキ宣言への対応

本試験はGCPを準用するものとする。また、臨床研究に関する倫理指針（厚生労働省告示、平成20年7月改正）およびヘルシンキ宣言（2013年改訂）を遵守して実施する。

２０．記録の保存

試験責任医師は、手順書に従って記録の保存を実施する。試験責任医師は、以下の試験に関する記録（文書及びデータを含む）を、試験の中止若しくは終了の後５年間適切に保存する。

(1) 試験実施計画書、総括報告書、症例報告書、試験責任医師又は試験分担医師が作成した文書又はその写し

(2) 試験実施医療機関の長から通知された臨床試験審査委員会の意見に関する文書、その他試験実施医療機関の長から入手した記録

(3) 試験を行うことにより得られたデータ

(4) 医療機器に関する記録。

２１．試験計画の登録および試験結果の公表

- 被験者登録を開始する前に、試験計画の内容を大学病院医療情報ネットワーク（UMIN）に登録する。
- 研究発表は、論文発表及び学会発表を通じて行う。

２２．試験組織

（氏名）　（所属機関）　（診療科）　（職名）　（ 連絡先）　（役割）

＜責任医師＞

○岩崎真一　東京大学医学部附属病院　耳鼻咽喉科　准教授　03-5800-8665　試験の統括・実施

＜分担医師＞

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鴨頭　輝　東京大学医学部附属病院　耳鼻咽喉科　大学院生　03-5800-8665　試験の実施

＜データセンター＞

高田宗典　東京大学医学部附属病院　臨床研究支援センター　助教　03-5800-9762　解析データセット作成

源　京子　東京大学医学部附属病院　臨床研究支援センター　医療技術職員 03-5800-9762 解析データセット作成

＜試験統計家＞

上村夕香理 東京大学医学部附属病院　臨床研究支援センター　助教　03-5800-9762 データ解析

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〒113-8655 東京都文京区本郷 7-3-1、

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２３．研究資金および利益相反

本試験は平成26年度厚生労働科学研究委託費の交付をうけて行うものである。試験機器は、TZK電子の作製したプロトタイプを基に、アニマ社が作製した。本試験の責任医師ならびに試験分担医師には、アニマ社、TZK電子との間に開示すべき利益相反はない。

本試験の責任医師ならびに試験分担医師は、本試験の計画・実施・報告において、試験の結果および結果の解釈に影響を及ぼすような新たな「利益相反」が生じていないかを1年に1度年度初めに確認し、試験の実施が被験者の権利・利益を損ねることが無いことを確認する。

２４．実施計画書等の変更

実施計画書や説明文書の変更（改訂）を行う場合は、臨床試験審査委員会の承認を得てから

行うこととする。

２５．参考資料・文献リスト

- Yamamoto Y et al. Noisy vestibular stimulation improves autonomic and motor responsiveness in central neurodegenerative disorders. Ann Neurol 2005　（資料１）
- Iwasaki S et al. Noisy vestibular stimulation improves body balance in bilateral vestibulopathy. Neurology 2014　（資料２）

実施日　　年　　月　　日

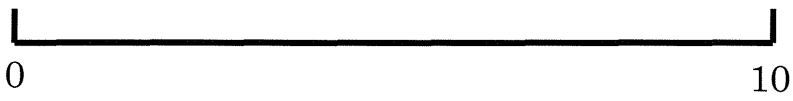
□30 分刺激 1 回目　　□30 分刺激 2 回目

□3 時間刺激

被験者 ID

刺激　　時間後

- 「身体（からだ）の揺れが全く無い状態」を 0、「想像できる最も激しい身体（からだ）の揺れ」を 10 と考えて、重心動揺計の上に立ったときの身体の揺れの程度が、0 から 10 の間のいくつぐらいで表せるかを下の線の上に記して下さい。



- 有害事象の有無　　□有　　□無

有害事象名	因果関係	発現日時	転帰日	重症度	重篤性	処置

- 自覚・他覚

自覚症状の有無　　□有　　□無

詳細　（　　）

他覚症状の有無　　□有　　□無

詳細　（　　）

試 験 成 績 書

依頼者名	アニマ株式会社
住所	〒182-0034 東京都調布市下石原 3-65-1
試験品名	携帯式前庭電流刺激装置
型名	PGS-100
定格	直流 3 V UM-3 形乾電池×2
製造番号	726S01
製造者名	アニマ株式会社
試験内容	JIS T 0601-1:1999 (医用電気機器 － 第 1 部:安全に関する一般的要求事項)
試験場所	一般財団法人　日本品質保証機構　安全電磁センター 〒157-8573 東京都世田谷区砧 1-21-25
試験結果	添付の試験報告書のとおり
試験年月日	2014 年 10 月 7 日から 2014 年 11 月 10 日

試験の結果は上記のとおりであることを証明します。

発行日　2014 年 12 月 1 日

一般財団法人 日本品質保証機構
安全電磁センター
所長　川上 広明

〒157-8573 東京都世田谷区砧 1-21-25

試験報告書

JIS T 0601-1:1999

医用電気機器
第1部: 安全に関する一般的要求事項

報告書

JQA ファイリング番号.....: 370-140065

試験実施者: .....: 山戸 文雄　　山戸 文雄 署名

検証者: .....: 西野 郷志　　西野 郷志 署名

試験年月日 .....: 2014年10月7日から2014年11月10日

発行年月日 .....: 2014年12月1日

申請者

申請者名.....: アニマ株式会社

住所.....: 〒182-0034 東京都調布市下石原 3-65-1

製造者

製造者名.....: アニマ株式会社

住所.....: 〒182-0034 東京都調布市下石原 3-65-1

試験機関

機関名 .....: 一般財団法人　日本品質保証機構

試験場所.....: 安全電磁センター　試験部　医療機器・信頼性試験課

住所.....: 〒157-8573 東京都世田谷区砧1丁目21番25号

機器／装置

機器名／装置名 .....: 携帯式前庭電流刺激装置

形名.....: PGS-100

製造番号.....: 726S01

電気定格

定格電圧・周波数・電流 .....: 直流3 V UM-3形乾電池×2

定格電力.....: -

附属品　本体、電極ケーブル、電極、取扱説明書

一般情報
設置方法の分類.....: 可搬形機器(携帯形機器)
電源への接続.....: 内部電源
附属品及び着脱品を含む評価 .....: 本体、電極ケーブル、電極、取扱説明書 オプション .....: -
要求事項に対する試験結果の適合性: - 要求事項が該当しない場合 .....: N/A - 試験結果が要求事項に適合した場合 .....: P - 試験結果が要求事項に適合しない場合 ..... : F
試験報告書の中で使用した略号: - 正常状態 .....:N.C. - 単一故障状態.....:S.F.C. - 機能絶縁 .....:OP - 基礎絶縁.....:BI - 異極間の基礎絶縁 .....:BOP - 補強絶縁.....:SI - 二重絶縁 .....:DI - 強化絶縁.....:RI
追記: 附属文書参照は、試験報告書に付随する追加情報を参照することである。 附属表参照は、試験報告書に付随する表を参照することである。

一般的な製品情報及び考察
6.8項 附属文書は、取扱説明書(REV 2.0.0)にて確認した。

様式第１９

学　会　等　発　表　実　績

委託業務題目「ノイズ様前庭電気刺激を利用した末梢前庭障害患者に対するバランス障害改善機器の開発」
機関名 東京大学医学部附属病院　耳鼻咽喉科

１．学会等における口頭・ポスター発表

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
高齢者のめまい：診断と治療（口演）	岩﨑真一	長崎　長崎めまい講演会	2014年7月23日	国内
経皮的ノイズ前庭電気刺激が前庭誘発眼筋電位（oVEMP）に及ぼす影響	岩﨑真一、狩野章太郎、鴨頭輝、木下淳、藤本千里、山岨達也	日本耳科学会総会	2014年10月16日	国内
Clinical usefulness of ocular vestibular evoked myogenic potentials (oVEMPs) and cervical vestibular evoked myogenic potentials (cVEMPs)	岩﨑真一	横浜 Joint meeting of Japan Society for Equilibrium Research and The Korean Balance Society	2014年11月7日	国内

２．学会誌・雑誌等における論文掲載

掲載した論文（発表題目）	発表者氏名	発表した場所（学会誌・雑誌等名）	発表した時期	国内・外の別
Dizziness and imbalance in the elderly: Age-related decline in the vestibular system.	Iwasaki S, Yamasoba T	Aging Dis	2015年2月	国外
Idiopathic latent vestibulopathy: a clinical entity as a cause of chronic postural instability.	Fujimoto C, Yamasoba T, Iwasaki S	Eur Arch Otorhinolaryngol	2015年1月	国外
Clinical characteristics of patients with abnormal ocular/cervical vestibular evoked myogenic potentials in the presence of normal caloric responses.	Iwasaki, S, Fujimoto C, Kinoshita M, Kamogashira T, Egami N, Yamasoba T	Ann Otol Rhinol Laryngol	2014年12月	国外
The effect of aging on the center-of-pressure power spectrum in foam posturography.	Fujimoto C, Egami N, Demura S, Yamasoba T, Iwasaki S		2015年3月	国外

（注１）発表者氏名は、連名による発表の場合には、筆頭者を先頭にして全員を記載すること。
（注２）本様式はexcel形式にて作成し、甲が求める場合は別途電子データを納入すること。

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Review Article

Dizziness and Imbalance in the Elderly: Age-related Decline in the Vestibular System

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ABSTRACT: Dizziness and imbalance are amongst the most common complaints in older people, and are a growing public health concern since they put older people at a significantly higher risk of falling. Although the causes of dizziness in older people are multifactorial, peripheral vestibular dysfunction is one of the most frequent causes. Benign paroxysmal positional vertigo is the most frequent form of vestibular dysfunction in the elderly, followed by Meniere's disease. Every factor associated with the maintenance of postural stability deteriorates during aging. Age-related deterioration of peripheral vestibular function has been demonstrated through quantitative measurements of the vestibulo-ocular reflex with rotational testing and of the vestibulo-collic reflex with testing of vestibular evoked myogenic potentials. Age-related decline of vestibular function has been shown to correlate with the age-related decrease in the number of vestibular hair cells and neurons. The mechanism of age-related cellular loss in the vestibular endorgan is unclear, but it is thought that genetic predisposition and cumulative effect of oxidative stress may both play an important role. Since the causes of dizziness in older people are multi-factorial, management of this disease should be customized according to the etiologies of each individual. Vestibular rehabilitation is found to be effective in treating both unilateral and bilateral vestibular dysfunction. Various prosthetic devices have also been developed to improve postural balance in older people. Although there have been no medical treatments improving age-related vestibular dysfunction, new medical treatments such as mitochondrial antioxidants or caloric restriction, which have been effective in preventing age-related hearing loss, should be ienvestigated in the future.

Key words: aging, vestibular, fall, rehabilitation.

Dizziness and imbalance are well-recognized problems among older people. A population-based study in the United States reported that 24% of people older than 72 years have dizziness [1]. Dizziness and imbalance in older people are a growing public health concern, because older individuals who suffer from dizziness have a significantly higher risk of accidental falls and consequent injuries [2,3]. Falls are the leading cause of hospital admission and accidental death in older people. Several studies have shown that older adults with a history of dizziness and imbalance are at a higher risk of falling [3-5]. Furthermore, vertigo and unsteadiness lead to a fear of falling, which is a strong predictor for those who will suffer one or more subsequent falls [6,7].

The underlying cause of dizziness in the elderly is complex and multi-factorial [8,9]. Postural stability is maintained by the integration of somatosensory, visual and vestibular inputs to the central nervous system, followed by outputs to the musculo-skeletal system (Fig. 1). Dizziness and imbalance can be caused by changes in any of the factors associated the balance system, be they of sensory, visual, vestibular, neurologic, and muscular origin. Function of all these components deteriorates with age [10].

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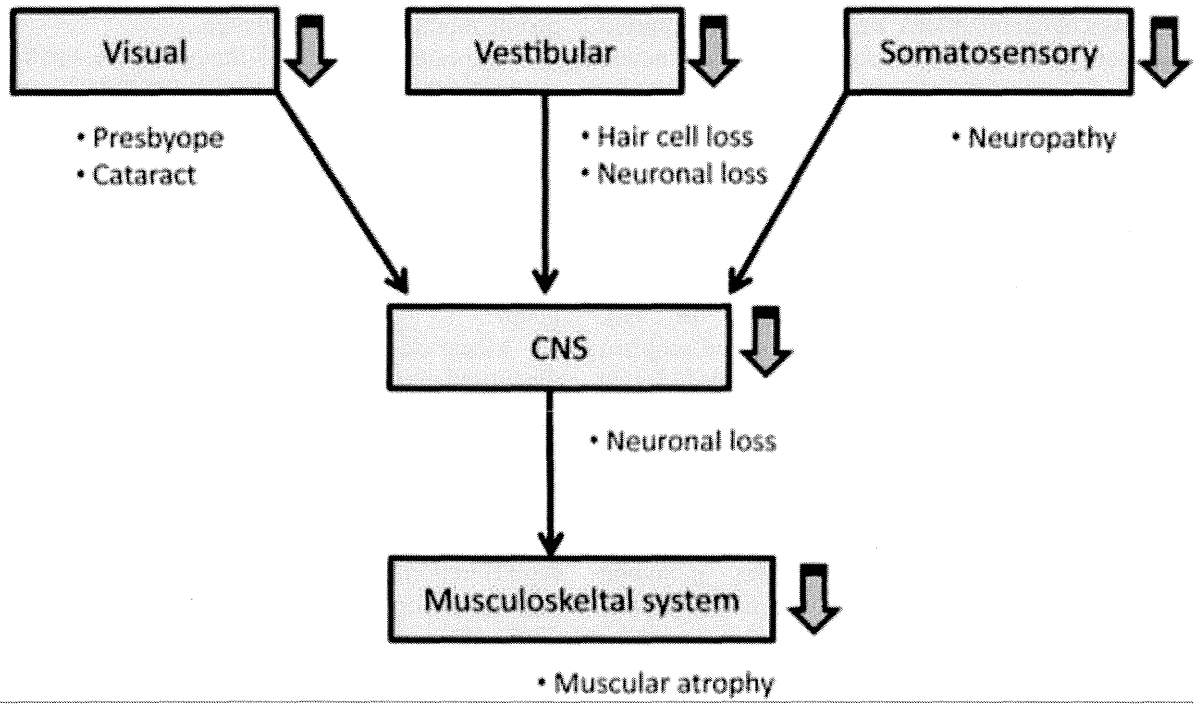

Figure 1. Age-dependent changes in the system maintaining postural stability. Postural stability is maintained by the integration of somatosensory, visual and vestibular inputs to the central nervous system, followed by outputs to the musculoskeltal system. Function of all the components deteriorates as the age advances.

This review will focus on the clinical characteristics of dizziness in the elderly and age-related changes in the peripheral and central vestibular systems, and will report some recent findings on cellular mechanism of aging and the possible treatment strategies for dealing with dizziness and imbalance in the elderly.

Prevalence of dizziness and imbalance in the elderly

Dizziness and imbalance are one of the most common complaints among older people. The prevalence ranges from approximately 20% to 30%, depending on the definition of dizziness and the population studied [1,11,12]. A population-based study in the United States found that 24% of people older than 72 years reported having an episode of dizziness within the previous 2 months, lasting for at least one month [1]. Another population-based study in the United Kingdom reported that 30% of people older than 65 years have dizziness [11]. The prevalence of dizziness has a tendency to increase with age [1,11]. A cross-sectional study in Sweden reported that the number of adults with dizziness increased up to approximately 50% in people older than 85 [13].

The underlying causes of dizziness in the elderly vary widely [1,8,14-17]. Multiple factors including neurologic, cardiovascular, visual, vestibular, and psychological problems can cause dizziness in older people. Previous studies have reported conflicting results regarding the etiologies of dizziness depending on the diagnostic criteria adopted and the population studied. General population studies have usually assigned the causes of dizziness mainly on the basis of interview without performing any clinical examinations. A population survey in Germany reported that a prevalence of vestibular vertigo was 14% in the general population older than 70 years [14]. Their diagnoses were based on telephone interviews by medical staff. Studies in clinical settings were biased by the types of clinics and physical examinations performed. A prospective case control study conducted in general practices, in which general physical examinations were performed, reported 18% of patients with dizziness who were over 60 years old had a peripheral vestibular disorder [8]. On the other hand, a

prospective study in a neurology clinic, in which detailed neuro-otological examinations were performed, reported that peripheral vestibular dysfunction was the principal cause of dizziness in 56% of patients older than 50 years [15]. Similarly, cerebrovascular causes range from 0% to 70% [8,18], and psychiatric causes in 0% to 40% in older patients with dizziness [8,15,19] depending on the clinical examination performed. In several studies, no specific diagnosis could be made to explain the symptoms in approximately 20% to 30% of older people with dizziness [8,9,17]. Belal and Glorig (1986) used the term presbystasis to describe this type of age-related problem that cannot be attributed to any known diagnosis [17]. On the other hand, other studies assigned multiple diagnoses in 18% to 85% of older people with dizziness [8,15,18]. Tinetti et al. (2000) proposed that dizziness in the elderly should be considered as a multifactorial geriatric syndrome involving many different symptoms and originating from many different causes, including cardiovascular, neurologic, sensory, psychological and medication-related problems [1].

Peripheral vestibular disorders in the elderly

In most studies regarding dizziness in the elderly, peripheral vestibular dysfunction is the first or the second most frequent cause of dizziness [8,9,15,20]. Benign paroxysmal positional vertigo (BPPV) is the most frequent form of peripheral vestibular dysfunction, followed by Meniere's disease and vestibular neuritis [9,15].

BPPV is the most common cause of vertigo and dizziness from childhood through to old age, peaking at about 60 years [21]. Several studies have demonstrated an increase in incidence of BPPV in older people [20,22,23]. A recent epidemiologic study obtained from a large cross-sectional neurotologic survey reported that lifetime prevalence of BPPV was estimated to be 2.4% and the one year prevalence of 1.6% but that one-year prevalence of BPPV in adults older than 60 years was approximately seven times higher than that of adults from 18 to 39 years old [22]. BPPV is usually diagnosed by the presence of episodic vertigo provoked by changes in head position and concomitant nystagmus observed during the positioning maneuver [24,25]; it is effectively treated by physical therapy [26-28]. Johkura et al. (2008) reported that about 50% of elderly patients with chronic dizziness who visited an emergency unit showed extremely weak, horizontal, direction changing apogeotropic nystagmus, which is characteristic of horizontal canal BPPV, and that some of symptoms in these patients was improved by daily positional exercises for BPPV [29]. The results suggest that the reported prevalence of BPPV in older people might be underestimated.

The cause of BPPV is thought to be small particles trapped in the semicircular canals [25,30]. These particles most likely consist of otoconia dislodged from the utricula maculae. Several studies have demonstrated that a high proportion of otoconia of the utricular macula degenerates in the elderly, and many have fractures [31,32]. Morphological changes in the otolith organs may be related to the increased prevalence of BPPV in the older people.

Meniere's disease accounts for 3% to 11% of diagnosed dizziness in neuro-otological clinics. Its annual incidence rate and point prevalence are estimated to be 15/100,000 and 218/100,000, respectively, in the general population [33]. Meniere's disease has generally been regarded as a disease of middle-aged people [34,35]. However, in a large case series study, Ballester et al. (2002) reported that 15% of patients with Meniere's disease are more than 65 years of age [34]. In that study, 40% of cases were a reactivation of longstanding Meniere's disease while 60% were de novo case of Meniere's disease. They also reported that drop attacks, which are caused by sudden otolithic dysfunction, were more frequent in older people compared to the general population. A multi-center survey in Japan reported the proportion of de novo cases of Meniere's disease in patients older than 60 years had increased during the previous 30 years [36] .

Vestibular neuritis accounts for 3% to 10% of diagnoses in oto-neurological clinics [20,37]. The epidemiological data on vestibular neuritis is scarce. An epidemiological survey in Japan reported that the prevalence of vestibular neuritis is 3.5/100,000 and the peak age distribution was between 40 to 50 years [38]. Although vestibular compensation relieves most of the symptoms of vestibular neuritis within a few weeks of onset, 30% to 40% of patients have chronic persistent dizziness [39-41]. Furthermore, deterioration in function of the intact side of the peripheral vestibular organs, vision, and the proprioceptive systems in the elderly may lead to a breakdown of vestibular compensation.

Functional deterioration of vestibular systems in the elderly

The stability of posture and gaze during standing and walking is maintained by the rapid processing of vestibular, visual and somatosensory inputs in the central nervous systems, followed by outputs to the musculoskeletal and visual systems. Every factor in this system deteriorates during aging.

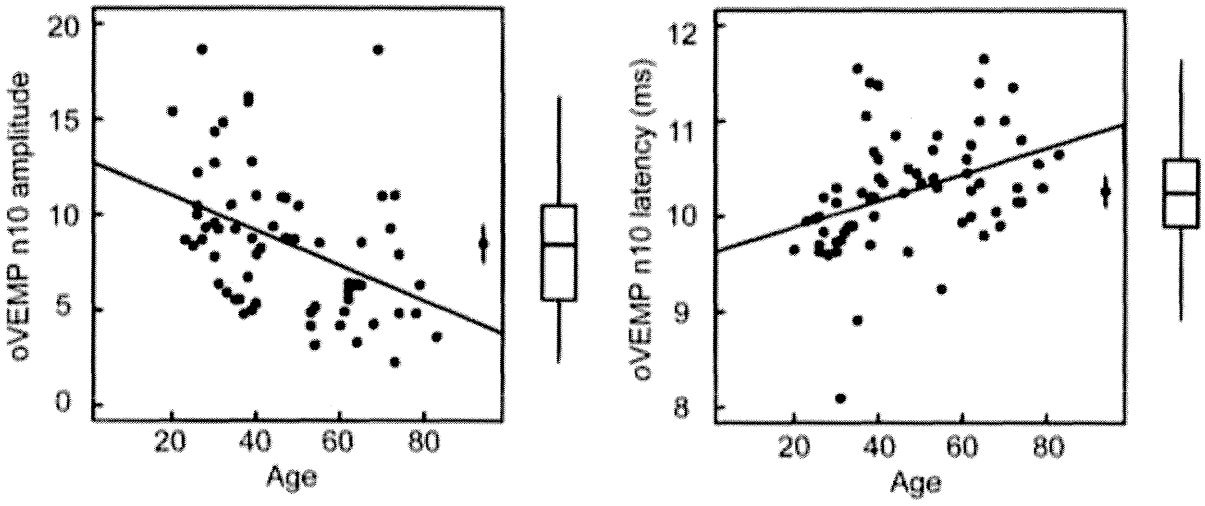

Figure 2. Age-dependent changes in amplitude and latency of oVEMPs to bone-conducted vibration. (Left panel) Amplitude of the n10 responses of oVEMP significantly decreases with age. (Right panel) Latency of the n10 responses of oVEMP significantly increases with age. The box and whisker plots show the median and quartiles (cited from ref. 54 with permission).

Age-related deterioration of peripheral vestibular function has been documented by measuring the vestibulo-ocular reflex (VOR) using rotational tests and/or caloric tests, both of which reflect function of the lateral semicircular canals [42-44]. Sinusoidal rotation tests in normal adults over the age of 75 years showed a decrease in VOR gain as well as the VOR time constant, especially with high velocity stimulation, as compared with young subjects [42]. In a longitudinal study of normal subjects older than 75 years old, a progressive decrease in VOR gain and an increase in phase lead were observed during five annual examinations [45] . Another study assessing performance in sinusoidal rotational tests and caloric tests in normal subjects from 7 to 81 years old reported a decline in the response amplitude and less of a compensatory response phase with increasing age in the rotational test, while the caloric test showed no consistent trends with age [44]. These results suggest that age-related changes in vestibular system preferentially affect the high-frequency component of the VOR since the caloric testing reflects the low frequency component of the VOR.

Age-related deterioration of peripheral vestibular function has been demonstrated in other vestibular tests. Vestibular evoked myogenic potentials (VEMPs) are short-latency muscle responses typically recorded from the neck muscles (cVEMPs) or from the eye muscles (oVEMPs) [46-48]. Clinical and physiological studies have shown that cVEMPs reflect the function of the saccule and the inferior vestibular nerve whereas oVEMPs reflects the function of the utricle and the superior vestibular nerve [49-52]. A cross sectional study of consecutive patients ranging from 7 to 91 years old showed an age-dependent decrease in cVEMP amplitude and an increase in cVEMP latency [53]. Similarly, oVEMPs show an age-dependent decrease in amplitude and an increase in latency (Fig.2) [54]. These results suggest that the function of the otolith organs as well as their central pathway also deteriorate with increasing age. Recently, Agrawal et al. (2012) measured the function of the semicircular canals, utricle, and saccule using the head thrust test, oVEMP, and cVEMP, respectively, in healthy subjects more than 70 years old [55]. They showed that the function of the semicircular canals as well as the otolith organs decline with age, although the magnitude of impairment was greater for the semicircular canals than the otolith organs. However, deterioration of the results of the head thrust test might reflect an element of deterioration of oculomotor function as well as the semicircular canal function.

Age-related changes in postural stability have been examined using posturography, in which changes of the center of pressure was measured during quiet standing [56-59]. For estimating the role of different sensory inputs on postural control, dynamic posturography using a moving platform or a foam rubber surface have also been developed. In most studies, all measures of balance

performance get worse in older subjects compared with younger subjects (Fig. 3) [57-59]. This age-related decline in balance control is correlated with deterioration of visual, vestibular, and sensorimotor function as well as reduction in strength of the lower muscles. Teasdale et al. (1991) have demonstrated that alteration in any two of the three sensory inputs (visual, vestibular and somatosensory) had a significantly greater effect on older subjects than in younger subjects whereas alteration in one input did not have a significant effect due to age [59]. These results suggest that decreased inputs from the vestibular, visual and somatosensory systems in older subjects lead to a decreased capacity for compensation by the other inputs in order to maintain postural stability.

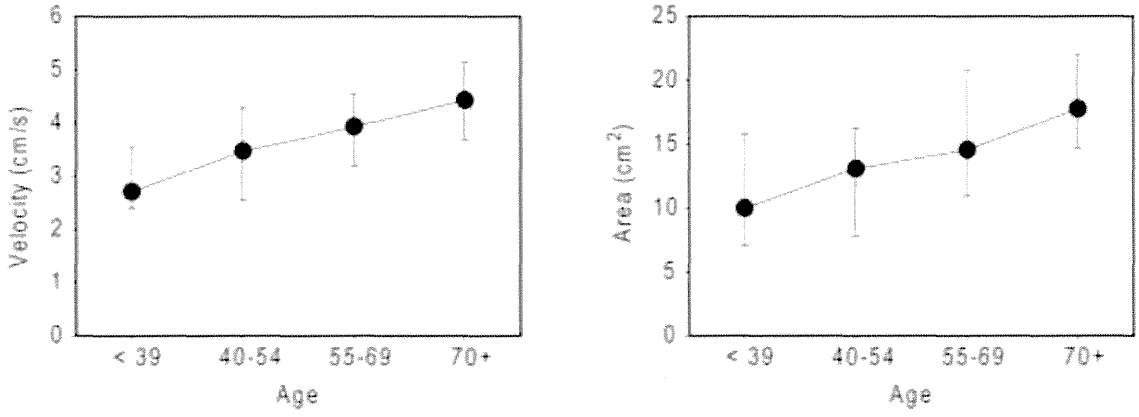

Figure 3. Age-dependent changes in the postural stability on the foam rubber. (Left panel) Age-dependent changes in the velocity of the center of pressure (COP) during standing with eyes closed on the foam rubber. (Right panel) Age-dependent changes in the envelopment area of the COP during standing with eyes closed on the foam rubber. Median value and interquatile ranges are shown (The data are from ref. 57).

Cellular changes in aging of the vestibular system

Hair cells and neurons in the vestibular system do not regenerate or increase basically in the mammals. A significant decrease in the number of hair cells and neurons in the vestibular system in older people has been described in the literature [60,61]. Richter (1980) examined the density of vestibular hair cells and nerve cells in Scarpa's ganglia in human temporal bones from subjects aged 9 to 91 years old [60]. He reported a decrease in the number of vestibular hair cells after the age of 20 years old and a decrease in the number of vestibular ganglion neurons after the age of 50 years. On the other hand, Merchant et al. (2000) reported a gradual loss in the number of vestibular hair cells in all endrogans, with relative sparing of the utricle, with increasing age [62]. These early reports, which estimated the number of vestibular hair cells and neurons from serial sections of the temporal bones, may have been biased as they were based on several assumptions such as the spherical shape and uniform size of the hair cells as well as the constant shrinkage and thickness of the specimen. Recently, using unbiased stereology which overcomes the shortcomings of previous methods, the number of hair cells and neurons in human temporal bones was re-evaluated [63,64]. Lopez et al. (2005) examined the number of hair cells in the semicircular canals using unbiased stereology and showed that the number of hair cells was decreased by 12% in adults in their 80s and by 25% in their 90s as compared with the younger group (42 to 67 years old) [63]. Gopen et al. (2003) used the same method to estimate the number of hair cells in the utricle but they failed to show an age-dependent decrease in the number of hair cells [64]. It remains unclear whether this result reflects the relative sparing of the utricle in age-related loss of hair cells [62], or is due to bias caused by the paucity of the number of temporal bones examined.

In contrast to numerous reports regarding animal models of age-related hearing loss, animal models of age-related vestibular dysfunction have rarely been reported.

Shiga et al. (2005) examined age-related changes of vestibular endorgans in C57BL/6 mice, which are considered to be an animal model of age-related hearing loss, and reported an age-related decline in hair cell density in the horizontal semicircular canals of 30%, with an associated mild decrease in the VOR gain at 0.8Hz [65]. Since the age-related decrease of VOR gain was not observed at the other frequencies tested, it was speculated that a differential loss of hair cell types might occur in the model mice.

The mechanism of age-related cellular loss in the vestibular endorgans is still unclear. However, the possible etiology of age-related hearing loss has been extensively studied [66-68], and it is now considered to be a multifactorial condition, representing outocome of multiple intrinsic (e.g. genetic predisposition) and extrinsic (e.g. noise exposure) factors acting on the inner ear over a life time [66]. A number of studies using animal models have suggested that the cumulative effect of oxidative stress could induce damage to macromolecules such as mitochondrial DNA and that the accumulation of mitochondrial DNA and the decline of mitochondrial function play an important role in inducing apoptosis of the cochlear cells [69-71]. Genetic investigations have shown that several genes, including those related to antioxidant defense and atherosclerosis, have an association with age-related hearing loss [72]. Exposure to noise is known to induce excess generation of reactive oxygen species in the cochlea [73]. A similar accumulation of oxidative stress and damage to mitochondrial DNA may be taking place in age-related changes in the vestibular endorgans.

Management of dizziness in the elderly

Since the causes of dizziness in older people are multi-factorial, management of this disease should be customized according to the etiology of dizziness in each individual. Management of dizziness includes various approaches, including medical and rehabilitative ones as well as the use of prosthetic devices.

Vestibular rehabilitation was first introduced by Cawthorne and Cooksey (1946) to rehabilitate patients with vestibular disorders [74]. The rehabilitation includes 1) VOR adaptation exercises to assist the central nervous system to adapt to a change or loss in inputs to the vestibular system, 2) habituation exercises to reduce pathologic responses to a provoking stimulus, and 3) substitution exercises to promote the use of the remaining sensory system [75]. Currently, these exercises are found to be effective in treating people with dizziness caused by vestibular dysfunction, anxiety, head injury, cerebellar dysfunction, or Parkinson's disease [76]. The effect of vestibular rehabilitation does not differ with respect to patients' age and gender [77]. Several randomized control studies have provided evidence that vestibular rehabilitation exercises are effective in improving postural control, reports of dizziness symptoms, and emotional status in dizzy patients with nonspecific causes [75,78,79].

Various prosthetic devices have been developed to improve postural balance in the elderly. Vibrotactile feedback devices, which fit around the waist and provide augmented feedback about body tilt thorough vibration, have been shown to improve postural balance during quiet standing and walking [80,81]. A tongue-placed biofeedback system which provides information about head position by electrotactile stimulation was also reported to improve head stability in space [82]. Vibrating insoles which enhance somatosensory input from the lower extremities have been reported to improve postural performance in the elderly [83].

So far, there are no medical treatments to improve age-related deterioration of vestibular function. However, several medications have been reported to be effective in preventing age-related changes in the inner ear. Oral supplementation with mitochondrial antioxidants such as alpha-lipoic acid and coenzyme Q10 has been shown to reduce age-dependent hair cell loss in the mouse inner ear [71]. Caloric restriction extends the lifespan of most mammalian species by down-regulation of the expression of apoptotic genes. It has been reported to be effective for preventing age-related hearing loss in animal studies [84]. These new treatments which have been effective in animal studies should be applied in older patients with vestibular dysfunction in the future.

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