表4　試験的鼓室開放術における手術所見の解釈（文献2を改変）

漏出		診断
あり	外リンパか脳脊髄液と証明された場合	外リンパ瘻
あり	組織液	他疾患
なし		他疾患
なし	自然治癒	外リンパ瘻
なし	間欠的漏出	外リンパ瘻
なし	迷路内破綻（collapse inside labyrinth）	外リンパ瘻

慢性に経過し，遅発性にメニエール病様症状を呈する場合には外傷性内リンパ水腫の可能性も考慮する。

迷路骨包保存型では，内耳振盪，外傷性良性発作性頭位めまい症（外傷性BPPV），内耳窓やminor fissureから外リンパが漏出する外リンパ瘻が考えられる。慢性に経過し，遅発性にメニエール病様症状を呈する場合には外傷性内リンパ水腫が原因と考えられる。これらについて以下に解説する。

(2)頭部外傷性外リンパ瘻

頭部外傷後に難聴，めまいを主訴に当科へ紹介された症例を検討したところ，5割に末梢性眼振が観察され，そのうち半数にBPPV様めまいと眼振を認めた。また，全体の3割の症例がCTP陽性であった。このCTP陽性外リンパ瘻確実例を検討したところ，めまい，難聴の程度は様々であったため，一定の傾向をつかむことは難しい。しかし，内耳骨包は保存され，乳突蜂巣に微細な側頭骨骨折しか認められないにも関わらず，受傷直後から患側聾となった症例がCTP陽性だったことは特筆すべき所見であった。恐らく全身打撲による脳脊髄圧上昇により外リンパ漏出をきたしたものと推測された。このような症例が的確に診断され内耳窓閉鎖術が施行されれば，後遺症軽減に役立つと考えられる。

(3)特に外リンパ瘻と鑑別が必要な疾患

・内耳振盪症

骨折が無い場合でも頭部打撲による衝撃で蝸牛，前庭，半規管が損傷を受ける。これを内耳振盪と呼ぶ。そのメカニズムはいまだ完全には明らかにされていないが，急速な加速度外傷（速度の急激な上昇と下降に伴う加速度変化）により前庭末梢器の剪断（shearing）や，感覚細胞の障害を生じると言われている[15]。軽症の場合の内耳機能障害は可逆的であることが多い。剪断により前庭の微小血管から出血し，これが迷路内の結合組織，瘢痕，骨の増成をもたらすと慢性機能障害を呈すると考えられている[16]。

内耳振盪の臨床診断の定義は曖昧である。一般には外傷直後に発症し，明らかな外傷性BPPV所見を呈さない内耳性めまい症例に用いられる事が多いが，文献によっては外傷後の難聴のことを示すこともある。

・外傷性BPPV

頭部打撲は耳石器に剪断性の外力を与え，はがれ落ちた耳石が内リンパ腔へ入り込む。これが原因となり，種々のタイプの前庭機能障害が生ずる。典型的なBPPVの症状（頭位変換時の発作性の回転性めまい）に合致しないめまい症状がみられることが多く，合併する耳石機能障害によるものと考えられる。外傷性BPPVが頭部外傷後に生じる頻度は8～20%程度と言われている。

外傷後のBPPVと通常の特発性BPPVを比較するとその病態が異なることが推察される[17]。外傷性では両側性が多いことも知られており14～19%と高率だが，特発性BPPVでは2～6%である[18]。特発性は通常女性に多いと言われるが外傷性では性差が無い。外傷性は治療に抵抗性があり，67%の症例で耳石置換法による治療を複数回必要としたが，特発性では14%であった。再発率も外傷性で57%，特発性では19%であった。外傷性BPPVが治療抵抗性である理由として，内耳における出血や組織が剪断され生化学的な変化を

きたした細かな半規管内浮遊物が塊を形成しやすいことが考えられている。

・外傷性遅発性内リンパ水腫

外傷後，数ヶ月から数年の経過後に発症するメニエール病様症状（耳閉感，耳鳴，変動する難聴，発作性のめまい）を呈する疾患のことである[19]。側頭骨骨折に伴い前庭水管に骨折が及んでいる症例では閉塞や狭窄により内リンパドレナージ機能が傷害されるため内リンパ水腫をきたすと推測されている[20][21]。

C．鼓膜・中耳外傷

本邦では耳かきが日常習慣的に行われており，中耳(鼓膜，耳小骨)外傷の最も多い原因である。湿性耳垢の多い白人社会では，耳垢は点耳薬で洗い流すものと教育されており，耳かき外傷は少ない。後上象限，すなわちアブミ骨付近に鼓膜穿孔をきたした症例では，アブミ骨外傷性外リンパ瘻を念頭において診療する。さらに骨導の悪化，末梢性眼振，めまい（回転性，浮動性）があれば外リンパ瘻の可能性が高くなる。CTでアブミ骨底の骨折や陥入を確認できれば確定診断となる。平手打ちによる鼓膜損傷も日頃よく経験するが，この受傷機転でCTP陽性だった症例は今のところ経験していない。

我々の経験では，耳かきによる鼓膜穿孔症例の90％に末梢性眼振が認められたが，めまいを自覚したのは後上象限穿孔例（全体の65％）にほぼ限られていた。後上象限穿孔例の80％からCTPが検出されており，アブミ骨外傷は外リンパ瘻をきたしやすいことが確認された。通常はアブミ外傷で外リンパ漏出が持続すれば，混合難聴が次第に増悪し聾になると予測される。しかし興味深いことに，CTP陽性例でも，骨導が悪化しない症例がみられた。これらの症例では，めまいの増悪や，末梢性眼振の方向が数時間から数日で変化する（麻痺性から，刺激性へ，さらに麻痺性へなど）ことが特徴的で，卵円窓の破綻においては前庭系の所見が病態の進行を鋭敏に反映していた。

ある一症例は受傷直後と安静治療後数日経過してから，２回サンプルを採取，両方ともCTPが陽性であった。持続的漏出が客観的に証明された本症例の骨導の悪化をきたさず軽度伝音難聴のみ，めまいが主訴であったことは，特筆に値する。以前から，難聴を伴わない，めまいのみの外リンパ瘻が存在することが提唱され[22][23]，通常の外リンパ瘻の概念を超えるものであり受け入れがたいとする意見もあったが，本症例はこの疾患カテゴリーが実在することを示唆している。

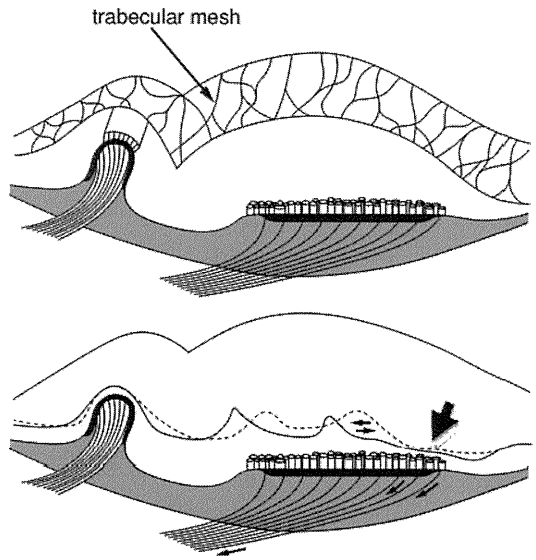

図１　外リンパ瘻の病態説明モデル Floating Labyrinth（文献24を改変）
部分的な虚脱を起こした膜迷路が耳石・半規管の感覚細胞を刺激する（矢印）

アブミ骨付近に鼓膜外傷があってもCTP陰性例もあった。外リンパ瘻以外にも中耳に外力が加わって骨導の悪化をきたすことは以前より知られており，内耳への物理的刺激による内耳振盪や音響外傷と診断される。

D．医原性外リンパ瘻（耳科手術）

アブミ骨手術後に感音成分増悪をきたした場合に，術後性外リンパ瘻の可能性を考慮する。発症時期により早期，晩期型の２つに分類される。変動する感音難聴，耳鳴，耳閉感に伴うめまいが特徴である。北米では，プロテーゼならびに卵円窓の閉鎖手技によるアブミ骨術後性外リンパ瘻頻度が報告されており，ゼルフォーム3.5％，脂肪1.9％，筋膜0.6％であった。

本邦では耳硬化症の頻度が少ないことからアブミ骨術後のめまいも報告が少ないが，最近筆者らは，術後10年以上経過してめまいを主訴に受診した症例でCTP陽性例を経験した。

5．外リンパ瘻と前庭症状

既述のように，極めて特徴に富み，多彩な臨床所見を呈する外リンパ瘻の病態を探るべく，以前から基礎的研究が行われてきた。外リンパ瘻の前庭症状の原因として“Floating” labyrinth 説がある。モルモットを用いた研究で，くも膜下腔に急速に 1-2 ml の液体を注入，もしくは正円窓から 4 μl の外リンパを吸引して作成した外リンパ瘻モデルが報告されている。Pars superior（半規管，球形嚢）には trabecular mesh があり膜迷路を支えているが，上記実験操作により mesh が様々な程度に破綻し，膜迷路が落ち込み，半規管膨大部，球形嚢の感覚細胞を刺激する病態が組織学的に観察された（図１）。外リンパ瘻における多様な前庭症状，検査所見を説明しやすい所見である[24]。前庭では虚脱のみが観察されたが，さらに蝸牛をみるとライスネル膜の病変は様々で，虚脱，破綻，膨隆いずれもが生じていた。これは前庭膜迷路の虚脱により内リンパが pars inferior へ入り込んだため生じた変化と考えられる。

6．治療法

A．保存的療法

自然閉鎖の可能性があるので，入院の上，脳脊髄圧を下げる目的で頭を30度挙上した状態で安静を保ちながら突発性難聴に準じた処方を行う。めまいで嘔吐が強いときには制吐薬を用いる。頻回に純音聴力検査を行い聴力の推移をみる。重量物の運搬や強い鼻かみ，過度のいきみを禁止する。

B．外科的療法

保存治療に反応しない例や，聴平衡機能の悪化，変動を示す例，安静解除で再び症状が出現する場合は，外科治療の適応となる。特発性外リンパ瘻 CTP 陽性例の経験では，術後，めまいは大多数の症例で消失するが難聴は約４割に治癒・著明改善，４割に改善，２割に不変・悪化がみられた。特に発症後14日以内に手術を行った症例で聴力改善が良好であるが，受傷後１月以上経過して手術した症例で治癒した症例もある。

手術は全身麻酔科，局所麻酔いずれでも可能である。耳内法で内耳窓を明視下に観察する。瘻孔と外リンパ瘻漏出を確認するように努める。特に正円窓では偽膜との鑑別を要する。内耳窓閉鎖は，自己組織の筋膜，軟骨膜，結合組織を用いて，瘻孔・漏出の確認の有無にかかわらず，前庭窓，蝸牛窓，fistula ante fenestram をそれぞれ覆い生体糊で固定する[25]。再発予防のため術後は頭部を30度上げ３日間ベッド上安静とする。術後の日常生活では３か月間は鼓室圧，髄液圧が高まるような動作を避けるよう指導する。術中所見から外リンパの漏出の有無を判断することは容易ではなく，客観的な判断指針が報告されている（表４）[4]。

アブミ骨外傷・手術後の外リンパ瘻疑い症例の治療方針決定の上でもっとも重要なポイントは，外リンパ漏出が持続しているか否かである。漏出が持続していれば，いずれ内耳機能が廃絶することが予想され手術的な修復が必要となる。軽度輪状靱帯損傷に伴う外リンパ漏出であれば筋膜による被覆のみで治療できるので，手術のリスクは低い。しかしアブミ骨底が陥入している場合にはアブミ骨を引き上げ整復するため，手術操作自体が内耳障害を増悪させる可能性がある。聴覚・前庭所見，その変動の様子を参考にしながら慎重に判断する。保存的に様子をみる方法と，再手術による瘻孔閉鎖術を比較した報告では，治癒率に明らかな有意差が無いという報告もあり，明らかに外リンパ瘻と考えられた場合にのみ手術を行うのが適切である[26]。

最後に

多彩な臨床像を呈する外リンパ瘻診療においては，前庭系の症候に特に注意が必要で，症例に応じた対応が必要である。

文　献

1）Schuknecht HF: Myths in neurotology. Am J Otol 13: 124-126, 1992

2）Shea JJ: The myth of spontaneous perilymph fistula. Otolaryngol Head Neck Surg 107: 613-616, 1992

3）Meyerhoff WL: Spontaneous perilymphatic fistula: myth or fact. Am J Otol 14: 478-481, 1993

4）Nomura Y: Perilymph fistula: concept, diagnosis and management. Acta Otolaryngol Suppl 514: 52-54, 1994

5）Minor LB: Labyrinthine fistulae: pathobiology and management. Curr Opin Otolaryngol Head Neck Surg 11: 340-346, 2003

6）Merchant SN, Rosowski JJ: Conductive hearing loss caused by third-window lesions of

the inner ear. Otol Neurotol 29: 282-289, 2008
7) Friedland DR, Wackym PA: A critical appraisal of spontaneous perilymphatic fistulas of the inner ear. Am J Otol 20: 261-276, 1999
8) Rauch SD: Transferrin microheterogeneity in human perilymph. Laryngoscope 110: 545-552, 2000
9) Ikezono T, Shindo S, Sekiguchi S, et al.: Cochlin-tomoprotein (CTP), a novel perilymph-specific protein and a potential marker for the diagnosis of perilymphatic fistula. Audiol Neurootol 14: 338-344, 2009
10) Ikezono T, Shindo S, Sekiguchi S, et al.: The performance of CTP detection test for the diagnosis of perilymphatic fistula. Audiol Neurootol 15: 168-174, 2009
11) 厚生省特定疾患急性高度難聴調査研究班平成2年度研究業績報告書：外リンパ瘻の診断基準　平成2年度（案），20頁，1990
12) Fitzgerald DC: Perilymphatic fistula and Meniere's disease. Clinical series and literature review. Ann Otol Rhinol Laryngol 110: 430-436, 2001
13) House JW, Morris MS, Kramer SJ, et al.: Perilymphatic fistula: surgical experience in the United States. Otolaryngol Head Neck Surg 105: 51-61, 1991
14) Dahiya R, Keller JD, Litofsky NS, et al.: Temporal bone fractures: otic capsule sparing versus otic capsule violating clinical and radiographic considerations. J Trauma 47: 1079-1083, 1999
15) Schuknecht HF: Mechanism of inner ear injury from blows to the head. Ann Otol Rhinol Laryngol 78: 253-262, 1969
16) Weissman JL, Curtin HD, Hirsch BE, et al.: High signal from the otic labyrinth on unenhanced magnetic resonance imaging. Am J Neuroradiol 13: 1183-1187, 1992
17) Gordon CR, Levite R, Joffe V, et al.: Is post-traumatic benign paroxysmal positional vertigo different from the idiopathic form? Arch Neurol 61: 1590-1593, 2004
18) Katsarkas A: Benign paroxysmal positional vertigo (BPPV): idiopathic versus post-traumatic. Acta Otolaryngol 119: 745-749, 1999
19) DiBiase P, Arriaga MA :Post-traumatic hydrops. Otolaryngol Clin North Am 30: 1117-1122, 1997
20) Rizvi SS, Gibbin KP: Effect of transverse temporal bone fracture on the fluid compartment of the inner ear. Ann Otol Rhinol Laryngol 88: 741-748, 1979
21) Paparella MM, Mancini F: Trauma and Meniere's syndrome. Laryngoscope 93: 1004-1012, 1983
22) Brandt T: Otolithic Vertigo. eds by Huy B, Toupet M. Karger AF Barsel. In Otolith function and disorders. Advances in Oto Rhino Laryngology 58: 34-47, 2001
23) 深谷　卓，野村恭也：聴力障害を欠く外リンパ瘻症例　試験鼓室開放術の適応拡大についての提案．耳鼻臨床　78：1398-1392，1985
24) Nomura Y, Okuno T, Hara M, et al.: "Floating" labyrinth. Pathophysiology and treatment of perilymph fistula. Acta Otolaryngol 112: 186-191, 1992
25) 池園哲郎：聴力改善手術　外リンパ瘻．耳喉頭頸　77：162-173，2005
26) Yamasoba T, Amagai N, Karino S et al.: Traumatic luxation of the stapes into the vestibule. Otolaryngol Head Neck Surg 129: 287-290, 2003

別刷請求先：池園哲郎

Neuroscience Letters 510 (2012) 73–77

Contents lists available at SciVerse ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Various levels of plasma brain-derived neurotrophic factor in patients with tinnitus

Fumiyuki Goto[a,b,*], Juri Saruta[c], Sho Kanzaki[b], Masahiro To[c], Tomoko Tsutsumi[a], Keiichi Tsukinoki[c], Kaoru Ogawa[b]

[a] Department of Otolaryngology, Hino Municipal Hospital, Japan
[b] Department of Otolaryngology, Keio University, Japan
[c] Department of Maxillofacial Diagnostic Science, Division of Pathology, Kanagawa Dental College, Japan

ARTICLE INFO

Article history:
Received 23 July 2011
Received in revised form 1 January 2012
Accepted 2 January 2012

Keywords:
Tinnitus
Plasma brain-derived neurotrophic factor
Depression

ABSTRACT

Objective: Thus far, no objective measure has been developed to evaluate tinnitus severity. There is a close relationship between tinnitus and depression, in which brain-derived neurotrophic factor (BDNF) has a pathophysiological role. To determine whether BDNF levels could be used to evaluate tinnitus severity, we evaluated plasma BDNF levels in patients with tinnitus.
Methods: Plasma BDNF levels were measured in 43 tinnitus patients and 30 healthy control patients. The severities of tinnitus, depression, and anxiety were measured using the tinnitus handicap inventory (THI) and the hospital anxiety and depression scale (HADS), respectively. Patients with tinnitus were divided into 2 groups depending on their THI scores: mildly handicapped (<36) and severely handicapped (>38). We also divided our subjects into 2 groups depending on the HADS score, which represents patient mood, including depression and anxiety.
Results: Plasma BDNF levels were significantly higher in the mildly handicapped group than in the severely handicapped and control groups ($P < 0.01$). Patients with HADS scores of ≤14 had significantly lower THI scores ($P < 0.05$) and higher BDNF levels ($P < 0.01$).
Conclusions: Our findings show for the first time that plasma BDNF levels vary with the severity of tinnitus, suggesting that plasma BDNF level is a useful tool for objective evaluation of tinnitus.

1. Introduction

Tinnitus is the perception of sounds in the absence of external noise. Subjective tinnitus is defined as the perception of phantom sounds. Tinnitus can affect the entire life of an individual, preventing intellectual work and generally impairing quality of life. In some cases, tinnitus can cause suicidal behavior [2]. Severe tinnitus is often accompanied by affective disorders such as depression. Psychiatric comorbidity occurs especially in individuals with severe tinnitus and adds considerably to patient suffering [2]. Major depressive disorder and anxiety disorder occur most frequently in individuals with chronic disabling tinnitus, with a prevalence of 60% or more [11,34]. Several studies have shown that tinnitus severity and tinnitus-related distress are correlated with depression [32].

In general, subjective tinnitus has no physical signs, and there are no objective clinical diagnostic tests to evaluate its severity. Currently, only patient descriptions can serve as a basis for clinical evaluation. It is therefore very important to develop objective tools for evaluation of tinnitus. The tinnitus handicap inventory (THI) is a very useful test to evaluate the handicap caused by tinnitus [21]. In a consensus meeting (additional) use of the THI was recommended for clinical studies in order to facilitate comparison of results from different studies [17].

Brain-derived neurotrophic factor (BDNF) is a member of the "neurotrophin" protein family of growth factors, which are related to the prototypical "nerve growth factor" NGF [3]. Neurotrophic factors are found in the brain and the periphery. BDNF acts on certain neurons of the central nervous system (CNS) and peripheral nervous system, supporting the growth, differentiation, and survival of neurons and synapses [3]. BDNF plays a central role in synaptic plasticity and neurogenesis in general. It was reported that brain BDNF levels correlate with serum BDNF concentrations [8];

Abbreviations: BBB, blood–brain barrier; BDNF, brain-derived neurotrophic factor; CNS, central nervous system; CSF, cerebrospinal fluid; ELISA, enzyme-linked immunosorbent assay; HADS, hospital anxiety and depression scale; HRP, horseradish peroxidase; NGF, nerve growth factor; NT-3, neurotrophin-3; NT-4, neurotrophin-4; THI, tinnitus handicap inventory; TMB, tetramethylbenzidine; BDI, Beck Depression Inventory.

* Corresponding author at: Department of Otolaryngology, Hino Municipal Hospital, 4-3-1 Tamadaira Hino-shi, Tokyo 191-0062, Japan. Tel.: +81 42 581 2677; fax: +81 42 581 2923.
E-mail address: amifumi@bc5.so-net.ne.jp (F. Goto).

0304-3940/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.neulet.2012.01.001

therefore, blood levels of BDNF may serve as an indirect measure of brain BDNF levels. According to Lommatzsch et al. [19], changes in plasma BDNF levels reflect BDNF concentration changes in the brain. It was recently reported that increased plasma BDNF concentrations observed during physical exercise in humans were due to the enhanced release of BDNF from the brain. These results indicate that serum BDNF is a non-specific trait marker of depression [25], whereas plasma BDNF is a state marker [8].

Strong evidence suggests that serum BDNF levels are abnormally low in patients suffering from major depressive disorder [29]. In addition, close relationships between BDNF gene expression levels and tinnitus have been reported [12,28,31]. Because tinnitus and depression tend to coexist, we reasoned that plasma BDNF levels may serve as tools for the evaluation of tinnitus.

BDNF levels may serve as markers for activity changes in the auditory system. Increased expression of BDNF and gamma-aminobutyric acid (GABA) in the inferior colliculus [24] as well as a reduction in local field potentials in the auditory cortex [30] were reported to be associated with tinnitus. BDNF-induced changes in glutamatergic signaling suggest that BDNF exerts modulatory effects on spontaneous neuronal firing rates in the auditory cortex [13].

In the present study, we examined plasma levels of BDNF in patients with tinnitus and in healthy controls. We tested for any correlations between plasma BDNF levels and clinical characteristics, including tinnitus severity. The objective of the study was to investigate the plasma levels of BDNF in patients with tinnitus.

2. Materials and methods

To investigate whether alterations in neurotrophin levels can be detected in subjects with tinnitus, we determined the peripheral levels (plasma) of BDNF in patients with tinnitus ($N = 43$; 14 male and 29 female) and healthy controls ($N = 30$; 15 male and 15 female). Our subjects included tinnitus patients without other inner ear disorders like sudden deafness or otitis interna. We carefully excluded subjects with tinnitus due to acute inner ear disorder by asking patients about recent history of hearing deterioration. The average age was 57.1 ± 15.2 years (average ± SD) and 50.7 ± 10.1 years, respectively. The severity of tinnitus was evaluated by the THI score. The proposed severity according to THI score was as follows: no handicap (0–16), mild handicap (18–36), moderate handicap (38–56), severe handicap (58–76) and catastrophic handicap (78–100) [22]. Patients with THI scores of less than 36 were classified as having mild tinnitus. Patients were classified as having severe tinnitus if the THI score was more than 38. Subjects were first-visit patients complaining of tinnitus at the Hino Municipal hospital. None of the patients had psychiatric disorders at the time of the first visit, and none reported taking drugs for the treatment of psychiatric disorders, including antidepressants and anxiolytics. Conventional audiological evaluation was conducted by pure tone audiometry. Severity of tinnitus was evaluated by the THI score. Mood, including anxiety and depression, was evaluated using the hospital anxiety and depression scale (HADS) [33]. We divided our subjects into 2 groups depending on the HADS score. In our previous study, we determined that a total score of 15 or more is indicative of mood disorder [10]. We classified patients with total scores of 14 or below as HADS ≤ 14 and those with scores of 15 or above as HADS ≥ 15. In addition we collected data on hearing threshold, site of tinnitus (left ear, right ear, bilateral, or intracranial), and duration of tinnitus from the initial onset. The hearing threshold was calculated as the average of 4 consecutive frequencies of 500, 1000, 2000, and 4000 Hz.

2.1. Plasma BDNF measurements

Blood samples from all subjects were drawn between 0900 and 1000 h. Approximately 4 mL of blood was collected in a vacuum tube with lithium heparin and immediately centrifuged at 3800 rpm for 10 min. Plasma was stored at −70 °C prior to use. Human BDNF was detected by sandwich ELISA according to the manufacturer's instructions (CYT306; Millipore Co., Billerica, MA, USA). All assays were performed in F-bottom 96-well plates (Nunc, Wiesbaden, Germany). Tertiary antibodies were conjugated to horseradish peroxidase (HRP). Color was developed with tetramethylbenzidine (TMB) and measured at 450/570 nm. BDNF content was quantified against a standard curve calibrated with known amounts of BDNF. The detection limit was <4 pg/mL. All samples were tested twice, and mean values were calculated. Cross-reactivity to related neurotrophins (NGF, NT-3, and NT-4) was less than 3%. Intra-assay and inter-assay coefficients of variation were 3.7% and 8.5%, respectively. Concentration was expressed as pg/mL. The relationship between the THI score and plasma BDNF concentration was investigated.

We tested for correlations between plasma BDNF levels, tinnitus handicap, depression, and anxiety. All experiments were carried out in accordance with the guidelines of the ethics committee of the Hino Municipal Hospital and the Declaration of Helsinki.

2.2. Statistical analysis

All data were analyzed using Microcal Origin R version 6.0 software (Microcal Software Inc., Northampton, MA, USA) and GraphPad Prism software (GraphPad Software Inc., La Jolla, CA, USA). Statistical analyses were performed using t-tests, repeated measures ANOVA, and chi-square tests. If the P value was less than 0.05, the results were considered statistically significant.

3. Results

Thirteen patients reported tinnitus in the right ear and 12, in the left ear. Eleven patients reported bilateral tinnitus, and 7 reported intracranial tinnitus. The average hearing threshold was 22.9 ± 20.3 dB for the right ear and 20.9 ± 14.8 dB for the left. THI ranged from 2 to 90 (average: 38.2 ± 23.4). The duration of tinnitus ranged from 2 days to 312 months (average duration: 25.5 ± 59.6 months). Initially, patients with tinnitus were divided into 2 groups depending on the duration of tinnitus. Tinnitus with duration of less than 2 months was defined as acute tinnitus. Tinnitus with duration of more than 3 months was defined as chronic tinnitus [20]. Twenty patients had acute tinnitus, and 22 patients had chronic tinnitus. When we compared BDNF levels, HADS scores, and THI scores between these groups, there were no significant differences. Therefore, we combined these 2 groups and treated them as 1 group for comparison purposes. The total HADS scores of tinnitus patients (14.5 ± 7.5) were significantly higher than those of controls (7.8 ± 5.4; $P < 0.0001$). Plasma BDNF levels ranged from 48.6 to 4045.4 pg/mL (average, 768.7 ± 961.4 pg/mL) in tinnitus patients and from 44.8 to 1289.9 pg/mL (average, 338.5 ± 287.7 pg/mL) in the controls (Table 1 and Fig. 1). The site of tinnitus, hearing threshold, and the duration of tinnitus did not correlate with the THI scores, HADS scores, or BDNF levels.

There were 25 patients with mild tinnitus and 18 with severe tinnitus. Fig. 1 shows that mild tinnitus patients showed significantly higher plasma levels of BDNF than severe tinnitus patients (1.321.9 ± 1266.1 vs. 385.1 ± 524.9 pg/mL; $P < 0.01$) and controls ($P < 0.01$; Fig. 1). Plasma BDNF levels were negatively correlated with HADS scores ($R = -0.35$, $P < 0.05$), while THI and HADS scores were positively correlated ($R = 0.55$ $P < 0.0001$). After adjusting for

Table 1
THI scores and plasma BDNF levels in patients with different mood statuses.

THI scores and plasma BDNF levels in patients with different mood statuses.

		Patients with tinnitus	
	controls	HADS≤14	HADS≥15
THI	N.A.	25.9 16.3	49.5 ± 23.5
		**	
BDNF	338.5 ± 287.7	1092.1 ± 1157.6	474.6 ± 634.1
		*	
HADS	7.8 ± 5.4		14.5 ± 7.5
		***	

*P<0.05, **P<0.01, ***P<0.001

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

possible effects of HADS scores, partial correlation coefficients for BDNF levels and THI scores indicated that there was no relationship between BDNF levels and THI scores. As shown in Table 1, patients with HADS scores of ≤14 had significantly lower THI scores ($P < 0.05$) and higher BDNF values ($P < 0.01$) than patients with HADS scores of ≥15.

4. Discussion

Tinnitus is a phantom auditory perception that is associated with hearing loss and altered neuronal excitability in peripheral and central auditory neurons [24]. BDNF is affected by changes in excitability and plasticity and is involved in neuronal survival and differentiation. BDNF is a key player in the mechanism of onset and persistence of salicylate-induced tinnitus. Increased BDNF expression in spiral ganglion neurons and increased spontaneous activity in the cochlear nerve and dorsal cochlear nucleus have been reported in a salicylate-induced tinnitus model [5]. Salicylate-induced upregulation of BDNF in the spiral ganglion neurons may result in an imbalance of central auditory neuronal activity, which is associated with tinnitus.

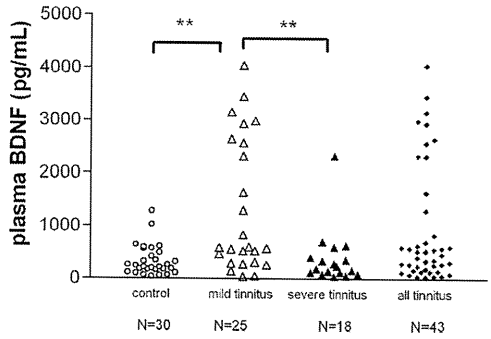

Fig. 1. Plasma BDNF levels in controls, patients with mild tinnitus, and patients with severe tinnitus. Plasma BDNF levels are significantly higher in patients with mild tinnitus. Both normal controls and patients with severe tinnitus showed low plasma BDNF levels. **$P < 0.01$.

To verify whether BDNF-related mechanisms are involved in tinnitus, we investigated whether peripheral circulating BDNF levels differ between patients with tinnitus and healthy patients. THI was developed to quantify the symptoms of tinnitus [21], so THI scores were used to evaluate tinnitus. Our results indicate that both normal controls and severely affected tinnitus patients had low plasma BDNF levels (Fig. 1). Interestingly, about 50% of the patients had low plasma BDNF levels, even mildly distressed patients (Fig. 1). Whether plasma BDNF levels are sensitive enough to serve as clinical biomarkers in tinnitus patients remains to be investigated. Future research will therefore focus on conditions that may affect BDNF levels. Since hearing levels were not correlated with the plasma BDNF levels in this study, elevated BDNF levels are unlikely to be linked to cochlear function. Tinnitus is likely associated with many parts of the central nervous system, in contrast to hearing function, which is associated with discrete CNS components.

BDNF is found in both serum and plasma in humans [9]. Human platelets contain a large amount of BDNF [9]. As a consequence, serum levels of BDNF are about 200-fold higher than plasma levels [27]. Since BDNF crosses the blood–brain barrier (BBB) in both directions, circulating BDNF might originate from neurons and glial cells in the brain [23]. Therefore, plasma BDNF may reflect circulating levels rather than BDNF stored in platelets.

Meta-analyses showed a reduction in both serum and plasma BDNF levels in major depression [4,6,29]. Previous studies have reported that serum BDNF levels are significantly lower in drug-free patients with major depression [14]. Karege et al. reported that both

serum and plasma BDNF levels were significantly lower in patients with major depression than in normal controls [14]. In addition, previous studies found lower serum BDNF levels in patients with higher Beck Depression Inventory (BDI) [1] sum scores [7].

It is unclear whether altered plasma BDNF levels are primary or secondary signs in patients with mild tinnitus. Changes in BDNF expression subsequent to the onset of tinnitus have been reported. BDNF is affected by changes in excitability, and plasticity and is one of the key players in the onset and persistence of salicylate-induced tinnitus [24]. Therefore, increased plasma BDNF levels in mild tinnitus patients may reflect increased BDNF levels in the central auditory system. In severe tinnitus patients, the relative reduction in plasma BDNF can be explained by stress-induced reduction of BDNF in the central nervous system. There was no correlation between THI scores and plasma BDNF levels after adjustment for HADS scores. BDNF levels may be more likely to be related to HADS scores than to THI scores, although our data cannot prove this. The fact that elevated BDNF levels occur only in patients with mild tinnitus is interesting. The limitation of the present study is that we evaluated tinnitus on the basis of THI scores alone. We did not measure tinnitus loudness in patients. If we had measured tinnitus loudness and tested for a correlation between tinnitus loudness and BDNF, we may have determined whether the plasma BDNF levels reflect auditory function. THI scores alone do not provide sufficient information to adequately determine the relationship between tinnitus and plasma BDNF levels. Psychiatric comorbidities, especially depression and anxiety disorders, are common phenomena in tinnitus patients. Our subjects did not have psychiatric diagnoses at the time of evaluation. However, the HADS scores indicated that the mood status in our patients differed from that of healthy subjects. Patients with HADS scores of $\geq$15 had lower plasma BDNF levels than those with HADS scores of $\leq$14 (Table 1). This result can be explained by the effect of mood of the patients. There is no simple explanation for the observed changes in plasma BDNF; however, these changes can be partly attributed to the effect of mood, including depression and anxiety.

It is unlikely that tinnitus and depression coexist by chance. Instead, these conditions represent a complex interplay between tinnitus and depression [18]. Whether altered BDNF levels are a result of depression caused by tinnitus or are due to the tinnitus alone is still not known.

We should therefore carefully consider the implications of the changes in BDNF levels in patients with mild tinnitus.

From a clinical point of view, it is important to note that in tinnitus patients, their suffering is frequently linked to concomitant depressive symptoms. Improvement of depression is paralleled by improvements in functional ability [16]. It is therefore important that clinicians who treat tinnitus patients are observant of comorbid psychiatric symptoms, especially depression and anxiety. It is especially important that these clinicians consider affective symptoms when providing treatment for tinnitus.

Whether plasma BDNF levels reflect dynamic changes in BDNF levels in the CNS is debatable. Intact BDNF in the peripheral circulation crosses the BBB using a high-capacity, saturable transport system [23]. Brain and serum BDNF levels undergo similar changes during maturation and aging processes in rats [15]. In addition, there is a significant positive correlation between plasma and cerebrospinal fluid (CSF) BDNF levels in psychiatric patients [26]. These results indicate that plasma BDNF concentrations reflect dynamic changes in the brain. Plasma BDNF levels may be used to objectively evaluate tinnitus severity and may assist in the identification of comorbid psychiatric disorders, including depression. Treatment of comorbid psychiatric disorders can substantially reduce the burden of the disease and improve the quality of life of individuals with tinnitus.

5. Conclusion

The results of our study suggest that plasma BDNF levels are higher in patients with mild tinnitus than in healthy controls. Our findings show for the first time that changes in peripheral levels of BDNF occur in patients suffering from different levels of tinnitus, suggesting a potential involvement of BDNF in the severity of tinnitus. These results suggest that differences in peripheral BDNF levels may help distinguish patients with mild tinnitus from healthy subjects. Further study is required to identify the possible physiological mechanisms responsible for altered BDNF levels in patients with tinnitus.

Conflict of interest

The authors declare no conflicting financial interests or commercial considerations related to the issues presented herein.

Acknowledgement

The part of this study was supported by Grant-in-Aid for Scientific Research (C) No. 23592494.

References

[1] A.T. Beck, C.H. Ward, M. Mendelson, J. Mock, J. Erbaugh, An inventory for measuring depression, Arch. Gen. Psychiatry 4 (1961) 561–571.
[2] S. Belli, H. Belli, T. Bahcebasi, A. Ozcetin, E. Alpay, U. Ertem, Assessment of psychopathological aspects and psychiatric comorbidities in patients affected by tinnitus, Eur. Arch. Otorhinolaryngol. 265 (2008) 279–285.
[3] D.K. Binder, H.E. Scharfman, Brain-derived neurotrophic factor, Growth Factors 22 (2004) 123–131.
[4] L. Bocchio-Chiavetto, V. Bagnardi, R. Zanardini, R. Molteni, M.G. Nielsen, A. Placentino, C. Giovannini, L. Rillosi, M. Ventriglia, M.A. Riva, M. Gennarelli, Serum and plasma BDNF levels in major depression: a replication study and meta-analyses, World J. Biol. Psychiatry 11 (2010) 763–773.
[5] T.J. Brozoski, C.A. Bauer, D.M. Caspary, Elevated fusiform cell activity in the dorsal cochlear nucleus of chinchillas with psychophysical evidence of tinnitus, J. Neurosci. 22 (2002) 2383–2390.
[6] A.R. Brunoni, M. Lopes, F. Fregni, A systematic review and meta-analysis of clinical studies on major depression and BDNF levels: implications for the role of neuroplasticity in depression, Int. J. Neuropsychopharmacol. 11 (2008) 1169–1180.
[7] B.A. Bus, I. Tendolkar, B. Franke, J. de Graaf, M.D. Heijer, J.K. Buitelaar, R.C. Oude Voshaar, Serum brain-derived neurotrophic factor: determinants and relationship with depressive symptoms in a community population of middle-aged and elderly people, World J. Biol. Psychiatry (2011) 19.
[8] B.S. Fernandes, C.S. Gama, K. Maria Cereser, L.N. Yatham, G.R. Fries, G. Colpo, D. de Lucena, M. Kunz, F.A. Gomes, F. Kapczinski, Brain-derived neurotrophic factor as a state-marker of mood episodes in bipolar disorders: a systematic review and meta-regression analysis, J. Psychiatr. Res. 45 (2011) 995–1004.
[9] H. Fujimura, C.A. Altar, R. Chen, T. Nakamura, T. Nakahashi, J. Kambayashi, B. Sun, N.N. Tandon, Brain-derived neurotrophic factor is stored in human platelets and released by agonist stimulation, Thromb. Haemost. 87 (2002) 728–734.
[10] F. Goto, T. Tsutsumi, K. Ogawa, Anxiety and depression levels measured using a hospital anxiety and depression scale in patients with an otolaryngological disorder, Pract. Otorhinolaryngol. 102 (2009) 1071–1075.
[11] J. Harrop-Griffiths, W. Katon, R. Dobie, C. Sakai, J. Russo, Chronic tinnitus: association with psychiatric diagnoses, J. Psychosom. Res. 31 (1987) 613–621.
[12] K.C. Horner, The emotional ear in stress, Neurosci. Biobehav. Rev. 27 (2003) 437–446.
[13] J.A. Kaltenbach, Neurophysiologic mechanisms of tinnitus, J. Am. Acad. Audiol. 11 (2000) 125–137.
[14] F. Karege, G. Bondolfi, N. Gervasoni, M. Schwald, J.M. Aubry, G. Bertschy, Low brain-derived neurotrophic factor (BDNF) levels in serum of depressed patients probably results from lowered platelet BDNF release unrelated to platelet reactivity, Biol. Psychiatry 57 (2005) 1068–1072.
[15] F. Karege, M. Schwald, M. Cisse, Postnatal developmental profile of brain-derived neurotrophic factor in rat brain and platelets, Neurosci. Lett. 328 (2002) 261–264.
[16] W. Katon, M. Sullivan, J. Russo, R. Dobie, C. Sakai, Depressive symptoms and measures of disability: a prospective study, J. Affect Disord. 27 (1993) 245–254.
[17] B. Langguth, R. Goodey, A. Azevedo, A. Bjorne, A. Cacace, A. Crocetti, L. Del Bo, D. De Ridder, I. Diges, T. Elbert, H. Flor, C. Herraiz, T. Ganz Sanchez, P. Eichhammer, R. Figueiredo, G. Hajak, T. Kleinjung, M. Landgrebe, A. Londero, M.J. Lainez, M. Mazzoli, M.B. Meikle, J. Melcher, J.P. Rauschecker, P.G. Sand, M. Struve, P. Van de Heyning, P. Van Dijk, R. Vergara, Consensus for tinnitus patient assessment

and treatment outcome measurement: tinnitus research initiative meeting, Regensburg, July 2006, Prog. Brain Res. 166 (2007) 525–536.
[18] B. Langguth, M. Landgrebe, T. Kleinjung, G.P. Sand, G. Hajak, Tinnitus and depression, World J. Biol. Psychiatry 12 (2011) 489–500.
[19] M. Lommatzsch, D. Zingler, K. Schuhbaeck, K. Schloetcke, C. Zingler, P. Schuff-Werner, J.C. Virchow, The impact of age, weight and gender on BDNF levels in human platelets and plasma, Neurobiol. Aging 26 (2005) 115–123.
[20] A.R. Moller, B. Langguth, D. De Ridder, T. Kleinjung, Chapter 5 epidemiology of tinnitu in adults, in: A.R. Moller (Ed.), Textbook of Tinnitus, Springer, New York, 2011, pp. 29–38.
[21] C.W. Newman, G.P. Jacobson, J.B. Spitzer, Development of the tinnitus handicap inventory, Arch. Otolaryngol. Head Neck Surg. 122 (1996) 143–148.
[22] C.W. Newman, S.A. Sandridge, G.P. Jacobson, Psychometric adequacy of the Tinnitus Handicap Inventory (THI) for evaluating treatment outcome, J. Am. Acad. Audiol. 9 (1998) 153–160.
[23] W. Pan, W.A. Banks, M.B. Fasold, J. Bluth, A.J. Kastin, Transport of brain-derived neurotrophic factor across the blood–brain barrier, Neuropharmacology 37 (1998) 1553–1561.
[24] R. Panford-Walsh, W. Singer, L. Ruttiger, S. Hadjab, J. Tan, H.S. Geisler, U. Zimmermann, I. Kopschall, K. Rohbock, A. Vieljans, E. Oestreicher, M. Knipper, Midazolam reverses salicylate-induced changes in brain-derived neurotrophic factor and arg3.1 expression: implications for tinnitus perception and auditory plasticity, Mol. Pharmacol. 74 (2008) 595–604.
[25] A. Piccinni, D. Marazziti, M. Catena, L. Domenici, A. Del Debbio, C. Bianchi, C. Mannari, C. Martini, E. Da Pozzo, E. Schiavi, A. Mariotti, I. Roncaglia, A. Palla, G. Consoli, L. Giovannini, G. Massimetti, L. Dell'Osso, Plasma and serum brain-derived neurotrophic factor (BDNF) in depressed patients during 1 year of antidepressant treatments, J. Affect Disord. 105 (2008) 279–283.
[26] A. Pillai, A. Kale, S. Joshi, N. Naphade, M.S. Raju, H. Nasrallah, S.P. Mahadik, Decreased BDNF levels in CSF of drug-naive first-episode psychotic subjects: correlation with plasma BDNF and psychopathology, Int. J. Neuropsychopharmacol. 13 (2010) 535–539.
[27] R.D. Rosenfeld, L. Zeni, M. Haniu, J. Talvenheimo, S.F. Radka, L. Bennett, J.A. Miller, A.A. Welcher, H. Fujimura, C.A. Altar, R. Chen, T. Nakamura, T. Nakahashi, J. Kambayashi, B. Sun, N.N. Tandon, Purification and identification of brain-derived neurotrophic factor from human serum Brain-derived neurotrophic factor is stored in human platelets and released by agonist stimulation, Protein Expr. Purif. 6 (1995) 465–471.
[28] P.G. Sand, B. Langguth, T. Kleinjung, P. Eichhammer, Genetics of chronic tinnitus, Prog. Brain Res. 166 (2007) 159–168.
[29] S. Sen, R. Duman, G. Sanacora, Serum brain-derived neurotrophic factor, depression, and antidepressant medications: meta-analyses and implications, Biol. Psychiatry 64 (2008) 527–532.
[30] J. Tan, L. Ruttiger, R. Panford-Walsh, W. Singer, H. Schulze, S.B. Kilian, S. Hadjab, U. Zimmermann, I. Kopschall, K. Rohbock, M. Knipper, Tinnitus behavior and hearing function correlate with the reciprocal expression patterns of BDNF and Arg3.1/arc in auditory neurons following acoustic trauma, Neuroscience 145 (2007) 715–726.
[31] R.S. Tyler, C. Coelho, W. Noble, Tinnitus: standard of care, personality differences, genetic factors, ORL J. Otorhinolaryngol. Relat. Spec. 68 (2006) 14–19, discussion 20–12.
[32] J. Unterrainer, K.V. Greimel, M. Leibetseder, T. Koller, Experiencing tinnitus: which factors are important for perceived severity of the symptom? Int. Tinnitus J. 9 (2003) 130–133.
[33] A.S. Zigmond, R.P. Snaith, The hospital anxiety and depression scale, Acta Psychiatr. Scand. 67 (1983) 361–370.
[34] S. Zoger, J. Svedlund, K.M. Holgers, Psychiatric disorders in tinnitus patients without severe hearing impairment: 24 month follow-up of patients at an audiological clinic, Audiology 40 (2001) 133–140.

Otology & Neurotology
32:1492–1499 © 2011, Otology & Neurotology, Inc.

Efficacy of a Vibrotactile Neurofeedback Training in Stance and Gait Conditions for the Treatment of Balance Deficits: A Double-Blind, Placebo-Controlled Multicenter Study

*Dietmar Basta, †Marcos Rossi-Izquierdo, ‡Andrés Soto-Varela, §Mario Edwin Greters, §Roseli Saraiva Bittar, ||Elisabeth Steinhagen-Thiessen, ||Rahel Eckardt, ¶Tatsuhiko Harada, #Fumiyuki Goto, **Kaoru Ogawa, and *Arne Ernst

**Department of Otolaryngology at UKB, Hospital of the University of Berlin, Charité Medical School, Berlin, Germany; †Department of Otolaryngology, University Hospital Lucus Augusti, Lugo; ‡Department of Otolaryngology, University Hospital of Santiago de Compostela, Santiago de Compostela, Spain; §Department of Otolaryngology, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil; ||Geriatrics Research Group, Charité Medical School, Berlin, Germany; ¶Department of Otolaryngology, International University of Health and Welfare, Atami; #Department of Otolaryngology, Hino Municipal Hospital; and **Department of Otolaryngology, Keio University, School of Medicine, Tokyo, Japan*

Objective: Vestibular rehabilitation strategies mostly require a long-lasting training in stance conditions, which is finally not always successful. The individualized training in everyday-life conditions with an intuitive tactile neurofeedback stimulus seems to be a more promising approach. Hence, the present study was aimed at investigating the efficacy of a new vibrotactile neurofeedback system for vestibular rehabilitation.
Study Design: Double-blinded trial.
Patients: One hundred five patients who experience one of the following balance disorders for more than 12 months were included in the study: canal paresis, otolith disorder, removal of an acoustic neuroma, microvascular compression syndrome, Parkinson's disease, and presbyvertigo.
Interventions: Vibrotactile neurofeedback training was performed daily (15 min) over 2 weeks with the Vertiguard system in those 6 tasks of the Standard Balance Deficit Test with the most prominent deviations from the normative values.
Main Outcome Measures: Trunk and ankle sway, dizziness handicap inventory, and vestibular symptom score were measured in the verum and placebo group before the training, on the last training day and 3 months later.
Results: A significant reduction in trunk and ankle sway as well as in the subjective symptom scores were observed in the verum group. Such an effect could not be found in any of the outcome parameters of the placebo group.
Conclusion: The vibrotactile neurofeedback training applied in the present study is a highly efficient method for the reduction of body sway in different balance disorders. Because the rehabilitation program is easy to perform, not exhausting, and time saving, elderly patients and those with serious, long-lasting balance problems also can participate successfully. **Key Words:** Neurofeedback—Postural control—Vestibular rehabilitation—Vibrotactile.
Otol Neurotol **32**:1492–1499, 2011.

Numerous diseases are accompanied by balance deficits, which are frequently characterized by an increase in body sway and a higher risk to fall. Different strategies in the conservative management of those balance deficits have been applied successfully over the last few decades to improve central compensation of the tonus imbalance within the vestibular system and to facilitate substitution (1) in different types of peripheral or central vestibular disorders (2,3). Various exercise programs (home or supervised) have been described, including physical training (4), Cawthorne-Cooksey interventions (5), and alternative strategies—such as Tai Chi (6).

Address correspondence and reprint requests to Dietmar Basta, Ph.D., Department of Otolaryngology at UKB, Warener Str. 7, 12683 Berlin, Germany; E-mail: dietmar.basta@ukb.de

This study was supported by a grant from the German Ministry of Education and Research (BMBF-01EZ0754).

However, these vestibular rehabilitation strategies mostly require a long-lasting, intensive training approach (i.e., over several weeks or even months) which is finally not always successful. Current studies have shown that rehabilitation strategies including a sensory feedback signal could be much more effective. The first feedback applications consisted of stance tasks with visual feedback (3,7,8), galvanic feedback (9,10), or vibrotactile feedback (11,12). Because patients tend to fall mostly in dynamic (i.e., movement) conditions, those stance tasks in balance rehabilitation should be accompanied by gait (or dynamic) tasks including daily-life situations. Earlier studies showed a high effectiveness of a free-field auditory neurofeedback training to reduce the body sway in patients with different peripheral vestibular disorders (13–15). This auditory neurofeedback application, however, is limited to the laboratory situation and those patients with good hearing (which is frequently not the case in the elderly or patients with a vestibular disorder). Therefore, an intuitive tactile neurofeedback stimulus could be superior for encoding of the individual sway information during the training of everyday-life conditions.

Hence, the present study was aimed at investigating the efficacy of a newly developed method for vestibular rehabilitation with a vibrotactile neurofeedback system.

MATERIALS AND METHODS

Patients' Characteristics

Patients which chronically experienced dizziness (longer than 12 mo) were recruited within 17 months from neuro-otologic or neurologic clinics.

The inclusion criteria to participate in the neurofeedback training program was a pathologic body sway (measured at the hip in pitch and roll direction) compared with normal age- and sex-related controls as recorded by the diagnostic, mobile posturography device Vertiguard-D (Vesticure GmbH, Germany). The pathologic sway should be found in at least one of the test conditions of the Standard Balance Deficit Test (SBDT) (15) or the Geriatric Standard Balance Deficit Test (gSBDT) (manual Vertiguard, Vesticure GmbH).

The SBDT contained the following 14 tasks: standing on 2 legs with eyes open/closed, standing on 1 leg with eyes open/closed, 8 tandem steps (1 foot in front of the other) with eyes open, standing with 2 legs on a foam support surface (height, 10 cm; density, 25 kg/m^3) with eyes open/closed, standing on 1 leg on a foam support surface, 8 tandem steps on a foam support surface, walking 3 m while rotating the head, walking 3 m while vertically pitching the head in rhythm, walking 3 m forward with eyes open/closed, and walking over 4 barriers (height of 26 cm with an interbarrier distance of 1 m).

The following tasks were skipped in the gSBDT (for patients older than 59 yr): standing on 1 leg with eyes closed and standing on 1 leg on a foam support surface.

The tasks "stand up" and "sit down" were added as last conditions to the gSBDT.

The recording time was 20 seconds for all stance tasks and as long as required for gait tasks (mostly <20 s).

Exclusion criteria for the study were as follows: the use of drugs, which actively influence the vestibular system (e.g., cinnarizine, dimenhydrinate, betahistidine); sensory deficits exceeding age-related values (e.g., auditory symptoms, blurred vision, anosmia); a combination of different types of vestibular disorders in 1 patient (e.g., canal paresis and otolith disorder) because 1 important aim of the present study was to investigate a possible correlation between the efficacy of the training and a specific vestibular disorder; an acute vestibular disorder (due to World Health Organization definition); and all included patients received no other treatment (whether medical, surgical, or rehabilitative) for their balance disorder during the study period.

Of the 132 patients who experienced dizziness or instability, 27 were excluded from the study. Seven of them showed a combination of different types of vestibular disorders; 4 had sensory deficits, which exceeded the normal age-related values (auditory symptoms); and 16 patients showed no pathologic body sway within the SBDT. In total, 105 patients were included in this study. The sample contained patients with 6 different peripheral or central balance disorders, including the following (for details, see Table 1): unilateral canal paresis (semicircular canal paresis [SCC]); otolith disorder (O), that is, unilateral or bilateral loss of sacculo-utricular function; patients after removal of an acoustic neuroma (AN) with resection of the vestibular nerve; micro(neuro) vascular compression syndrome (MVCS) of the VIIIth cranial nerve; Parkinson's disease (PD); and presbyvertigo (P), that is, patients older than 59 years with no specific vestibular deficit but an increase in body sway as result of this complex disorder.

Patients with an otolith disorder showed a combined sacculo-utricular dysfunction. All the vestibular tests were applied to all patients to exclude an overlapping of group-specific pathologies. Pathologic findings in the vestibular testing of the same side as affected by an AN or a micro(neuro) vascular compression were related to the disorder of the VIIIth nerve function. The vestibular test battery contained the following procedures: caloric testing (pathologic results: side differences of more than 15% [slow phase velocity]); cervical vestibular evoked myogenic potentials (pathologic results: absence of N1/P1 even if the required tonic muscle activity was achieved); and subjective haptic vertical (pathologic results: side asymmetry or difference to the vertical of more than 10 degrees).

TABLE 1. *Characterization of treatment subgroups and classification criteria*

Subgroup	Age	n	Female	Male	Classification criteria
Semicircular canal function loss	60.2 + 13.6	25	10	15	Pathologic results during caloric irrigation
Otolith disorder	54.6 + 13.8	21	10	11	Pathologic vestibular evoked myogenic potentials or subjective haptic vertical
Acoustic neuroma removal	60.2 + 10.1	10	4	6	Surgical removal of an acoustic neuroma
Microvascular compression syndrome	52.0 + 10.8	12	6	6	Radiographic defined 8. Nerve-anterior inferior cebellar artery contact
Parkinson's disease	68.1 + 9.1	10	2	8	Idiopathic type
Presbyvertigo	73.4 + 6.0	13	6	7	Dizzy elderly patients (>59 yr) without a vestibular disease

After calculating the minimal sample size for the control (placebo) group by using the software G*Power 3.1.2 (University Kiel, Germany) (16) with an effect size of 0.9, $p = 0.05$, and a statistical power of 0.8, 14 patients were randomly selected from the initial study sample of 105 patients under consideration of the initial distribution of balance disorders and sex. Six female subjects (64.0 ± 9.6 yr) and 8 male subjects (58.8 ± 8.5 yr) were included in the control group with the following distribution of balance disorders: SCC, 28.6%; O, 21.4%; AN, 14.3%; MVCS, 14.3%; PD, 7.1%; and P, 14.3%.

All other patients were included in the treatment group. This group contained 91 patients (39 female subjects—59.1 ± 14.1 yr; 52 male subjects—61.7 ± 12.7 yr). The distribution of balance disorders and sex was similar to that of the control group. Table 1 shows the details of the treatment subgroups and the classification criteria.

Vestibular Rehabilitation Training

The training was performed using the Vertiguard training device (Vesticure GmbH). It contains a battery-driven main unit (120 × 76 × 32 mm, 190 g) which is fixed on a belt at the center of body mass (hip) and 1 vibration stimulator on the front, back, left, and right side, respectively (Fig. 1). The vibration stimulators are mounted on the same belt as the main unit. They are adjustable by sliding them over the belt into the correct position of the individual patient. The main unit continuously records the Coriolis force during body movements in pitch and roll by inbuilt gyroscopes and compares those values with individually preset thresholds for the stimulator activation in the specific direction. Preset thresholds were task specific. They were determined for the individual patient based on the maximum age- and sex-related normative sway in the specific SBDT condition and sway direction. The thresholds were stored for each training task in the main unit. Training tasks were selected automatically by analyzing the results of the SBDT or gSBDT. Only those 6 tasks with the most prominent deviations from the normative values were included in the training program. The number of training tasks was limited by the device capacity. This is related to the assumption that almost all patients show a pathologic sway in not more than 6 conditions of the SBDT. The patient was able to switch between the tasks by pressing a button on the main unit. To prevent the selection of wrong thresholds for the performed task, the chosen task was shown together with the patient's name in the display of the main unit. No vibrotactile feedback stimulus was delivered via the stimulators if the patients' sway were below the preset thresholds. In contrast to this, if the body sway exceeded the thresholds, the perceived vibration was increased with the amplitude of body sway. The patients were instructed daily by a nurse to adjust the vibratory stimulation step by step (within a scale of 10 steps) at the beginning of each selected training task by pressing the sensitivity buttons (up/down) on the main unit. During this procedure, the individual preset thresholds were similarly decreased for all sway directions of the specific training condition until the patient perceived a vibration during performing the training task.

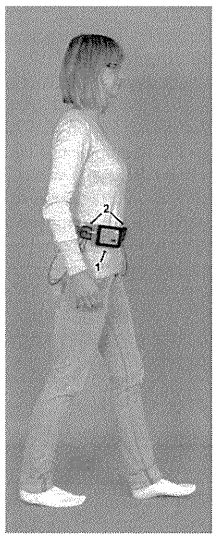

FIG. 1. Application of the vibrotactile neurofeedback system Vertiguard for the treatment of balance disorders. The system with the main unit (1) and the vibration stimulators (2) is fixed on a belt at the center of body mass. Only 2 of the 4 vibration stimulators are visible in the picture.

Vestibular rehabilitation exercises were performed daily over a 2-week period with 10 days of exercising (weekends excluded). Each session contained 5 repetitions of the selected tasks. The time limit for 1 repetition was 20 seconds for all stance tasks and as long as needed for gait tasks (similar to the recording time of the SBDT/gSBDT). The total daily training time was approximately 15 to 20 minutes.

Patients of the control group performed the similar protocol with a sham device (emitting randomly assigned signals to the vibrators). The patients as well as the supervisor did not know the group classification (double-blinded study design).

Evaluation of the Effects of the Vestibular Rehabilitation

Trunk sway of the patients was measured in pitch and roll for each exercise task (without feedback) before and after the training by means of the Vertiguard D system (Vesticure GmbH). The results were averaged across all tasks.

The composite score of the sensory organization test (SOT) of the BalanceMaster (Nicolet Biomedical, Clackamas, OR, USA) ankle-sway referenced system (platform), the dizziness handicap inventory (DHI) (17), and the vestibular symptom score (VSS) (18) were obtained before the training, on the last training day, and 3 months later.

Objective measures of trunk sway (pitch and roll) and ankle sway (SOT composite score) were used as primary end points. The SOT composite score is scored between zero (fall) and 100 (maximum stability). The results of questionnaires (DHI and VSS) were classified as secondary end points. Lowering of DHI or VSS scores indicate a decline of handicaps or symptoms. Primary and secondary end points were statistically compared in the treatment group (also for all subgroups) and placebo group before and after the rehabilitation period by the t test for dependent samples or the Wilcoxon's test (depending on data distribution). The similar tests were used for the comparison between the results of all investigated parameters before the training and after the follow-up (SPSS 11.0). A Bonferroni alpha correction was applied for multiple comparisons. In the case of missing values, the patient was excluded from the analysis of the related parameters. Data were tested for a normal distribution by the Kolmogoroff-Smirnoff test.

The statistical power and effect size was determined by post hoc calculations for each comparison with the software G*Power 3.1.2 (University Kiel, Germany) (16). Statistical power estimates

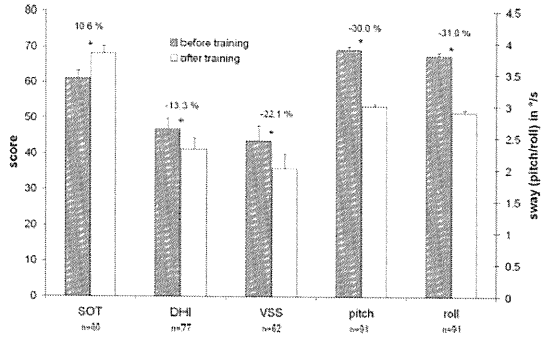

FIG. 2. Mean values (+ standard error of the mean [SEM]) and percentage changes of the SOT (BalanceMaster/Neurocom), the DHI, the VSS, and the body sway (pitch/roll) before and after a vibrotactile neurofeedback training in the treatment group. Numbers given below represent the number of patients included in the measurement. *Asterisks* indicate significant differences.

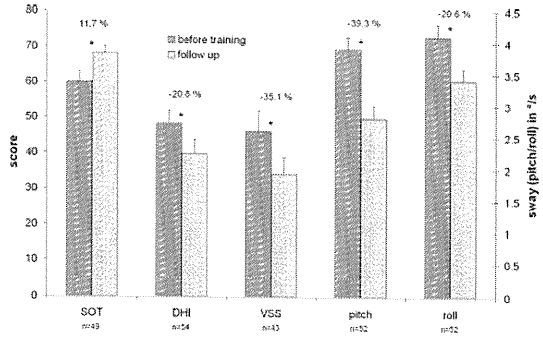

FIG. 3. Mean values (+SEM) and percentage changes of the SOT (BalanceMaster/Neurocom), the DHI, the VSS, and the body sway (pitch/roll) before a vibrotactile neurofeedback training and 3 months after the training in the treatment group. Numbers given below represent the number of patients included in the measurement. *Asterisks* indicate significant differences.

the probability of detecting a change, given that a change has occurred and effect size emphasizes the size of the change rather than confounding this with sample size. Both are very useful for the practical evaluation of the p value. The highest (best) value for the statistical power is 1. A sufficient effect size is higher than 0.5. The level of significance in all tests applied was $p < 0.05$.

A review board approved the study protocol. The patients gave their written, informed consent to participate in the study.

This study was carried out in accordance with the requirements of DIN EN ISO 14155-1/2.

RESULTS

Total Treatment and Placebo Group

The study was conducted from August 2009 until December 2010. No statistically significant differences could be determined with respect to age and sex between the treatment and placebo group (treatment/placebo: sex 42.8%/42.9% female, 57.2%/57.1% male; age 60.6 ± 13.3/61.3 ± 9.2).

The results of the primary end points before and immediately after the training were statistically significantly different in the treatment group (Fig. 2). The trunk sway decreased in the pitch direction by 30% (power, 1.00; effect size, 0.81) and 31% in roll direction (power, 0.99; effect size, 0.65).

The composite score of the SOT increased significantly (increase of stability) by 10.6% on average (power, 0.99; effect size, 0.64). This increase was mainly related to an improved performance in Tasks 5 and 6 of the SOT (Table 2).

The data of the secondary end points, the scores of the questionnaires DHI and VSS, were significantly reduced (reduced symptoms) after the training (power, 0.99; effect size, 0.48; and power, 0.99; effect size, 0.63, respectively). Significant differences also were found for all investigated parameters at the follow-up over time (Fig. 3), although only 60% of the initial patients attended the follow-up measures.

No statistically significant differences could be observed for trunk sway measures or in the SOT immediately after the training of the placebo group (Fig. 4) even if the SOT tasks were separately analyzed (Table 2). The same holds true for the secondary end points, the DHI, and the VSS (Fig. 4).

Treatment Subgroups

Analysis of Pathologic Conditions

The percentage of patients with a pathologic sway is shown for each condition of the SBDT in Figure 5. In all subgroups, the most frequent training tasks were on a foam support surface. There seems to be a trend for a lower occurence of pathologic sway in walking conditions for patients with otolith disorders. Patients of the PD, MVCS, and P subgroup showed a pathologic sway also frequently in walking tasks.

TABLE 2. *Results of the Sensory Organization Test on the BalanceMaster (Neurocom) for tasks 1 to 4 and 5 to 6*

	Treatment group			Placebo group		
Task	Before training	After training	p value	Before training	After training	p value
SOT 1 4	80.9 + 1.6	82.5 + 1.5	0.074	74.5 + 7.0	78.7 + 5.4	0.103
SOT 5 6	40.9 + 3.2	54.0 + 3.1	0.001*	47.2 + 11.4	54.0 + 8.4	0.475

Data shown are for the treatment and placebo groups. Asterisks indicate significant differences between values before and after the training.

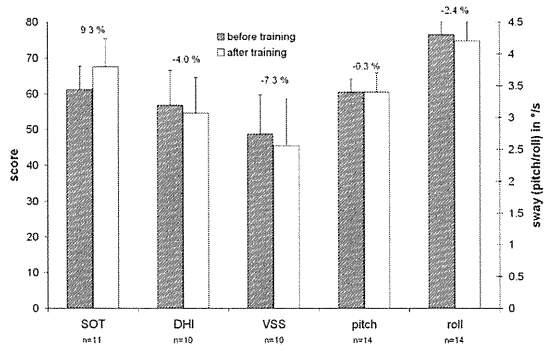

FIG. 4. Mean values (±SEM) and percentage changes of the SOT (BalanceMaster/Neurocom), the DHI, the VSS, and the body sway (pitch/roll) before and after a vibrotactile neurofeedback training in the placebo group. Numbers given below represent the number of patients included in the measurement. *Asterisks* indicate significant differences.

Effect of Training on Trunk Sway

The trunk sway in pitch direction was decreased significantly (Fig. 6) in all subgroups (SCC: power, 0.98; effect size, 0.77; O: power, 0.83; effect size, 0.59; AN: power, 0.76; effect size, 0.81; MVCS: power, 0.58; effect size, 0.63; P: power, 0.98; effect size, 1.13; PD: power, 0.98; effect size, 1.28). Figure 7 shows the mean group values of the trunk sway in roll direction before and after the training. The trunk sway in roll direction was significantly decreased after the training in all subgroups with the exception of the MVCS patients (SCC: power, 0.91; effect size, 0.61; O: power, 0.63; effect size, 0.45; AN: power, 0.81; effect size, 0.86; P: power, 0.75; effect size, 0.68; and PD: power, 0.99; effect size, 1.38).

Effect of Training on SOT Composite Score

A significant increase of the SOT composite score (Conditions 1–6) could be observed in the SCC (power, 0.95; effect size, 0.73), O (power, 0.7; effect size, 0.55), P (power, 0.84; effect size, 0.77), and PD (power, 0.84; effect size, 0.91) subgroups (Fig. 8). Patients of the AN and MVCS subgroups increased their stability on the platform not statistically significantly on average (Fig. 8).

Effect of Training on DHI Score

The DHI score, as one of the secondary end points, showed significant differences only in the SCC and PD groups (Fig. 9) with a statistical power of 0.7 (effect size, 0.55) and 0.95 (effect size, 1.15), respectively.

Only a trend for a reduced DHI score was visible for the AN, MVCS, and P group.

Effect of Training on VSS Score

The other secondary end point, the VSS scores, was significantly reduced in the SCC and O groups (Fig. 10). The statistical power was 0.94 (effect size, 0.9) for the SCC and 0.93 (effect size, 0.84) for the O group. A trend for a reduction of the mean VSS score was observed for all other investigated subgroups. Patients of the PD group were not asked to fill in the VSS questionnaire.

DISCUSSION

The present results indicate that a specific vibrotactile neurofeedback rehabilitation program, which is "tailored" to meet the needs of the individual balance deficit, can significantly improve the postural control in stance and gait situations. This could be demonstrated by the significant reduction of body sway in pitch and roll directions during everyday-life test conditions and the significant increase of stability (SOT composite score) in different sensorimotor stance conditions (force plate measurements). The performance on the SOT improved especially in the more vestibular related Tasks 5 and 6. This finding indicates the specific effect of the training on vestibular rehabilitation.

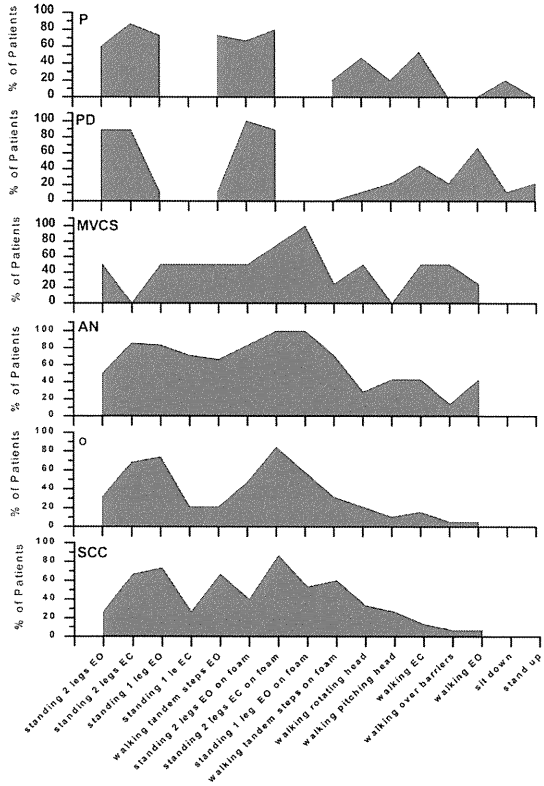

FIG. 5. Percentage of patients with a pathologic body sway during the conditions of the Standard Balance Deficit Test. Patients were analyzed within the following subgroups: P, presbyvertigo; PD, Parkinson's disease; SCC, semicircular canal paresis; O, otolith disorder; AN, removal of an acoustic neuroma; MVCS, micro(neuro) vascular compression syndrome. P and PD patients performed the geriatric Standard Balance Deficit Test where the "standing on 1 leg EC" and the "standing on 1 leg EO on foam" tasks were replaced by "sit down" and "stand up." All other subgroups performed the Standard Balance Deficit Test, which not includes the "sit down" and "stand up" tasks.

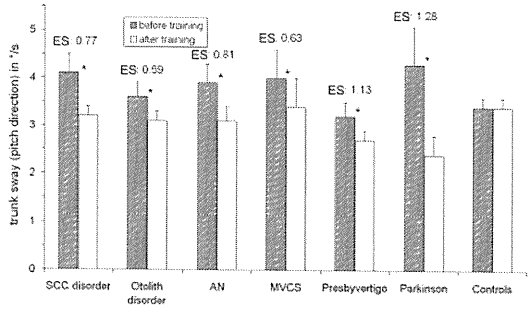

FIG. 6. Mean values (+SEM) of the body sway in pitch direction before and after a vibrotactile neurofeedback training in treatment subgroups. *Asterisks* indicate significant differences. ES indicates effect size.

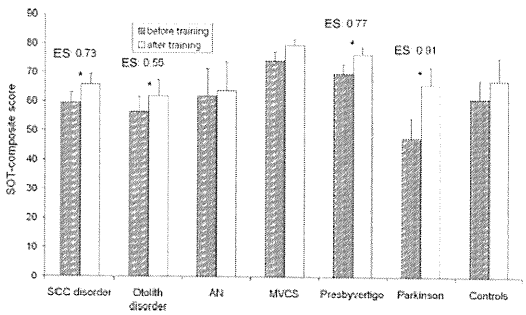

FIG. 8. Mean values (+SEM) of the SOT (BalanceMaster/ Neurocom) before and after a vibrotactile neurofeedback training in treatment subgroups. *Asterisks* indicate significant differences.

The reliability and clinical relevance of the results could be proven by a power value of approximately 1 and an effect size of more than 0.6. Moreover, the improvement was present only in patients of the feedback-training group compared with the controls. The finding that training with a sham device had no influence on body sway is in contrast to earlier studies, which investigated the effect of physical exercises in healthy subjects (19). It could be possible that the training sessions of the present study were too short to induce such learning effects by repetition. Each of the exercise was repeated only 5 times for 20 seconds in the daily sessions. This is in line with previous studies of short training sessions in everyday-life conditions, which had no significant effect on the postural stability without applying an additional feedback signal during the training (15).

The underlying neural mechanisms for the training effect might involve operant learning (20) and the multisensory convergence of enhanced processing of different sensory modalities (21). When the patients' reactions to the vibrotactile feedback signal result in a reduction of trunk sway, they have to memorize the activation template of the proprioceptive system for this situation. Without vibrotactile feedback, the activation template of the proprioceptive system has to be maintained at the same level to ensure postural control. Those neural structures encoding more than one sensory modality are best suited for spatial information processing (22). In primates, the parietal cortex seems to play a key role in this procedure (23).

However, each learning process should be followed by unlearning. The improvements induced by the vibrotactile training in the present study also were observed after a 3-months' follow-up. Although, all patients were invited to the follow-up measures, only 60% attended. One reason or implication is that 40% of the patients had no further interest in the study because his/her vestibular problems disappeared after the training. It is a very frequent effect in clinical practice. If this holds true, only patients with consisting vestibular problems were included in the follow-up measures. The effect of the training is possibly much higher than reported after 3 months.

The observed long-term effect is in line with earlier studies in chronic unilateral vestibular hypofunction or in PD where only a small number of supervised sessions were sufficiently enough to obtain a long-lasting improvement of postural stability (3,6).

The vibrotactile neurofeedback signal seems to be a very effective stimulus for vestibular rehabilitation

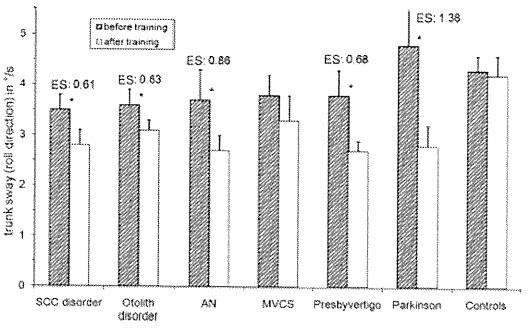

FIG. 7. Mean values (+SEM) of the body sway in roll direction before and after a vibrotactile neurofeedback training in treatment subgroups. *Asterisks* indicate significant differences.

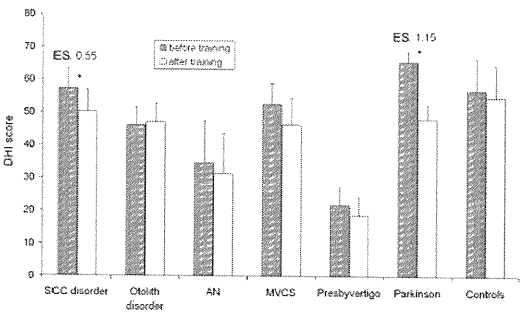

FIG. 9. Mean values (+SEM) of the DHI before and after a vibrotactile neurofeedback training in treatment subgroups. *Asterisks* indicate significant differences.

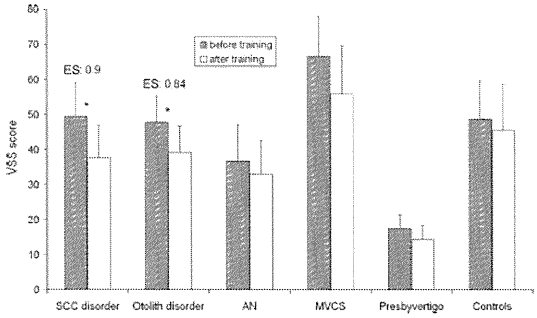

FIG. 10. Mean values (+SEM) of the VSS before and after a vibrotactile neurofeedback training in treatment subgroups. *Asterisks* indicate significant differences.

because its perception by the patients during the training is very intuitive. Furthermore, no important, other sensory input channels (e.g., auditory, visual) are impaired by the vibrotactile signal so that no sensory conflict occur, and the signal processing is not influenced by simultaneous vestibular stimulation (as known for auditory signals [24]). However, a vibration-induced illusion of movement was described in previous studies (25), but the strength and duration of vibration, which is necessary to induce such effects, cannot be provided by the vibrotactile feedback system used in the present study (Vertiguard). The vibrotactile stimulation applied with the Vertiguard was very short (approximately 1 s) and only slightly above the perception threshold. If there is nevertheless an influence of the vibration itself on some trunk muscle reflexes, these reflexes would act in the same direction as intended by the training (move to the opposite site) and would therefore support the intended application of the device.

The subjective parameters—such as DHI and VSS scores—were significantly reduced with a high statistical power and effect size in the treatment group only. The controls showed a small, but not significant, reduction of these symptom-related scores. This is somewhat surprising because the dissociation between self-perception and actual vestibular handicap was reported previously (26,27).

Treatment Subgroups

The broad distribution of training tasks within each subgroup indicates the need of an individualized training program, which is based on a standardized body sway analysis. This holds true even if some tasks were more frequent pathologic in 1 subgroup than in another subgroup. The most frequent pathologic tasks were quite similar in all subgroups. Therefore, it seems not to be possible to develop a specific training procedure for specific pathologies with this method.

The analysis of disease-related subgroups within the total treatment sample showed different training effects in some of the investigated parameters. Even if body sway during everyday life conditions could be significantly reduced in all subgroups, patients with PD or presbyvertigo showed the highest absolute reduction. The high efficacy of the neurofeedback training in these subgroups is possibly related to the fact that central compensation could occur without pathologic inputs of the peripheral vestibular organs. This hypothesis is supported by the present results of the SOT on the BalanceMaster (stance conditions). Patients with an irregular input of peripheral vestibular afferents (e.g., MVCS subgroup) showed a nonsignificant improvement. In these patients, the peripheral vestibular afferents depend largely on variable parameters such as blood pressure and pulse rate, which in turn trigger the functional status of the corresponding artery—that is, the anterior inferior cerebellar artery.

The results of the investigated subjective parameters differed between the subgroups. Only patients of the SCC group showed a significantly decreased DHI and VSS score after the training. The VSS scores, but not the DHI scores, were decreased in patients with an otolith disorder. This is in accordance with previous results of auditory neurofeedback training in those patients (15).

The highest reduction of symptom scores, combined with the largest statistical power and effect size, was observed in the PD group. However, the mean values of these patients before and after the training was the highest of all investigated subgroups. The subjective parameters (VSS/DHI) of the P group were not significantly reduced even if the objective decrease of body sway was statistically significant. On the one hand, this could rely on a correlation between the absolute changes of the scores and the low pretraining values. The overall extent of reductions in DHI scores was, for example, 11.9% for the SCC group (statistically significant) and 14.8% for the P group (not statistically significant). On the other hand, the dissociation between self-perception and postural handicap holds possibly particularly true for the elderly (26,27).

In essence, the vibrotactile neurofeedback training applied in the present study is a highly efficient method for the reduction of body sway in different balance disorders. Because the rehabilitation program is easy to perform, not exhausting and time saving, elderly patients and those with serious, long-lasting balance problems also can participate successfully.

REFERENCES

1. Curthoys IS. Vestibular compensation and substitution. *Curr Op Neurol* 2000;13:27 30.
2. Hansson EE, Mansson NO, Hakansson A. Effects of specific rehabilitation for dizziness among patients in primary health care. A randomized controlled trial. *Clin Rehab* 2004;18:558 65.
3. Rossi-Izquierdo M, Soto-Varela A, Santos-Pérez S, Sesar-Ignacio A, Labella Caballero T. Vestibular rehabilitation with computerized dynamic posturography in patients with Parkinson's disease: improving balance impairment. *Disabil Rehabil* 2009;31:1907 16.
4. Asai M, Watanabe Y, Shimizu K. Effects of vestibular rehabilitation on postural control. *Acta Otolaryngol Suppl* 1997;528:116 20.
5. Topuz O, Topuz B, Ardic FN, Sarhus M, Ogmen G, Ardic F. Efficacy of vestibular rehabilitation on chronic unilateral vestibular dysfunction. *Clin Rehab* 2004;18:76 83.

6. McGibbon CA, Wayne PM, Scarborough DM, Parker SW. Tai Chi and vestibular rehabilitation effects on gaze and whole-body stability. *J Vest Res* 2004;14:467 78.
7. Pavlou M, Lingeswaran A, Davies RA, Gresty MA, Bronstein AM. Simulator based rehabilitation in refractory dizziness. *J Neurol* 2004;251:983 95.
8. Viirre E, Sitarz R. Vestibular rehabilitation using visual displays: preliminary study. *Laryngoscope* 2002;112:500 3.
9. Danilov YP, Tyler ME, Skinner KL, Hogle RA, Bach-y-Rita P. Efficacy of electrotactile vestibular substitution in patients with peripheral and central vestibular loss. *J Vestib Res* 2007;17:119 30.
10. Barros CG, Bittar RS, Danilov Y. Effects of electrotactile vestibular substitution on rehabilitation of patients with bilateral vestibular loss. *Neurosci Lett* 2010;476:123 6.
11. Kentala E, Vivas J, Wall C 3rd. Reduction of postural sway by use of vibrotactile balance prosthesis in subjects with vestibular deficits. *Ann Otol Rhinol Laryngol* 2003;112:404 9.
12. Wall C 3rd. Application of vibrotactile feedback of body motion to improve rehabilitation in individuals with imbalance. *J Neurol Phys Ther* 2010;34:98 104.
13. Dozza M, Horak FB, Chiari L. Auditory biofeedback substitutes for loss of sensory information in maintaining stance. *Exp Brain Res* 2007;178:37 48.
14. Hegemann J, Honegger F, Kupper M, Allum JHJ. The balance control of bilateral peripheral vestibular loss subjects and its improvement with auditory prosthetic feedback. *J Vest Res* 2005;15:1 8.
15. Basta D, Singbartl F, Todt I, Clarke A, Ernst A. Vestibular rehabilitation by auditory feedback in otolith disorders. *Gait Posture* 2008;28:397 404.
16. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods* 2007;39:175 91.
17. Jacobson GP, Newman CW. The development of the dizziness handicap inventory (DHI). *Arch Otolaryngol Head Neck Surg* 1990; 116:424 7.
18. Tschan R, Wiltink J, Best C, et al. Validation of the German version of the Vertigo Symptom Scale (VSS) in patients with organic or somatoform dizziness and healthy controls. *J Neurol* 2008;255: 1168 75.
19. Brandt T, Krafczyk S, Malsbenden I. Postural imbalance with head extension: improvement by training as a model for ataxia therapy. *Ann NY Acad Sci* 1981;34:636 49.
20. Taub E, Crago JE, Burgio LD, et al. An operant approach to rehabilitation medicine: overcoming learned non-use by shaping. *J Exp Anal Behav* 1994;61:281 93.
21. Foxe JJ, Schroeder CE. The case for feedforward multisensory convergence during early cortical processing. *Neuroreport* 2005; 16:419 23.
22. Schlack A, Sterbing-D'Angelo SJ, Hartung K, Hoffmann KP, Bremmer F. Multisensory space representations in the macaque ventral intraparietal area. *J Neurosci* 2005;25:4616 25.
23. Bremmer F, Schlack A, Duhamel JR, Graf W, Fink GR. Space coding in primate posterior parietal cortex. *Neuroimage* 2001;14: 46 51.
24. Probst T, Wist ER. Impairment of auditory processing by simultaneous vestibular stimulation: psychophysical and electrophysiological data. *Behav Brain Res* 1990;41:1 9.
25. Verschueren SM, Swinnen SP, Desloovere K, Duysens J. Vibration-induced changes in EMG during human locomotion. *J Neurophysiol* 2003;89:1299 307.
26. Perez N, Martin E, Garcia-Tapia R. Dizziness: relating the severity of vertigo to the degree of handicap by measuring vestibular impairment. *Otolaryngol Head Neck Surg* 2003;128:372 81.
27. Whitney SL, Wrisley DM, Brown KE, Furman JM. Is perception of handicap related to functional performance in persons with vestibular dysfunction? *Otol Neurotol* 2004;25:139 43.

ELSEVIER

Auris Nasus Larynx 39 (2012) 208–211

AURIS NASUS LARYNX
INTERNATIONAL JOURNAL OF ORL & HNS

www.elsevier.com/locate/anl

A new device for delivering drugs into the inner ear: Otoendoscope with microcatheter

Sho Kanzaki *, Hideyuki Saito, Yasuhiro Inoue, Kaoru Ogawa

Department of Otolaryngology, Head and Neck Surgery, Keio University, School of Medicine, 35 Shinanomachi, Shinjuku, Tokyo 160-8582, Japan

Received 19 December 2010; accepted 22 April 2011
Available online 20 May 2011

Abstract

Objectives: Intratympanic injection (ITI) of drugs into the inner ear is an attractive way to deliver therapy. However, if the round window membrane (RWM) cannot be visualized, adhesions need to be removed first before ITI can be performed. We developed and tested a novel otoendoscopy device that allows visualization of the RWM for the purpose of ITI.
Methods: Our otoendoscope consists of a catheter channel for delivering drugs and a suction channel.
Results: The novel otoendoscope for inner ear drug delivery has a fine needle with catheter, which can be used to remove or perforate round window niche (RWN) mucosal adhesions. The elliptical shape of the otoendoscope effectively captures the field in the light-guided area, resulting in bright images.
Conclusions: Our otoendoscope can be used to apply drugs directly onto the surface of the RWM and to verify the correct placement of an inner ear drug delivery system, ensuring that it is safely in place.

Keywords: Inner ear; Round window membrane; Otoendoscope; Catheter; Drug delivery system

1. Introduction

The intratympanic injection (ITI) of drugs into the inner ear is a very attractive way for delivering therapy in Meniere's disease and idiopathic sensorineural hearing loss [1]. Delivering steroids by ITI is more efficient than by systemic injections. Trials have demonstrated that ITI is effective and decreases chances of side effects related to systemic steroid injections [1,2]. ITI, however, is a blind procedure. When the round window niche (RWN) is covered with fibrous or connective tissue, which occurs in about 10–30% of cases [1,3,4], it is impossible for drugs injected by ITI to reach the perilymph of the scala tympani via the round window membrane (RWM).

Therefore, if the RWM cannot be visualized, adhesions covering the RWM should be removed first through otoendoscopy before drugs are delivered [1]. Anatomic barriers to the RWM may be a significant cause of ITI failure [5]. Although drugs have been delivered successfully into the inner ear with the aid of microcatheters [6] or otoendoscopes [7] employing a working channel for drug injection, a separate instrument is needed to remove adhesions overlying the RWM. To address this issue, we developed a new otoendoscopy device that allows visualization of the RWM, removal of adhesions, and drug delivery.

2. Materials and methods

We developed an otoendoscope that consists of a fiber optic lens (0.6 mm) for viewing and two working channels (1.0 mm and 0.3 mm, respectively); a catheter channel for delivering drugs; and a suction channel for removing adhesions (Machida Corporation, Tokyo, Japan). The working length is 50 mm. The diameter of this device is

* Corresponding author. Tel.: +81 3 5363 3827; fax: +81 3 3353 1261.
E-mail address: skan@a7.keio.jp (S. Kanzaki).

0385-8146/$ – see front matter © 2011 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.anl.2011.04.006

only 2.4 mm × 1.4 mm, which is small enough for use in the inner ear and for approaching the small space around the RWN. The small diameter of such devices, however, exposes them to four potential problems—(1) low-quality images, (2) increased chance of clogging the channel with drug solution, (3) increased effort required to clean the channel, and (4) increased fragility—all of which we took into account during the development of our improved otoendoscope.

The otoendoscope system for inner ear drug delivery has the following features:

1. A 30-gauge needle attached to a catheter to remove or perforate RWN mucosal adhesions and to inject drugs (Fig. 1).
2. A catheter threaded inside the channel to deliver drug solutions so liquids never directly contact the working channel, preventing channel clogging.
3. An elliptical shape that enables our otoendoscopy device to more effectively capture the field in the light-guided area than prototype otoendoscopes, resulting in brighter and higher-quality images.

This modified otoendoscope has a similar bore as previous ones, but it is less fragile and less troublesome to use. We tested a conventional otoendoscope, a prototype otoendoscope, and the newly developed otoendoscope on cadaver temporal bones. Prior to using the drug delivery device, under otoendoscopy conventional myringotomy was performed with a small blade (2 mm) at the junction between the posteroinferior quadrants, and then the otoendoscope combined with a catheter was inserted into the inner ear.

All research was conducted with the approval of the Keio University Hospital Institutional Review Board and in accordance with the Helsinki Declaration. The novel otoendoscope inner ear drug delivery device is currently being developed for clinical use.

3. Results

We observed complete obstruction of the RWN in 2 of 5 cadaver temporal bones (Table 1). We also compared our otoendoscope with prototype (Machida Corporation, Tokyo Japan) or conventional otoendoscopes (Olympus Corporation Tokyo, Japan). After performing myringotomy, we used the three different types of otoendoscopes to view the RWM and found that our novel otoendoscope produced good-quality images of the RWM (Fig. 2A). However, because the lens contained within our otoendoscope is only 0.6 mm in diameter, image resolution was not as high-quality as that of the conventional otoendoscope we tested. Thus, the lens requires additional refinement. Although 30°-angled otoendoscopy is typically used to view the RWN, straight (0°) otoendoscopy

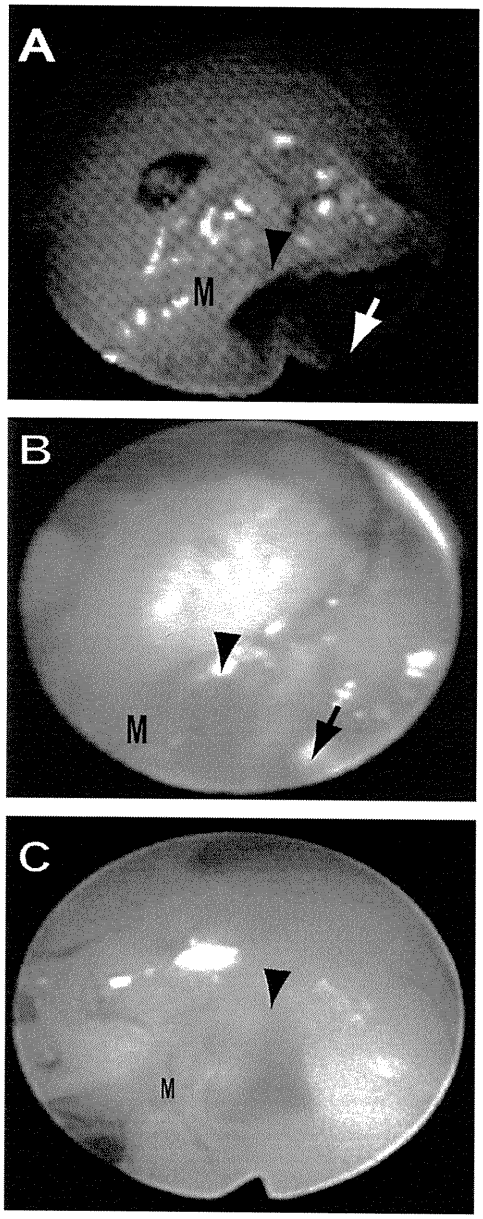

Fig. 1. Novel otoendoscope developed in our clinic. (A) Frontal view of the otoendoscope showing the lens (L) and two channels (W, working channel; *, suction channel). (B) Side view of the otoendoscope with catheter and needle. Scale bar: 5 cm. (C) High magnification view of the tip of the otoendoscope (E) showing the catheter (Ca) and needle (N). A catheter for angiography is also available for this scope. For inner ear procedures, a 30-gauge needle (*) is inserted into the tip of the catheter.

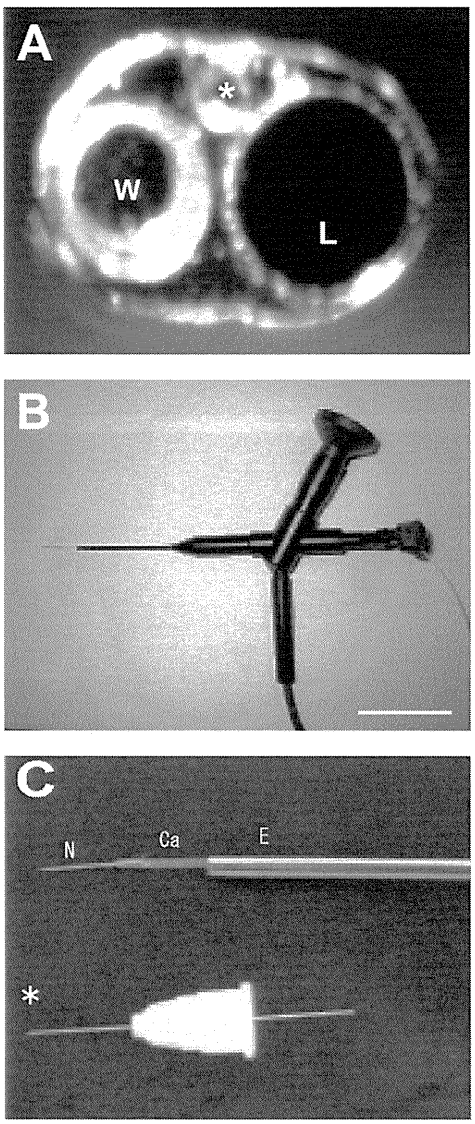

Fig. 2. Round window membrane (RWM indicated by "M" and arrowheads) images as visualized through different otoendoscopes. RWM images captured with the novel otoendoscope (A), a prototype otoendoscope (B), and a 30-angled (1.9 mm; Olympus) conventional otoendoscope (C). The image shown in panel C was especially of high quality. (A and B) Using a needle, we opened up the connective tissue overlying the RWN and injected a solution onto the RWM (M). The needles are indicated by arrows.

can also capture images of the RWM (Fig. 2). Because 0°-angled otoendoscopes are easier to handle, it may be easier to view RWM images through 0°-angled otoendoscopy than through 30°-angled otoendoscopy.

Table 1
RW obstruction of cadaver.

Case (age, sex)	Cadaver condition	RW obstruction
Unknown, F	Fixed	+
Unknown, F	Fixed	–
90 y/o, F	Unfixed	+
94 y/o, F	Unfixed	+/–
92 y/o, F	Unfixed	–

RWM obstruction +: present, +/–: partial present, –: not present.

Table 2
Comparison of different otoendoscopes.

	Results of comparison
Observation of RWM	C > N = P
Treatment of adhesions	N = C > P
Otoendoscope diameter (mm)	N(1.5) > C(1.9) > P(2.4)

C, conventional otoendoscope; N, novel otoendoscope with catheter; P, prototype otoendoscope with catheter.

4. Discussion

Our otoendoscope represents a new concept in treating and diagnosing inner ear-associated hearing loss. If ITI is unsuccessful, the RWM should be examined. This can be carried out conveniently with our otoendoscope. Additionally, our otoendoscope can be used also for diagnosing perilymphatic fistulas and for providing related therapy.

We compared the advantages and disadvantages of the novel otoendoscope, a prototype otoendoscope, and a conventional otoendoscope (Table 2). Although our otoendoscope is smaller than other types of otoendoscopes, it still captures an adequate image of the RWN. Moreover, our otoendoscope combined with a catheter can be used to evaluate the RWN before a local drug delivery system is put into place; to apply drugs directly onto the surface of the RWM; and to verify the correct placement of an inner ear drug delivery system, ensuring that it is safely in place.

Acknowledgements

We thank Mr. Ishikawa and his colleagues at Machida Corporation for helping develop the otoendoscope. This work was supported by grants from the Ministry of Health, Labor, and Welfare in Japan (H16-008 K.O. and S.K.), and Ministry of culture, sports, science and technology in Japan (20390444 K.O., R.T. and S.K.).

References

[1] Silverstein H, Choo D, Rosenberg SI, Kuhn J, Seidman M, Stein I, et al. Intratympanic steroid treatment of inner ear disease and tinnitus (preliminary report). Ear Nose Throat J 1996;75:468–71.