厚生労働科学研究研究費補助金

長寿科学総合研究事業

脳内移行性アンジオテンシン変換酵素（ＡＣＥ）阻害剤投与によるアルツハイマー病の新規治療法の確立に関する研究

平成 17 年度～平成 18 年度　総合研究報告書

主任研究者　大類　孝

平成 19(2007)年 3 月

目　　次

Ⅰ．総合研究報告

脳内移行性アンジオテンシン変換酵素（ACE）阻害剤投与による
アルツハイマー病の新規治療法の確立に関する研究

大類　　孝 ---------- 1

Ⅱ．研究成果の刊行に関する一覧表 ---------- 5

Ⅲ．研究成果の刊行物・別刷 ---------- 7

厚生労働科学研究費補助金（長寿科学研究事業）

総合研究報告書

脳内移行性アンジオテンシン変換酵素（ＡＣＥ）阻害剤投与による アルツハイマー病の新規治療法の確立

主任研究者　大類　孝　東北大学病院　老年科助教授

研究要旨：高齢化がますます加速するわが国において、認知症疾患の中でアルツハイマー病（AD）の増加は顕著で、その克服は最重要課題である。本研究で私は、高血圧を合併したAD患者230名（男性49名、平均年齢76歳）を、無作為に脳移行性アンジオテンシン変換酵素（ACE）阻害剤（ペリンドプリル）投与群（n=75、男性17名、平均年齢76歳）、脳非移行性ＡＣＥ阻害剤（エナラプリル）投与群（n=64、男性13名、平均年齢77歳）およびカルシウム拮抗剤（ニフェジピン）投与群（n=91、男性19名、平均年齢76歳）の3群に分け、1年間にわたって認知機能（Mini Mental State Examination＝MMSE）を追跡調査した。その結果、1年間のMMSEスコアの平均変化率は、ペリンドプリル群：-0.9±0.2、エナラプリル群：-4.8±0.9、ニフェジピン群：-5.2±1.2と、ペリンドプリル群では、その他の降圧剤に比してAD患者の認知機能の低下を有意に抑制する事が明らかにされた（$p<0.01$）。また、各群間の血圧値に有意差を認めなかった事から、その効果は降圧作用以外の機序でもたらされるものと考えられた。以上の結果から、脳移行性ACE阻害剤投与は、高血圧合併AD患者の新しい予防法の一つになる可能性が示唆された。

漢方薬の加味温胆湯は、アセチルコリン合成酵素の産生を増加させADにおける認知機能を改善することが確認されている。そこで今回私は、代表的なコリンエステラーゼ阻害剤である塩酸ドネペジルと加味温胆湯との併用効果について、ランダム化比較研究で検討した。臨床的に診断基準を充たす38名のAD患者を無作為に2群に分け、一方にドネペジル単独治療を、もう一方にはドネペジルと加味温胆湯の併用治療を各々12週間行った。その結果、12週間の治療の前後で、MMSE、ADAS-cogともに併用治療群で有意な改善を示し、また局所脳血流評価でも併用治療群のみ前頭葉で有意な上昇を示していた。結果として、加味温胆湯には塩酸ドネペジルに対する相補的効果があるものと考えられた。統合医療は認知症の治療に有益であることが示唆された。

分担研究者:岩崎　鋼　東北大学　先進漢方治療医学講座助教授

A. 研究目的

（１）わが国の超高齢化社会において、介護を必要とする痴呆性高齢者の絶対数は年々増加しており、厚労省によれば2,015年にはその総数は250万人に達すると予想されている。それら痴呆性疾患の中でアルツハイマー病（Alzheimer’s disease:AD）は６割以上を占め、その増加は顕著であリADの克服は最重要課題である。これまで、ADの治療法として主としてコリンエステラーゼ阻害剤が用いられてきたが、その長期効果には限界があると報告された。最近の諸外国の研究によると、ADの患者では脳内のアンジオテンシン変換酵素（ACE）の活性が亢進しており、結果として過剰産生されるアンジオテンシンIIが、脳神経細胞からのアセチルコリンの遊離を抑制し、その結果、認知機能の低下が生じると報告された。私は本研究で、わが国で使用されている降圧剤の中で、脳内移行性が確認されているACE阻害剤（ペリンドプリル）の投与が、AD患者において脳内のACE活性を抑制することにより病勢の進行を抑える事を明らかにし、ADの新たな治療法を確立する事を目的にする。

（２）アルツハイマー病（AD）の治療法はcholinesterase阻害剤の登場以来、大きな進展を見せていない。単一のcholinesterase阻害剤(CE-I)の効果には限界があるため、経過的な方策として、種々の薬物の併用療法が試みられている。一方、CE-Iは脳に於けるアセチルコリン合成酵素（choline acetyltransferase）活性を抑制する可能性も指摘されており、この酵素の活性を高める薬剤との併用療法はCE-Iにとって望ましい治療法となりうる。漢方方剤の加味温胆湯（かみうんたんとう）は、アセチルコリン合成酵素の産生を増加させADにおける認知機能を改善することが既に報告されている。そこで今回私共は、代表的なCE-Iである塩酸ドネペジルと加味温胆湯との併用効果について、観察者を盲検化したランダム化比較研究で検討した。

B. 研究方法

（１）東北大学病院およびその関連病院の高血圧を合併したAD患者230名（男性49名、平均年齢76歳）を、無作為に脳移行性アンジオテンシン変換酵素（ACE）阻害剤（ペリンドプリル）投与群（n=75、男性17名、平均年齢76歳）、脳非移行性ACE阻害剤（エナラプリル）投与群（n=64、男性13名、平均年齢77歳）およびカルシウム拮抗剤（ニフェジピン）投与群（n=91、男性19名、平均年齢76歳）の3群に分け、1年間にわたって認知機能（Mini Mental State Examination＝MMSE）を追跡調査した。そして、得られた結果を統計学的に解析し、脳移行性ACE阻害剤が他の降圧剤と比較して、高血圧合併AD患者の認知機能の低下を抑制するか否かについて検討した。

（２）臨床的に診断基準を充たす38名のAD患者をランダムに２群に分け、一方にドネペジ

ル単独治療(n=20, 年齢 74.6 ± 3.9 歳, 男:女=4:16)を、もう一方にはドネペジルと加味温胆湯併用治療(n=18, 年齢 73.7 ± 5.6 歳, 男:女=4:14)を各々12 週間行った。各群で、盲験化された観察者が治療前後の認知機能を Mini Mental State Examination (MMSE)、及び Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog)で評価し、また脳血流を ^{123}I-IMP-ARG single photon emission computed tomography (^{123}I-IMP-SPECT, Wellcome Department of Imaging Neuroscience, London, UK)で観察した。加味温胆湯を構成する１３種の生薬；半夏 5.0;茯苓 4.0;竹茹・陳皮・酸棗仁各 3.0;甘草・大棗・枳実・遠志・玄参・人参・地黄各 2.0;乾生姜 1.0 は（株）ツムラから提供を受けた。これらは日本国内で医薬品として承認を受けたものであり、厚生労働省の定めた GMP (Good Manufacturing Practice) 基準を満たしている。経過観察は "last observation carried forward" 法によって行い、MMSE、ADAS-cog は繰り返しのある t 検定と repeated measure ANOVA によって評価した。

（倫理面での配慮）研究においては、プライバシーの保護などの倫理面での配慮を行った。

C. 研究結果

（１）１年間の MMSE スコアの平均変化率は、ペリンドプリル群：-0.9±0.2、エナラプリル群：-4.8±0.9、ニフェジピン群：-5.2±1.2 と、ペリンドプリル群では、その他の降圧剤に比してＡＤ患者の認知機能の低下を有意に抑制する事が明らかにされた（$p<0.01$）。また、各群間の血圧値に有意差を認めなかった。

（２）ドネペジル単独群および漢方薬併用群の両群間の初期値について、年齢、性別、認知症重症度、無症候性脳梗塞合併頻度、深部白質病変グレード、脳室周囲病変に有意差を認めなかった。12 週間の治療の前後で、MMSE(前値 18.9 ± 4.9 、後値 21.6 ± 4.2, $P=.001$; -4.17 < 95% C.I < -1.28), ADAS-cog(21.0 ± 7.6 から 16.8 ± 7.1, $P<.0001$; 2.54 < 95% C.I < 5.80)ともに併用治療群のみで有意な改善を示し、また局所脳血流評価でも併用治療群のみ前頭葉で有意な上昇を示していた(P <.05 corrected: BA 9;(x, y ,z)=(8, 50, 24) Z=5.19; BA 8;(x, y ,z)=(26, 28, 46) Z=5.04; BA 9;(x, y ,z)=(8, 54, 36) Z=4.99; k_E=6029)。一方塩酸ドネペジル単独群ではいずれの値についても有意な変化は認めなかった。また、加味温胆湯・ドネペジル併用群では特に副作用は認めなかった。一方ドネペジル単独群においては下痢によって内服中断を余儀なくされたケースがみられた。

D. 考察

（１）これまで、AD の治療法として主としてコリンエステラーゼ阻害剤が用いられてきたが、その長期効果には限界があると報告され (Courtney et al. Lancet 2004)、新しい治療法の開発が期待されている。これまで、私共の研究によって、大脳の主要な働きの１つである

認知機能に、脳内のレニン一アンジオテンシン系が関与する事が明らかにされている（Ohrui et al. J Am Geriatr Soc 2004, Ohrui et al. Neurology 2004）。また、諸外国の研究によると、AD の患者では脳内のアンジオテンシン変換酵素（ACE）の活性が亢進しており、結果として過剰産生されるアンジオテンシン II が、脳神経細胞からのアセチルコリンの遊離を抑制し、その結果、認知機能が低下すると報告された（Savaskan et al. Neurobiol Aging 2001）。私は本研究で、わが国で使用されている降圧剤の中で、脳内移行性が確認されている ACE 阻害剤の投与が、AD 患者において脳内の ACE 活性を抑制することにより病勢の進行を抑える事を明らかにした。このような視点での AD の治療法は、これまで全く提唱されておらず、世界的にみて極めて独創的かつ画期的な方法と考えられる。

（２）塩酸ドネペジルと漢方薬の併用効果について観察者を盲検化したランダム化比較試験で検討した。今回の観察症例の内、ドネペジル単独群の 33%、併用群の 44%が無症候性脳梗塞を合併していた。従って本研究は厳密に言えば脳血管障害を合併するアルツハイマー病患者に於ける漢方薬と塩酸ドネペジルの併用効果を検討したものといえる。但しこれらの数値はアルツハイマー病の平均的な脳血管障害合併率 30.2％(Heyman et al.)に近いものである。

E. 結論

（１）脳内移行性 ACE 阻害剤は、その他の降圧剤に比して、AD 患者の認知機能の低下を有意に抑制する事およびその効果は降圧作用以外の機序でもたらされる事が明らかにされた。

（２）加味温胆湯には塩酸ドネペジルに対する相補的効果があるものと推察する。統合医療は認知症の治療に有益であることが示唆された。

F. 研究発表

１．論文発表

１）He M, Ohrui T, Maruyama M, Tomita N, Higuchi M, Nakayama K, Furukawa K, Arai H. ACE activity in CSF of patients with mild cognitive impairment and Alzheimer's disease. **Neurology** 67:1309-1310, 2006.

２）大類　孝.　ACE阻害薬は認知能力を保持する. **呼と循**54:369-374, 2006.

３）Maruyama M, Tomita N, Iwasaki K, Ootsuki M, Matsui T, Nemoto M, Okamura N, Higuchi M, Tsutsui M, Suzuki T, Seki T, Kaneta T, Furukawa K, Arai H. Benefits of combining donepezil plus traditional Japanese herbal medicine on cognition and brain perfusion in Alzheimer's disease: A 12-week observer-blind, donepezil monotherapy-controlled trial. **J Am Geriatr Soc.** 54: 869-71, 2006.

G. 知的財産権の出願

特になし。

別紙４

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Maruyama M, Ishizawa K, Tomita N, et al.	Lithium therapy and cerebrospinal fluid biomarker levels in Alzheimer's disease.	***Geriatr Gerontol Internat.***	*5*	*298-300*	*2005*
Ohrui T, Tanaka K, Chiba K, et al.	Cognitive decline in patients with long-term domiciliary oxygen therapy.	***Tohoku J Exp Med***	*206*	*347-352*	*2005*
Ueda H, Yamada T, Ohrui T, et al.	Correction of maxillary occlusal plane relieves persistent headache and shoulder stiffness.	***Tohoku J Exp Med***	*205*	*319-325*	*2005*
Ohrui T, He M, Tomita N, et al.	Homicides of disabled older persons by their caregivers in Japan.	***J Am Geriatr Soc***	*53*	*553-554*	*2005*
Yamada M, Ohrui T, Asada M, et al.	Acarbose attenuates hypoglycemia from dumping syndrome in an elderly man with gastrectomy.	***J Am Geriatr Soc***	*53*	*358-359*	*2005*
He M, Ohrui T, Maruyama M, et al.	ACE activity in CSF of patients with mild cognitive impairment and Alzheimer's disease.	***Neurology***	*67*	*1309-1310*	*2006*

Geriatr Gerontol Int 2005; 5: 298–300

Lithium therapy and cerebrospinal fluid biomarker levels in Alzheimer's disease

Masahiro Maruyama,[1] Kota Ishizawa,[1] Naoki Tomita,[1] Miyako Nemoto,[1] Hiroyasu Yasuda,[1] Satoru Ebihara,[1] Takashi Ohrui,[1] Takashi Seki,[2] Koh Iwasaki,[2] Nobuyuki Okamura,[3] Makoto Higuchi,[4] Hiroshi Yoshida,[5] Yukitsuka Kudo,[6] Hiroyuki Arai[2] and Hidetada Sasaki[1]

Departments of [1]Geriatric and Respiratory Medicine, [3]Pharmacology, and [6]Biomedical Engineering Research Organization, Tohoku University Graduate School of Medicine, and [2]Department of Geriatric and Complementary Medicine, Center for Asian Traditional Medicine Research, Sendai, [4]Laboratory for Proteolytic Neuroscience, RIKEN Brain Science Institute, Wako-shi, Saitama and [5]Research and Development Laboratory, Nipro Corporation, Shiga, Japan

Recent studies suggest that lithium may retard pathological deterioration by inhibiting aberrant phosphorylation of tau in Alzheimer's disease (AD). Here, we describe three cases of AD who were treated with lithium for agitation. However, there was no obvious improvement either in global cognition, agitation or cerebrospinal fluid markers that were thought to reflect Alzheimer's pathology. Increased dosages of lithium were not tolerated by the patients because of adverse effects. It is likely that AD patients do not benefit from lithium therapy as an alternative choice of treatment.

Keywords: Alzheimer's disease, beta amyloid 1-42, tau.

Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder with a pathological presentation of both senile plaques and neurofibrillary tangles.[1] It is well known that senile plaques are deposits of beta amyloid proteins and neurofibrillary tangles consisting of hyperphosphorylated tau proteins.[2,3] Recent evidence that lithium degrades beta amyloid 1–42 ($A\beta_{1-42}$) proteins and inhibits hyperphosphorylation of tau via inhibition of glycogen synthase kinase-3α (GSK-3α) and GSK-3β activity *in vitro* suggests that lithium might reduce the rate of plaque and tangle formation in AD.[4–6] Cerebrospinal fluid levels of $A\beta_{1-42}$ (CSF-$A\beta_{1-42}$) decrease as AD progresses.[7] Also, total (CSF/total-tau) and phosphorylated at threonine 181 (CSF/p_{181}-tau) tau protein, which may reflect the rate of neuron loss, are elevated even in the earliest stages of AD.[8] Moreover, CSF-$A\beta_{1-42}$ concentration is negatively correlated with plaque levels.[9] A clinical case report suggests that lithium may be effective in treating agitation or aggressive behavior associated with dementia.[10] Here, we examined cognitive status and a variety of CSF markers (CSF-$A\beta_{1-42}$, total and p_{181}-tau) before and after treatment with lithium in three AD patients with agitation.

Accepted for publication 18 May 2005.

Correspondence: Dr Masahiro Maruyama, Department of Geriatric Medicine, Tohoku University Graduate School of Medicine, Sendai 980-8574, Japan. Email: mmaru@geriat.med.tohoku.ac.jp

Case report

Three women, all of whom were home-makers, (cases 1, 2 and 3 were aged 78, 64 and 72 years, respectively) were referred to our outpatient clinic with approximately a 2-year history of disturbed memory function. They had no paralysis, Parkinsonism or visual hallucinations, and met the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria of AD.[11] Furthermore, they showed manifestations of agitation.

Oral administration of Donepezil chloride 5 mg/day was begun and continued for 3 months. As the agitated state persisted, lithium 400 mg/day was given orally for

an additional three months. Before and after lithium treatment, CSF was taken by lumbar puncture following informed consent from both patients and family members, and biomarkers for AD were evaluated according to the previous methods.[7,8,12] The Mini-Mental State Examination (MMSE) score was 14 in case 1, 17 in case 2 and 21 in case 3 at the start of lithium therapy. After lithium treatment, cognition levels in MMSE decreased to 11 in case 1, to 13 in case 2 and did not change in case 3. Before and after lithium treatment, respectively, CSF/total-tau was 642.4 and 642.0 pg/mL, CSF/p_{181}-tau was 66 and 70 pmol/L, and CSF-$A\beta_{1-42}$ was 331 and 359 pg/mL in case 1, CSF/total-tau was 382.3 and 484 pg/mL, CSF/p_{181}-tau was 56 and 63 pmol/L, CSF-$A\beta_{1-42}$ was 398 and 296 pg/mL in case 2 and CSF/total-tau was 987 and 1065 pg/mL, CSF/p_{181}-tau was 118 and 114 pmol/L, CSF-$A\beta_{1-42}$ was 373 and 385 pg/mL in case 3 (see Fig. 1). Final serum concentration of lithium at a dosage of 400 mg/day treatment was 0.58 mmol/L in case 1, 0.28 mmol/L in case 2 and 0.32 mmol/L in case 3 (normal range: 0.6–1.2 mmol/L). After three months of lithium at 400 mg/day in case 2, lithium was discontinued because cognition became extremely poor. In the other two patients, the dosage was increased to 600 mg/day after 3 months of treatment at 400 mg/day, but the medication was stopped because of loss of appetite.

Discussion

The sample size in this study was too small to perform statistical comparisons. However, we found that 3 months of lithium treatment resulted in no obvious improvement either in global cognition, agitation or any of the CSF markers. In cases 1 and 3, changes in all of the CSF markers were within a 10% range. In case 2, CSF/total and p_{181}-tau increased 27% and 13%, respectively, and $A\beta_{1-42}$ decreased 26%, contrary to our expectation.

Lithium is known to be effective not only in bipolar affective disorders but also in agitation or aggressive behavior associated with dementia,[10] but adverse effects including nausea, tremors and renal dysfunction have been well documented.

Deposition of β amyloid and neurofibrillary degradation are two hallmark brain lesions of AD. Aβ synthesized from amyloid precursor protein (APP) is known to be regulated not only by β/γ secretase but also by GSK-3α, and tau phosphorylation is known to be regulated by GSK-3β. In AD, it is supposed that Aβ accumulation and abnormal tau phosphorylation lead to a massive neuron loss, which may give rise to increased total and phosphorylated tau levels in CSF.[13,14] Iqbal *et al.* postulated that efficacy would be reflected by CSF levels of total and phosphorylated tau protein if the regulator of the phosphorylation of tau affected the AD brain.[15] Phiel *et al.* reported that lithium inhibited GSK-3α activity, which potentiated the production of Aβ, and consequently reduced the production of Aβ not the processing of APP.[4] Klein *et al.* reported that GSK-3β activity (not measured in this study) was inhibited by 2 mmol/L of lithium *in vitro*.[5] We expected that the levels of CSF markers that were thought to reflect molecular pathological changes would change if GSK-3α/β were regulated by therapeutic concentration of lithium.

In light of these results, we decided to use lithium, which was well expected not only to stabilize mood but also to improve the mechanistic molecular pathology of AD patients. To prevent the adverse effects of lithium, we initially started treatment with low doses. However, initial treatment with lithium failed to improve agitation/cognition and did not appreciably change CSF markers. It is likely that the lower concentrations of lithium used in this study may not be sufficient to regulate phosphorylation of tau.

In summary, improvement in agitation/cognition and CSF markers with therapeutic doses of lithium were limited. These observations indicate that we must await the development of a new class of safer and more selective GSK-3 inhibitors.

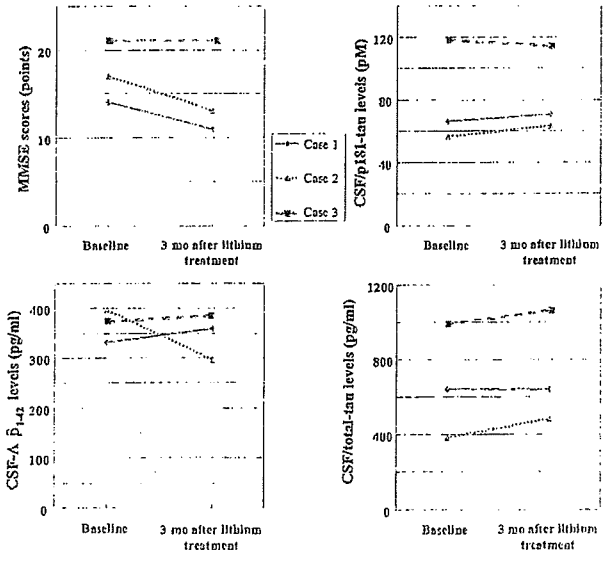

Figure 1 Mini-Mental State Examination (MMSE) scores and total tau, p181-tau and $A\beta_{1-42}$ levels in cerebrospinal fluid before and after 3 months of lithium treatment.

References

1 Alzheimer A. Über eine eigenartige Erkränkung der Hirnrinde. *Allgemeine Zeitschrife Psychiatrie* 1907; 64: 146–148.
2 Selkoe DJ. The molecular pathology of Alzheimer's disease. *Neuron* 1991; 6: 487–498.
3 Grundke-Iqbal I, Iqbal K, Tung YC, Quinlan M, Wisniewski HM, Binder LI. Abnormal phosphorylation of the microtubule-associated protein tau (tau) in Alzheimer

cytoskeletal pathology. *Proc Natl Acad Sci U S A* 1986; 83: 4913–4917.
4 Phiel CJ, Wilson CA, Lee VM, Klein PS. GSK-3alpha regulates production of Alzheimer's disease amyloid-beta peptides. *Nature* 2003; 423: 435–439.
5 Klein PS, Melton DA. A molecular mechanism for the effect of lithium on development. *Proc Natl Acad Sci U S A* 1996; 93: 8455–8459.
6 Takahashi M, Yasutake K, Tomizawa K. Lithium inhibits neurite growth and tau protein kinase I/glycogen synthase kinase-3beta-dependent phosphorylation of juvenile tau in cultured hippocampal neurons. *J Neurochem* 1999; 73: 2073–2083.
7 Maruyama M, Arai H, Sugita M *et al.* Cerebrospinal fluid amyloid beta (1–42) levels in the mild cognitive impairment stage of Alzheimer's disease. *Exp Neurol* 2001; 172: 433–436.
8 Schonknecht P, Pantel J, Hunt A *et al.* Levels of total tau and tau protein phosphorylated at threonine 181 in patients with incipient and manifest Alzheimer's disease. *Neurosci Lett* 2003; 339: 172–174.
9 Strozyk D, Blennow K, White LR, Launer LJ. CSF Abeta 42 levels correlate with amyloid-neuropathology in a population-based autopsy study. *Neurology* 2003; 60: 652–656.
10 Havens WW, Cole J. Successful treatment of dementia with lithium. *J Clin Psychopharmacol* 1982; 2: 71–72.
11 McKhaan G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under auspices of the Department of Health and Human Services Task Force on Alzheimer's disease. *Neurology* 1984; 34: 939–934, 944.
12 Arai H, Terajima M, Miura M *et al.* Tau in cerebrospinal fluid: a potential diagnostic marker in Alzheimer's disease. *Ann Neurol* 1995; 38: 649–652.
13 Vandermeeren M, Mercken M, Vanmechelen E *et al.* Detection of tau proteins in normal and Alzheimer's disease cerebrospinal fluid with a sensitive sandwich enzyme-linked immunosorbent assay. *J Neurochem* 1993; 61: 1828–1834.
14 Vanmechelen E, Vanderstichele H, Davidsson P *et al.* Quantification of tau phosphorylated at threonine 181 in human cerebrospinal fluid: a sandwich ELISA with a synthetic phosphopeptide for standardization. *Neurosci Lett* 2000; 285: 49–52.
15 Iqbal K, Grundke-Iqbal I. Inhibition of neurofibrillary degeneration: a promising approach to Alzheimer's disease and other tauopathies. *Curr Drug Targets* 2004; 5: 495–502.

Tohoku J. Exp. Med., 2005, **206**, 347-352

Cognitive Decline in Patients with Long-Term Domiciliary Oxygen Therapy

TAKASHI OHRUI,* KAZUNORI TANAKA,[3*] KAZUE CHIBA,[3] TOSHIFUMI MATSUI, SATORU EBIHARA, MEI HE, ICHIRO TSUJI,[1] HIROYUKI ARAI[2] and HIDETADA SASAKI

Department of Geriatric and Respiratory Medicine, [1]Division of Epidemiology, Department of Public Health, [2]Department of Geriatric and Complementary Medicine, Tohoku University Graduate School of Medicine, Sendai, and [3]Teijin Home Healthcare East Japan Limited, Saitama, Japan

OHRUI, T., TANAKA, K., CHIBA, K., MATSUI, T., EBIHARA, S., HE, M., TSUJI, I., ARAI, H. and SASAKI, H. *Cognitive Decline in Patients with Long-Term Domiciliary Oxygen Therapy.* Tohoku J. Exp. Med., 2005, **206** (4), 347-352 —— Cognitive and psycho-physiological condition in patients with long-term domiciliary oxygen therapy (DOT) remains uncertain. A cross sectional analysis was performed to investigate the age-related changes in cognitive and psycho-physiologic functions in patients with chronic respiratory failure receiving long-term DOT. Two expert practitioners visited the patient's home and examined them for analysis of cognitive function, emotional status, physical activity and degree of dyspneic sensation. One hundred and thirty-five patients completed the study. Control data from a cohort of 718 community dwellers were also included in this study. Male patients had significantly higher rates of chronic obstructive pulmonary disease (71% vs 47%, p = 0.001), lower values of forced expiratory volume in one second (FEV1.0) % (49.7 ± 10.3 [standard deviation, S.D.] vs 66.0 ± 7.5% predicted, p = 0.002) and higher Borg score, an indicator of dyspneic sensation, during daily exercise (3.2 ± 0.8 [S.D.] vs 1.4 ± 0.6, p = 0.01) compared with female patients. Linear regression analysis based on mean Mini-Mental State Examination scores, an indicator of cognitive function, showed that age-related cognitive decline was more pronounced in female patients than in female controls (–0.524/year, R^2 = 0.426 vs –0.120/year, R^2 = 0.027, $p < 0.0001$), while there was no significant difference between male patients and male controls (–0.156/year, R^2 = 0.054, vs –0.077/year, R^2 = 0.016, p = 0.231). These results demonstrate that age-related cognitive decline is more exaggerated in female patients receiving long-term DOT which should be taken into consideration in caring for patients with chronic respiratory failure. ——— chronic respiratory failure; domiciliary oxygen therapy; long-term survivor; cognitive function; Borg scale

Received October 1, 2004; revision accepted for publication May 31, 2005.

*The first two authors contributed equally to this work.

Correspondence: Takashi Ohrui, M.D., Department of Geriatric and Respiratory Medicine, Tohoku University Graduate School of Medicine, 1-1 Seiryomachi, Aoba-ku, Sendai 980-8574, Japan.
e-mail: ohrui@geriat.med.tohoku.ac.jp

Previous studies have reported that patients with chronic respiratory failure frequently suffer from neuropsychologic deficit and experience a disturbed mood, personality and life quality (Grant et al. 1982; Heaton et al. 1983; Incalzi et al. 1993). In a study assessing the neuropsychologic profile of patients with chronic obstructive pulmonary disease (COPD), diffuse mental deterioration characterized the study population with particular impairment of higher cognitive functions, and this was thought to be due to accelerated aging of the brain (Grant et al. 1982). To date, although long-term domiciliary oxygen therapy (DOT) has been proved to prolong survival of patients with chronic respiratory failure (The Medical Research Council Working Party 1981), its impact on cognitive function in long-term survivors remains uncertain.

In the present study, we, therefore, examined the cognitive and psycho- physiologic functions in patients receiving long-term DOT and compared them with those in age-matched community dwellers. We focused especially on the issue of the sex-related difference in cognitive function in patients with long-term DOT, because it remains unclear whether there is a gender difference in age-related cognitive decline in these subjects (Heaton et al. 1983; Scherr et al. 1988; Incalzi et al. 1993; Mortensen and Hogh 2001). We also aimed to identify possible contributing factors for the alteration in cognitive function in patients with long-term DOT.

Patients and Methods

A total of 264 patients with COPD, sequelae of tuberculosis or chronic interstitial pneumonia, who were ex-smokers and had been followed as outpatients in the Pneumology Department for 9 to 16 years, were recruited from 34 medical institutions in Sendai, Japan. They were receiving continuous oxygen therapy (24 h/day) at home via nasal prongs sufficient to maintain a PaO_2 between 60 and 80 mmHg from the start of oxyhemoglobin desaturation. One hundred and sixty- seven of the 264 patients agreed to participate in this study in the period from March 2001 to July 2002.

Two expert nurses unaware of the findings at clinical examination visited the patient's home and examined them for analysis of cognitive function, emotional status, degree of dyspneic sensation and physical activity, by Mini-Mental State Examination (MMSE) score (Folstein et al. 1975), geriatric depression scale (GDS) (Sheikh and Yesavage 2000), Borg scale (Borg 1982) and functional/performance status (Katz index) (Katz et al. 1970), respectively. Cognitive impairment was present if total MMSE score was 23 or below. At the time of the study, patients were receiving a regular dose of oxygen. Patients were excluded from this study if they used sedative drugs or they had cardio- and cerebro-vascular diseases, major psychiatric disorders, and acute infectious diseases.

Control data from a cohort of community dwellers were also included in this study. These data were obtained from the Tsurugaya Aging Study comprised of several studies of the biomedical and psychological determinants of cognitive ageing conducted in July 2002 in Sendai, Japan. The control group included 718 subjects (male 301) of comparable age, sex, duration of education and socio- economic status to patients receiving long-term DOT. This study was approved by the Tohoku University Ethical Committee and informed consent was obtained from each subject.

Student's *t*-test or chi-square test for independent samples was performed to determine whether clinical variables and cognitive and psycho-physiological functions of patients with long-term DOT differed from those of control subjects and whether there was a gender difference among these parameters. Linear regression analysis was used to evaluate the relation between age and cognitive function in male and female patients with long-term DOT vs control subjects. The strength of the relations was quantified by partial correlation coefficients. SPSS version 10.0 (SPSS, Chicago, IL, USA) statistical packages were used. A p value of < 0.05 was regarded as significant.

Results

Of the 167 participating patients, 8 subjects refused to complete all subsets of examinations because of fatigue, 10 subjects were admitted to other hospitals and 14 died during the study period. Finally, 135 subjects (male 101) completed the study. Clinical characteristics of control subjects and patients with long-term DOT are described in Table 1. The mean duration of DOT was 4.2 yr (4.3 yr and 3.6 yr for male and female

patients, respectively) and the mean oxygen flow was 1.2 l/min (1.1 l/min and 1.4 l/min for male and female patients, respectively). There were no significant differences between male and female patients among these values. However, male patients had a significantly higher rate of COPD (71% vs 47%, $p = 0.001$) and lower values of forced expiratory volume in one second (FEV_1) (49.7 ± 10.3 [standard deviation, S.D.] vs 66.0 ± 7.5% predicted, $p = 0.002$) compared with female patients (Table 1).

The proportion of patients with cognitive impairment (MMSE, lower than 23 points) was significantly higher in female patients than in male patients with long-term DOT (14[41%] vs 15[15%], respectively; $p = 0.01$, after correction for differences in age, education, and disease duration). In contrast, there were no significant differences between male and female controls in these data (Table 2). The relation between MMSE score and age is illustrated in Fig. 1. There were significant negative correlations between MMSE

TABLE 1. *Clinical characteristics*

Variable	Controls		Patients		*p* value*
	Male ($n = 301$)	Female ($n = 417$)	Male ($n = 101$)	Female ($n = 34$)	
Age (yr)	77.4 ± 8.2	78.3 ± 9.2	77.4 ± 8.3	79.0 ± 7.3	0.96
Education (yr)	11.4 ± 2.7	10.8 ± 2.1	11.3 ± 1.9	10.9 ± 2.2	0.08
COPD diagnosed - No. (%)	36(12)	25(6)	72(71)	16(47)	0.001
FEV1.0 (% predicted)	82.7 ± 19.6	87.5 ± 24.6	49.7 ± 10.3	66.0 ± 7.5	0.002
Blood gas analysis					
PaO_2 (mmHg)	85.2 ± 3.6	84.4 ± 5.3	71.0 ± 6.8	69.0 ± 7.3	0.23
$PaCO_2$ (mmHg)	42.8 ± 2.7	41.2 ± 3.4	48.9 ± 2.2	47.6 ± 3.1	0.44
PH	7.41 ± 0.2	7.42 ± 0.1	7.37 ± 0.1	7.36 ± 0.1	0.88

Plus-minus values are means ± S.D. *Comparisons were made between male patients and female patients with long-term DOT.

Blood gas data refer to the patient breathing oxygen at the usual therapeutic concentration via nasal prongs. COPD and FEV1.0 denote chronic obstructive pulmonary disease and forced expiratory volume in one second.

TABLE 2. *Clinical outcomes*

Variable	Controls		Patients		*p* value*
	Male ($n = 301$)	Female ($n = 417$)	Male ($n = 101$)	Female ($n = 34$)	
MMSE score	27.0 ± 3.0	26.4 ± 3.4	26.0 ± 2.4	23.4 ± 2.1	0.02
≦ 23 No. (%)	18(6)	29(7)	15(15)	14(41)	0.01
> 24 No. (%)	283(94)	388(93)	86(85)	20(59)	
GDS score	4.4 ± 2.8	4.2 ± 2.9	6.2 ± 3.4	5.9 ± 2.6	0.16
Functional/performance status (Katz index)	6.2 ± 1.8	6.2 ± 2.1	7.7 ± 3.3	7.0 ± 2.4	0.17
Borg score	1.1 ± 1.0	1.2 ± 1.1	3.2 ± 0.8	1.4 ± 0.6	0.01

Plus-minus values are means ± S.D. *Comparisons were made between male patients and female patients with long-term DOT.

MMSE and GDS denote Mini-Mental State Examination and Geriatric depression scale.

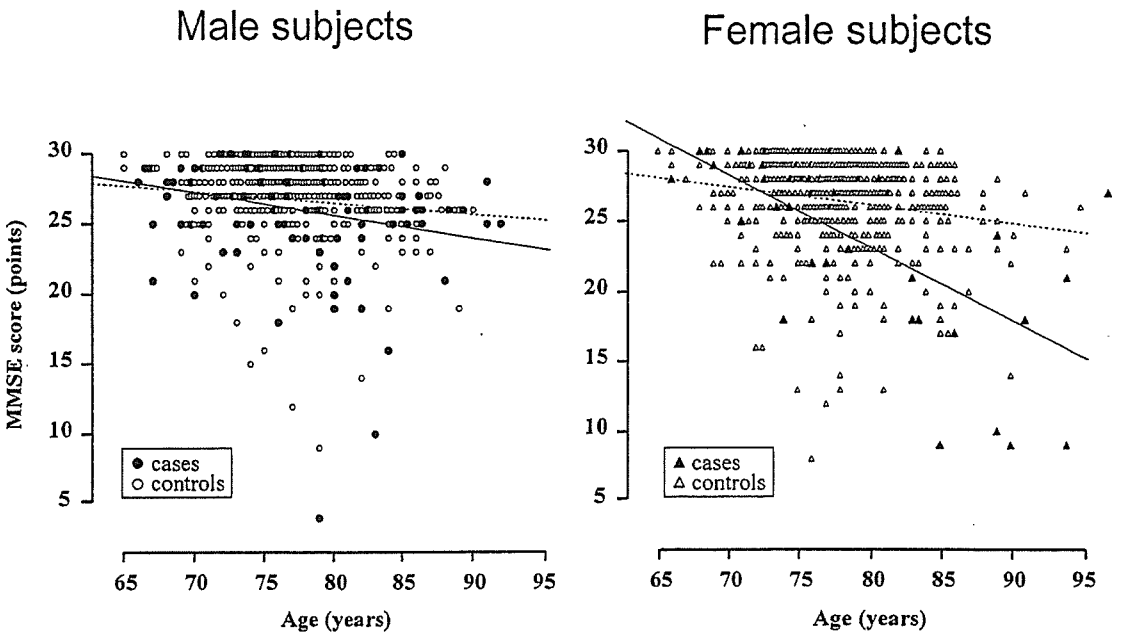

Fig. 1. Correlation between MMSE score and age in male and female subjects.
Open circles indicate male controls and closed circles indicate male patients receiving long-term DOT. Open triangles indicate female controls and closed triangles indicate female patients receiving long-term DOT. The straight lines are fitted to patients with long-term DOT and dashed lines to controls. MMSE denotes Mini-Mental State Examination and DOT denotes domiciliary oxygen therapy.

score and age in both controls and patients receiving long-term DOT. There was no significant difference in declining rate of MMSE score between male controls and patients (–0.077/year, R^2 = 0.016 vs –0.156/year, R^2 = 0.054, respectively, p = 0.231) (Fig. 1). By contrast, a significant difference in declining rate of MMSE score was observed between female controls and patients (–0.120/year, R^2 = 0.027 vs –0.524/year, R^2 = 0.426, respectively, $p < 0.0001$). Furthermore, although there was no significant difference in declining rate of MMSE score between male and female controls, a significant difference was observed between male and female patients (–0.156/year, R^2 = 0.054 vs –0.524/year, R^2 = 0.426, respectively, p = 0.021), which demonstrated age-related cognitive decline was more pronounced in female patients receiving long-term DOT (Fig. 1). Male patients had a significantly higher Borg score during daily exercise compared with female patients (3.2 ± 0.8 [S.D.] vs 1.4 ± 0.6, p = 0.01, respectively) (Table 2). There seemed to be a positive correlation between the MMSE score and the Borg score in both male and female patients, whereas it was not statistically significant (data not shown). There were no correlations between the MMSE score and the FEV_1%, GDS score, Katz index, PaO_2, $PaCO_2$ or the duration of DOT by multi-regression analysis in male and female patients with long-term DOT (Table 2).

Discussion

Oxyhemoglobin desaturation is reported to be an important determination of mental deterioration (Heaton et al. 1983; Incalzi et al. 1993). A previous study has shown that 6 months oxygen treatment is associated with small but definite improvement in brain functioning among patients with hypoxemic COPD (Heaton et al. 1983). However, cognitive function in patients receiving long-term oxygen treatment and its gender differ-

ence has not been studied. The present study demonstrated that age-related cognitive decline was more pronounced in female patients receiving long-term DOT, while cognitive function in male patients was fairly preserved compared with control subjects of the same age. To the best of our knowledge, there are no published data concerning interactions between sex and cognitive outcome after long-term DOT. There were no significant differences among several clinical parameters except the Borg score, probably due to the difference in the lung function, between male and female patients. Despite the lack of clear knowledge of the mechanism for the interaction of sex and cognitive outcome after long-term DOT, a possible explanation for this finding might be a contribution of substance P (SP) in the CNS. Several findings indicate involvement of tachykinins in stress-related anxiety and depressive states (Megens et al. 2002). Especially, SP plays a role in dyspnea perception and in some autonomic reflexes and behaviors (Megens et al. 2002). SP release is suggested in stressful situations in the CNS (Culman and Unger 1995) and the NK_1 receptor antagonist has been shown to improve anxiety and depression rating scales in depressed patients (Rupniak and Kramer 1999). SP might be released significantly in the CNS in male patients with long-term DOT and an increased release of SP might up-regulate neprilysin (Stefano et al. 1992), a major amyloid-β peptide degrading enzyme in the brain, leading to protection against cognitive decline in male patients (Iwata et al. 2000).

That continuous oxygen therapy did not provide a complete protection against the deteriorating cognition in both male and female patients is not surprising, since several factors related chronic respiratory failure other than hypoxemia are known to affect cognition. Among these factors, hypercapnia, acidosis, and hypocapnia resulting from hypoxemia-induced hyperventilation should be taken into consideration (Heaton et al. 1983; Incalzi et al. 1993).

The limitation of the present study should be discussed. First, we did not conduct a longitudinal but a cross-sectional analysis of the cognitive and psychologic functions in patients receiving long-term DOT. A longitudinal study for a long-term period may provide more detail information about the age-related cognitive decline in each subject. Second, the absolute number of the female patients with long-term DOT is limited, which is pointed out in other previous reports (Heaton et al. 1983; Incalzi et al. 1993). This is probably due to a gender difference in the prevalence of pulmonary diseases such as COPD, which require DOT in the case of disease progression. Third, although a significant negative correlation between MMSE scores and age in both controls and patients with long-term DOT was found, the correlation coefficient values were low in individual groups. A further study with a large number of patients is needed to translate the present findings to patients with DOT in general. However, we believe that our data provide sufficient grounds for a reexamination of the effect of long-term DOT on cognitive function in those patients.

In conclusion, the current study demonstrates that the effect of long-term DOT on cognitive outcome differs between men and women. The increased life expectancy of patients with chronic respiratory failure after the introduction of the oxygen therapy implies that a growing fraction of physically disabled and to a various extent mentally impaired patients can be alive until old age especially in female patients (Sasaki et al. 1998; Kubo et al. 2005). Thus, end-stage pulmonary diseases will become a growing geriatric problem, and health care systems should be prepared to deal with it.

Acknowledgments

The authors thank G. Crittenden for assistance with English.

References

Borg, G. (1982) Psychophysical bases of perceived exertion. *Med. Sci. Sports Exercise*, 14, 377-381.

Culman, J. & Unger, T. (1995) Central tachykinins: mediators of defense reaction and stress reactions. *Can. J. Physiol. Pharmacol.*, 73, 885-891.

Folstein, M.F., Folstein, S.E. & McHugh, P.R. (1975) "Mini-Mental State": a practical method for grading the cognitive state of patients for clinicians. *J. Psychiatr. Res.*, 12,

189-198.
Grant, I., Heaton, R.K., McSweeny, A.J., Adams, K.M. & Timms, R.M. (1982) Neuropsychologic findings in hypoxemic chronic obstructive pulmonary disease. *Arch. Intern. Med.*, **142**, 1470-1476.
Heaton, R.K., Grant, I., McSweeny, A.J., Adams, K.M. & Petty, T.L. (1983) Psychologic effects of continuous and nocturnal oxygen therapy in hypoxemic chronic obstructive pulmonary disease. *Arch. Intern. Med.*, **143**, 1941-1947.
Incalzi, R.A., Gemma, A., Marra, C., Muzzolon, R., Capparella, O. & Carbonin, P. (1993) Chronic obstructive pulmonary disease: an original model of cognitive decline. *Am. Rev. Respir. Dis.*, **148**, 418-424.
Iwata, N., Tsubuki, S., Takai, Y., Watanabe, K., Sekiguchi, M., Hosoki, E., Kawashima-Morishima, M., Lee, H.J., Hama, E., Sekine-Aizawa, Y. & Saido, T.C. (2000) Identification of the major Aβ 1-42 degrading catabolic pathway in brain parenchyma: suppression leads to biochemical and pathological deposition. *Nat. Med.*, **6**, 143-150.
Katz, S., Downs, T.D., Cash, H.R. & Grotz, R.C. (1970) Progress in development of the index of ADL. *Gerontologist*, **10**, 20-30.
Kubo, H., Nakayama, K., Ebihara, S. & Sasaki, H. (2005) Medical treatments and cares for geriatric syndrome: new strategies learned from frail elderly. *Tohoku J. Exp. Med.*, **205**, 205-214.
Megens, A.A., Ashton, D., Vermeire, J.C., Vermote, P.C., Hens, K.A., Hillen, L.C., Fransen, J.F., Mahieu, M., Heylen, L., Leysen, J.E., Jurzak, M.R. & Janssens, F. (2002) Pharmacological profile of (2R-trans)-4-[1-[3,5-bis (trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-piperidinyl]-N-(2,6-dimethylphenyl)-1-acetamide (S)-Hydroxybutanedioate (R116301), an orally and centrally active neurokinin-1 receptor antagonist. *J. Pharmacol. Exp. Ther.*, **302**, 696-709.
Mortensen, E.L. & Hogh, P. (2001) A gender difference in the association between APOE genotype and age-related cognitive decline. *Neurology*, **57**, 89-95.
Rupniak, N.M.J. & Kramer, M.S. (1999) Discovery of the antidepressant and antiemetic efficacy of substance P receptor (NK1) antagonists. *Trends Pharmacol. Sci.*, **20**, 1-12.
Sasaki, H., Sekizawa, K., Yanai, M., Arai, H., Yamaya, M. & Ohrui, T. (1998) Effects of air pollution and smoking on chronic obstructive pulmonary disease and bronchial asthma. *Tohoku J. Exp. Med.*, **186**, 151-167.
Scherr, P.A., Albert, M.S., Funkenstein, H.H., Cook, N.R., Hennekens, C.H., Branch L.G., White, L.R., Taylor, J.O. & Evans, D.A. (1988) Correlates of cognitive function in an elderly community population. *Am. J. Epidemiol.*, **128**, 1084-1101.
Sheikh, J.I. & Yesavage, J.A.M. (2000) 9/Geriatric depression scale (GDS) recent evidence and development of a shorter version. *Clin. Gerontologist*, **5**, 165-173.
Stefano, G.B., Paemen, L.R. & Hughes, T.K., Jr. (1992) Autoimmunoregulation: differential modulation of CD10/ neutral endopeptidase 24.11 by tumor necrosis factor and neuropeptides. *J. Neuroimmunol.*, **41**, 9-14.
The Medical Research Council Working Party (1981) Long-term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. *Lancet*, **1**, 681-686.

Tohoku J. Exp. Med., 2005, **205**, 319-325

Correction of the Maxillary Occlusal Plane Relieves Persistent Headache and Shoulder Stiffness

HIROYASU UEDA, TOSHISUKE YAMADA,[1] TAKASHI OHRUI, SATORU EBIHARA, MINORU KURAISHI,[1] YASUO KOBAYASHI,[1] MINORU TAMURA,[1] ATSUSHI SHIMIZU,[1] MEI HE and HIDETADA SASAKI

Department of Geriatric and Respiratory Medicine, Tohoku University Graduate School of Medicine, Sendai, and
[1]Department of Dentistry Oral Surgery, Nagano Municipal Hospital, Nagano, Japan

UEDA, H., YAMADA, T., OHRUI, T., EBIHARA, S., KURAISHI, M., KOBAYASHI, Y., TAMURA, M., SHIMIZU, A., HE, M. and SASAKI, H. *Correction of the Maxillary Occlusal Plane Relieves Persistent Headache and Shoulder Stiffness.* Tohoku J. Exp. Med., 2005, **205**(4), 319-325 —— It has been known for many years that deformations of the occlusal plane of the teeth cause indefinite symptoms such as headaches or stiffness of the shoulders. However, how the occlusal plane of the teeth should be corrected remains uncertain. The purpose of this study was to examine whether a correction of the deviation of the maxillary occlusal plane (MOP) from the center of dens of axis vertebrae (DAV) improves symptoms in patients having intractable headache or shoulder-stiffness. Forty patients who complained of dental abnormalities and persistent headache or shoulder-stiffness that had not responded to conventional medical treatment and 17 healthy controls were recruited. All subjects received a lateral cephalometric x-ray examination to measure a distance from the MOP and the center of DAV. In the healthy subjects, both the upper and the lower shift of the MOP from the center of DAV were minimal (the upper shift was 1 ± 2 [mean ± S.D.] mm and the lower shift was 4 ± 4 mm). By contrast, the patients had a significantly greater deviation of the MOP from the center of DAV. Dental adjustment treatment was performed in fourteen patients who had a substantial deviation of the MOP from the center of DAV. Those patients were asked about their symptoms which were scored using a point system and were compared before and after treatment. An adjustment procedure of the MOP passing through the DAV significantly relieved clinical symptoms in these patients (before 42.5 ± 34.4 vs after 7.0 ± 8.2, $p < 0.01$). Correction of the MOP passing through the near center of DAV might be effective in relieving clinical symptoms associated with dental deformities. ——— maxillary occlusal plane; dens; cervical vertebrae; clinical symptoms; neck rotation

Received September 28, 2004; revision accepted for publication January 6, 2005

Present address for correspondence: Hidetada Sasaki, M.D., Ph.D., President, Akita Nursing and Welfare University, 2-3-4 Shimizu, Oodate, Akita 017-0046, Japan.
e-mail: h-sasaki@well.ac.jp

It has been known for many years that deformations between the occlusal plane of the teeth not only cause adverse effects on the periodontal tissues, but occasionally they may also result in various indefinite physical symptoms such as headaches or stiffness of the shoulders (Huggare et al. 1991; Tsang et al. 1997; Milani et al. 1998; Motoyoshi et al. 2000; Yagi et al. 2003). Although these physical symptoms due to dental deformities may be relieved by correcting these deformities of the teeth, how the occlusal plane of the teeth should be corrected still remains uncertain (Motoyoshi et al. 2000). The occlusion of the teeth may bring various effects on the skull and neck (Solow and Sonnesen 1998). The force on the occlusal plane generated by the mandibula is as strong as 40 to 60 kg at the first molar (Jenkins 1978). Since the dens of axis vertebrae (DAV) is an unique one which has an axis to rotate the atlas, the occlusal plane of the teeth through the dens might be the most effective way to transfer the rotating force to the neck. On the contrary, if the occlusal plane of the teeth crosses cervical vertebrae other than the DAV, the rotating force of the head might not be as smooth as that on the DAV because there is no axis for rotation. The DAV through which the occlusal plane of the teeth passes, is assumed to be the only special process providing support when the neck is rotated left and right.

We hypothesized that the deviation of the maxillary occlusal plane (MOP) from the center of dens of axis vertebrae (DAV) might be responsible for symptoms in patients with intractable headache or shoulder-stiffness. To test this hypothesis, in the present study, we examined the occlusal planes in healthy volunteers and those in patients who suffered from persistent physical symptoms such as headaches or shoulder stiffness that had not responded to conventional medical treatment. We adjusted the occlusal planes of the teeth passing through the DAV and examined whether clinical symptoms were relieved or not in these patients.

Materials and Methods

Forty patients visiting a dental clinic due to dental abnormalities as well as physical symptoms such as headaches and stiffness of the shoulders, who had not responded to conventional medical care for more than two years, (23 women / 17 men, age 47 ± 15 [mean ± S.D.] years, age range 18-82 years) were examined by lateral cephalometric x-rays (Tsang et al. 1997) to investigate whether the occlusal plane connecting the second premolar and the first molar passed through the DAV or not. This was because the teeth demonstrating the strongest force on the occlusal planes are the second premolar and the first molar. In order to investigate the occlusal planes passing through the second premolar and the first molar of the maxilla, a straight orthodontic wire was fixed to the right and left sides of the maxilla and then lateral cephalometric x-rays were taken. The patients sat inside the x-ray lucent frame, in a natural head position. From the frame, two rods were extended and attached to the external auditories of both sides in order to fix the head straight forward. The positions of the two rods fixing the head were used for repeated cephalometric x-rays. The distance from the x-ray source to the x-ray film was 165 cm and that from the center of the head to the x-ray film was 15 cm. Therefore, there would be approximately 10% magnification error in measuring the shift of the occlusal plane from the DAV. Seventeen healthy subjects who had no complaints of dental abnormalities and physical symptoms with at least 24 teeth and were over 70 years old (5 women / 12 men, age 78 ± 8 years, age range 70-96 years) were also examined to see if the MOP passed through the DAV or not. The healthy subjects were those who were recognized to be in excellent condition by a physical examination including a regular community dental examination conducted annually by a community organization.

All of the patients received regular treatment for dental caries and periodontal diseases. The patients were randomly (by random numbers table) divided into two groups. One was a control (11 women / 9 men, age 49 ± 14 years) who received only regular treatment for dental caries and periodontal diseases, and the other was a treated group (12 women / 8 men, age 46 ± 16 years) who received not only regular dental treatments but also adjustments of the occlusal plane by occlusal reshaping or by wearing resin splints on the teeth so that the maxillary occlusal plane (MOP) passed through the DAV as much as possible during a period of one month to a maximum

of one year, but mostly for half a year. Adjustments of the occlusal plane were checked by lateral cephalometric x-rays when necessary.

The patients were asked about their clinical symptoms before and after dental treatment, and the symptoms were scored using a point system for a follow-up study. The symptoms of which the patients complained were 84 modified items of dental distress syndrome ranging from tooth pain to a feeling of physical symptoms that were relatively diverse including shoulder stiffness, trembling of hands, easy fatigue, nausea, eye twitching, chronic diseases, etc (Fonder 1989). Regarding each item, the patients were questioned intermittently based on four categories. When no symptoms were detected, 0 points were given, and 1, 2 and the highest 3 points were given based on the severity of the symptoms. The total points were monitored before treatment, one month after treatment and to a maximum of one year. The total points were zero if there were no symptoms and the maximum points were $84 \times 3 = 252$ points.

Comparisons were made between pre- and post-treatment values of occlusal planes as well as clinical symptoms using the paired *t*-test. Significance was accepted at $p < 0.05$. The Tohoku University Ethics Committee granted ethical approval, and a full explanation concerning the influence of the occlusal plane was given and informed consent of the treatment was obtained from each patient.

Results

Fig. 1 shows examples of cephalometric x-rays where the MOPs are across the center of the DAV (Fig. 1A), shifted upward to the direction of the DAV (Fig. 1B) and shifted downward to the direction of the DAV (Fig. 1C). The center of the DAV is marked as the middle crossing points of the dens extending from the axis vertebrae (height of approximately 11 mm) and the width of dens (approximately 5 mm). The shift of the occlusal planes was not changed by the upward or downward movement of the skull. In the healthy subjects, the upper shift of the MOP from the center of DAV was 1 ± 2 mm and the lower shift was 4 ± 4 mm. These results revealed that the area covering the upper 3 mm or the lower 8 mm from the center of the DAV (0 mm) was recognized as a normal range at a risk of 95%.

Among the 40 patients, 17 control patients (12 women / 5 men, age 43 ± 16 years) and 14 treated patients (8 women / 6 men, age 51 ± 15 years) completed the study. Fig. 2 shows an example of a patient in whom right and left MOPs were dislocated to the upper side of the center of the DAV. After the dental adjustment treatment, the bilateral MOPs entered the DAV and the scores of indefinite symptoms declined from 82 points to 19 points. Deviation of the MOP from the center of the DAV was recorded as 0 mm (at the center of the dens) and the upward (negative) shift or downward (positive) shift as 1mm interval after dental adjustment treatment.

Fig. 3 shows the distance from the MOP to the center of the DAV in the group of patients showing lower (positive) shifts or upper (negative) shifts. The control group of patients showed no changes in the occlusal plane before and after regular treatments for dental caries and periodontal diseases (data not shown). In contrast, the MOP of patients with both regular dental treatment and dental adjustment treatment was significantly corrected toward the center of the DAV both in the right and in the left sides (Fig. 3).

Fig. 4 shows the change in symptom scores in patients with only regular dental treatment (control) or in those with both regular dental treatment and adjustment treatment, before and after treatment. The symptom scores of the control group showed no significant differences. On the other hand, the symptom scores in the adjustment treatment group were significantly improved (before 42.5 ± 34.4 vs after 7.0 ± 8.2, $p < 0.01$). However, no correlations were found between the baseline symptom scores and the absolute values of the shifts of the MOP from the center of DAV in either positive or negative shift.

Discussion

Numerous investigators describe the effect of an altered mandibular position on cranial posture (Costianes 1983; Fonder 1989; Alonen 2002). Forward and lateral positions change the mandible, hyoid bone, and tongue (Darnell 1983). There is compression in the upper cervical facet joints, causing muscular nerve entrapments. Nerve root compression or posterior vertebrae

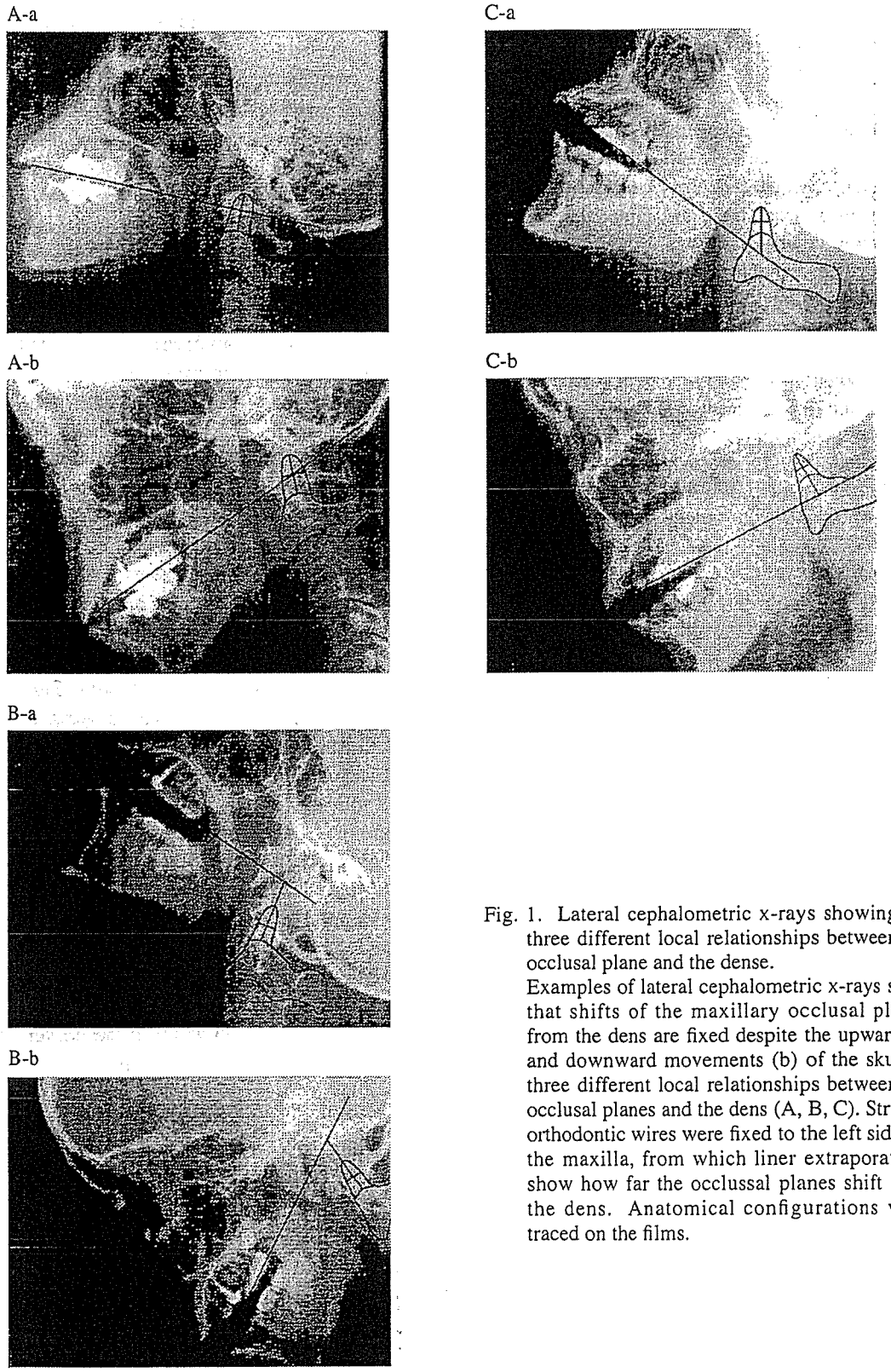

Fig. 1. Lateral cephalometric x-rays showing the three different local relationships between the occlusal plane and the dense.
Examples of lateral cephalometric x-rays show that shifts of the maxillary occlusal planes from the dens are fixed despite the upward (a) and downward movements (b) of the skull in three different local relationships between the occlusal planes and the dens (A, B, C). Straight orthodontic wires were fixed to the left sides of the maxilla, from which liner extraporations show how far the occlussal planes shift from the dens. Anatomical configurations were traced on the films.