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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

平成 17 年度 総括研究報告書

主任研究者 大類 孝

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総括研究報告書

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：東北大学病院ものわすれ外来に通院中のアルツハイマー病（AD）患者およびADの前段階である軽度認知障害（MCI）患者および健常人から、同意を得た上で脳脊髄液を採取しそのアンジオテンシン変換酵素（ACE）活性を測定した結果、MCIおよびAD患者の脳脊髄液のACE活性が健常人に比して、有意に上昇している事実を確認した。また、AD患者では、脳内移行性ACE阻害剤のペリンドプリル投与によって、脳脊髄液中のACE活性が有意に抑制される事を明らかにした。さらに、東北大学病院もしくはその関連病院および介護施設に通院および入院中の高血圧合併ADの患者を、本人および家族の同意を得た上で、無作為に脳内移行性ACE阻害剤（ペリンドプリル）投与群、対照として脳内非移行性ACE阻害剤（エナラプリルまたはイミダプリル）投与群およびカルシウム拮抗剤（ニフェジピンまたはニルバジピン）投与群に分け、各群において12ヶ月にわたりMini-Mental-State-Examination (MMSE) ScoreとClinical Dementia Rating (CDR) scaleを指標にした認知機能およびバーセルインデックスを用いた日常生活活動度（ADL）を追跡調査中である。

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

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。

A. 研究目的

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、わが国で使用されている降圧剤の中で、脳内移行性ACE阻害剤（ペリンドプリル）

B. 研究方法

1) 東北大学病院ものわすれ外来通院中のアルツハイマー病（AD）患者およびADの前段階である軽度認知障害（MCI）患者および健常人から、同意を得

た上で脳脊髄液を採取しその中のACE活性を測定し、脳内ACE活性と認知機能障害の関連を明らかにする。

2) 高血圧合併AD患者を無作為に脳内移行性ACE阻害剤(ペリンドプリル)投与群、脳内非移行性ACE阻害剤(エナラプリルまたはイミダプリル)投与群およびカルシウム拮抗剤(ニフェジピンまたはニルバジピン)投与群に割りつけ、対象者のその後12ヶ月にわたる[Mini-Mental-State-Examination (MMSE) Score]と[Clinical Dementia Rating (CDR) scale]を指標にした認知機能およびバーセルインデックスを用いた日常生活活動度(ADL)を追跡調査し、得られた結果を統計学的に解析し3群間の比較検討を行う。

(倫理面への配慮)

研究は十分な説明の後同意を得て行われ、得られたデータのプライバシーに十分に配慮した。

C. 研究成果

1) アルツハイマー病(AD)患者および軽度認知障害(MCI)患者および健常人の脳脊髄液中のACE活性を測定した結果、MCIおよびAD患者のACE活性が健常人に比して、有意に上昇している事が明らかにされた(MCI: 0.29 ± 0.03 IU/L, $n=17$, AD: 0.23 ± 0.02 IU/L, $n=31$, 健常人: 0.19 ± 0.02 IU/L, $n=15$, $p<0.01$)。また、AD患者では、脳内移行性ACE阻害剤のペリンドプリル投与によって、脳脊髄

液中のACE活性が有意に抑制される事が明らかにされた[0.24 ± 0.02 IU/L (投与前) vs 0.13 ± 0.03 IU/L (投与後), $n=7$, $p=0.038$]。

2) 平成17年12月までの半年で、約300名の高血圧合併AD患者を無作為に脳内移行性ACE阻害剤投与群、脳内非移行性ACE阻害剤投与群およびカルシウム拮抗剤投与群に割りつけし、AD患者のその後1年間における認知機能および日常生活動作(ADL)を追跡調査中である。

D. 考察

これまでの諸外国の剖検研究によると、ADの患者では脳内ACE活性が亢進しており、結果として過剰産生されるアンギオテンシン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(Neurobiol Aging 2001)。本研究で、私は、生存中のMCIおよびAD患者の脳脊髄液中ACE活性が、健常人に比して有意に上昇している事を初めて明らかにし、AD患者における脳内ACE活性抑制の治療戦略の意義を確認した。

E. 結論

MCIおよびAD患者の中枢神経系のACE活性が健常人に比して、有意に上昇している事実を確認した。また、AD患者では、脳内移行性ACE阻害剤のペリンドプリル投与によって、脳脊髄液中のACE活性が有意に抑制される事を明

らかにした。脳内移行性ACE阻害剤は、AD患者の病勢進行を抑制する可能性が示唆され、現在も実際の登録患者で研究が進行中である。

F. 健康危険情報

特になし。

G. 研究発表

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H. 知的財産権の出願・登録状況

特になし。

厚生労働科学研究費補助金（長寿科学総合研究事業）

分担研究報告書

認知症の心理行動学的症状と ADL に対する

漢方薬抑肝散の効果に関する研究

分担研究者 岩崎鋼 東北大学大学院医学系研究科助教授

研究要旨：認知症における心理行動学的症状(BPSD)と ADL に対する漢方薬抑肝散の効果と安全性を観察者盲検ランダム化比較臨床研究で検討した。BPSD を有する 52 名の認知症患者をランダムに二群に分け、一群には漢方薬抑肝散を内服させ、他方の群は従来の治療を継続したところ、抑肝散投与群では BPSD 指標の NPI が 37.9 ± 16.1 から 19.5 ± 15.6 (mean \pm SD) へ有意に改善し、また Barthel index で評価した ADL も 56.4 ± 34.2 から 62.9 ± 35.2 へと有意に改善した。

A. 研究目的

認知症における心理行動学的症状(BPSD)と ADL に対する漢方薬抑肝散の効果と安全性を観察者盲検ランダム化比較臨床研究で検討した。

(MMSE) を認知機能の、さらに Barthel Index を ADL の指標として用い、両群共に前値及び 4 週後の値を評価した。錐体外路症状他あらゆる有害事象について記録した。

(倫理面への配慮)

B. 研究方法

52 名の認知症患者（男性 18 名女性 34 名、平均年齢 80.3 ± 9.0 歳）をランダムに二群に分け、一群(n = 27)には抑肝散エキスを 4 週間内服させ、非服用群(n = 25)をコントロールとした。The Neuropsychiatric Inventory (NPI) test を心理行動学的症状(BPSD)の指標とし、また Mini-Mental State Examination

全ての被検者或いはその家族から十分な説明の後文書による同意を得た。

C. 研究結果

抑肝散投与群では NPI が 37.9 ± 16.1 から 19.5 ± 15.6 (mean \pm SD) へ有意に改善した。同時に Barthel index で評価した ADL も 56.4 ± 34.2 から 62.9 ± 35.2 へと有意に改善した。MMSE で

みた全般的認知機能には有意な変化を認めなかった。コントロール群ではいずれの指標も有意な変化を生じなかった。錐体外路症状は両群とも観察されなかった。

D. 考察

抑肝散は認知症患者に於けるBPSDを改善し、同時にADLを阻害することなく、むしろ有意に改善した。

E. 結論

従来の抗精神病薬とは異なり錐体外路症状を伴わずにBPSDを改善する抑肝散の有用性について今後placeboを用いた大規模二重盲検ランダム化比較研究が望まれる。

F. 安全危険情報

特になし

G. 研究発表

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日本東洋医学会 2005 年度学術集会
「痴呆症の心理行動学的症状(いわゆる問題行動, BPSD)と ADL に対する抑肝散の効果, ランダム化単純盲検比較試験」(日本東洋医学雑誌(0287-4857)56 巻別冊 Page223)

H. 知的財産権の出願・登録状況

なし

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
<u>Ohru T</u> , 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, <u>Ohru T</u> , et al.	Correction of maxillary occlusal plane relieves persistent headache and shoulder stiffness	Tohoku J Exp Med	205	319-325	2005

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

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Departments of ¹Geriatric and Respiratory Medicine, ³Pharmacology, and ⁶Biomedical Engineering Research Organization, Tohoku University Graduate School of Medicine, and ²Department of Geriatric and Complementary Medicine, Center for Asian Traditional Medicine Research, Sendai, ⁴Laboratory for Proteolytic Neuroscience, RIKEN Brain Science Institute, Wako-shi, Saitama and ⁵Research 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-3 α (GSK-3 α) and GSK-3 β 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/p₁₈₁-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 p₁₈₁-tau) before and after treatment with lithium in three AD patients with agitation.

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

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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/p₁₈₁-tau was 66 and 70 pmol/L, and CSF-A β ₁₋₄₂ was 331 and 359 pg/mL in case 1, CSF/total-tau was 382.3 and 484 pg/mL, CSF/p₁₈₁-tau was 56 and 63 pmol/L, CSF-A β ₁₋₄₂ was 398 and 296 pg/mL in case 2 and CSF/total-tau was 987 and 1065 pg/mL, CSF/p₁₈₁-tau was 118 and 114 pmol/L, CSF-A β 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 p₁₈₁-tau increased 27% and 13%, respectively, and A β 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. A β synthesized from amyloid precursor protein (APP) is known to be regulated not only by β/γ secretase but also by GSK-3 α , and tau phosphorylation is known to be regulated by GSK-3 β . In AD, it is supposed that A β 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-3 α activity, which potentiated the production of A β , and consequently reduced the production of A β not the processing of APP.⁴ Klein *et al.* reported that GSK-3 β 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-3 α/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.

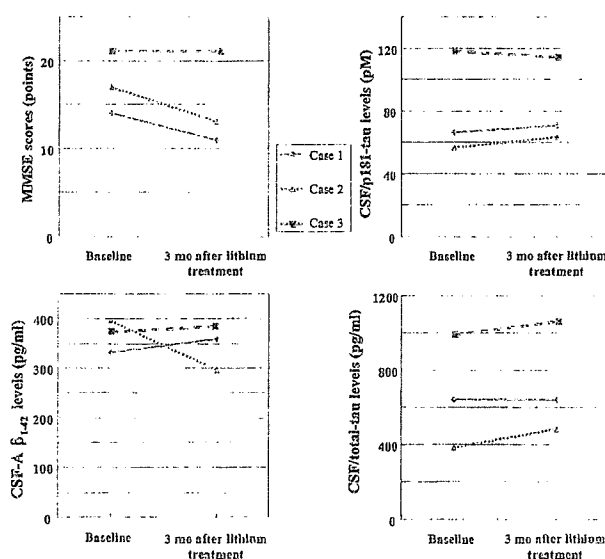


Figure 1 Mini Mental State Examination (MMSE) scores and total tau, p₁₈₁-tau and A β ₁₋₄₂ levels in cerebrospinal fluid before and after 3 months of lithium treatment.

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

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UEDA, H., YAMADA, T., OHROI, 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 \pm 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

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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 \pm 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 auditory 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

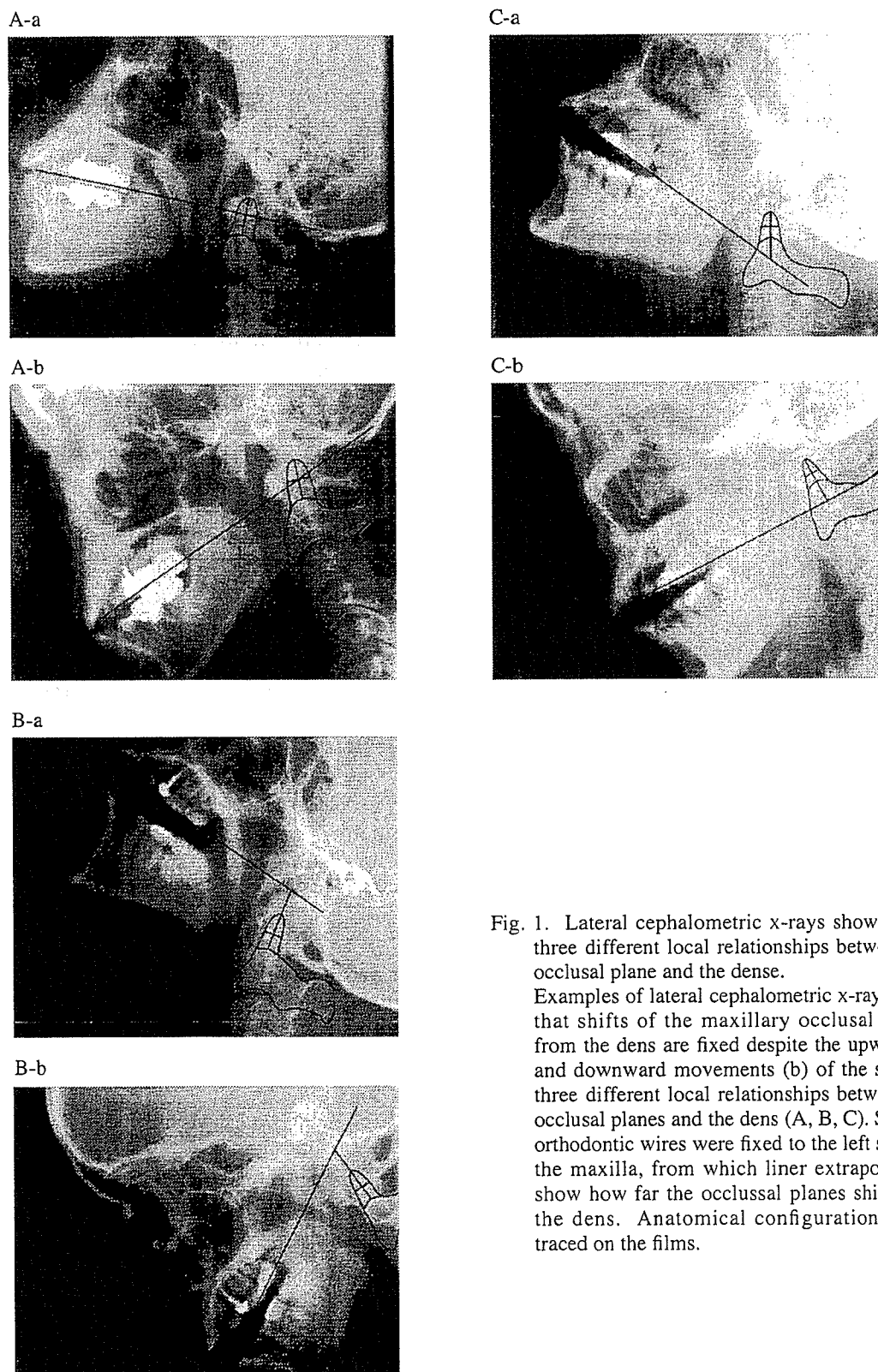


Fig. 1. Lateral cephalometric x-rays showing the three different local relationships between the occlusal plane and the dens.

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 extrapolations show how far the occlusal planes shift from the dens. Anatomical configurations were traced on the films.

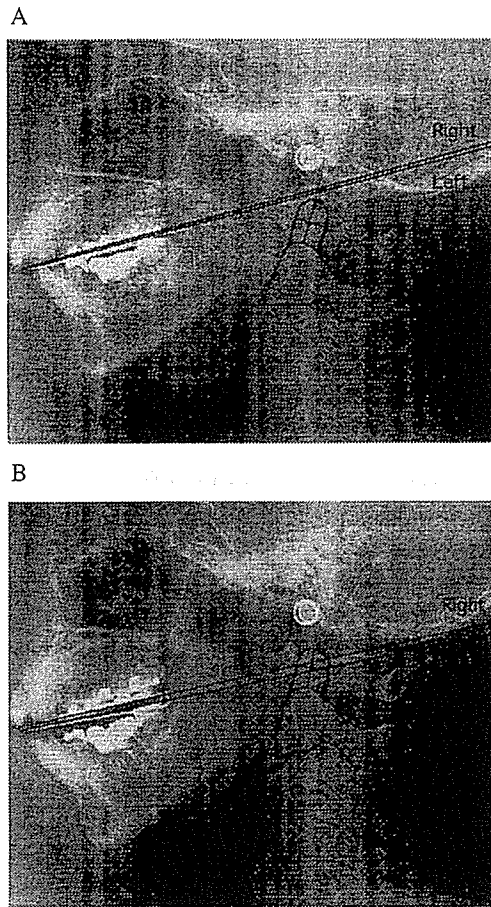


Fig. 2. Representative lateral cephalometric x-ray profiles in a patient before and after dental adjustment treatment.

Two rings show the external auditorys of both sides. Zero mm of the dens is shown as a rectangular cross point (center). Before treatment, the occlusal plane shifted upwards by 9 mm on the right and 7 mm on the left side from the center of the dens (A). After dental adjustment treatment, the occlusal plane passed through the dens (B) and clinical symptom scores were reduced from 82 points to 19 points.

facet irritation or restriction result in peripheral entrapment neuropathies (Kopell and Thompson 1976). One common entrapment is the greater or lesser suboccipital nerves that pass between the occiput and atlas (Jones 1984). This may cause headaches or pain in the facial region. Many dental teams investigated and treated maloccluded teeth providing ideal dental occlusion by acrylic

overlay fillings placed on all mandibular and maxillary first and second molars, and observed relief of clinical symptoms (Costianes 1983; Fonder 1989; Alonen 2002). However, they did not adjust the occlusal plane to the center of the dens of the axis of cervical vertebrae. According to this procedure, the rotating force of the neck would be most effectively applied to the dens but not to the other cervical vertebrae. In the present study, we have shown that patients who visited dentists due to dental problems as well as physical symptoms demonstrated significantly higher frequency of shifts from the center of the DAV compared with healthy subjects. This report will be the first which proved that an adjustment of the MOP crossing the DAV would be effective in reducing physical symptoms associated with dental deformities.

A very complex structure and functions are found in the oral cavity. Considering mastication of foods as an example, a strong force is generated on the occlusal plane daily and it is natural to assume that even a slight inefficiency causes an accumulated load. In addition to the concept that the teeth are aligned neatly, if the occlusal plane is corrected to pass through the near center of the dens, the dens supports the neck to avoid shifts by minimizing the loads in the right and left side of the neck during mastication of food and, as a result, a stable neck may be obtained.

However, a precise mechanism for the effect of correction of MOP on physical symptoms such as headache or shoulder stiffness was not clarified in the present study. It might or might not be that all known mammals have an occlusal plane almost passing through the 1st and the 2nd cervical vertebrae, which might be very important in making the cervical vertebrae stable. In the future, it is necessary to find out whether the same phenomenon occurs in mammals or to prove the phenomenon by measuring the loads of the forces to the vertebrae. The present method demonstrated an initial step in showing a direction of the correction of the dental occlusal plane. There are many elderly people with dentures who complain of the unpleasant feeling of dentures, which might be caused by not being aware of an inadequate

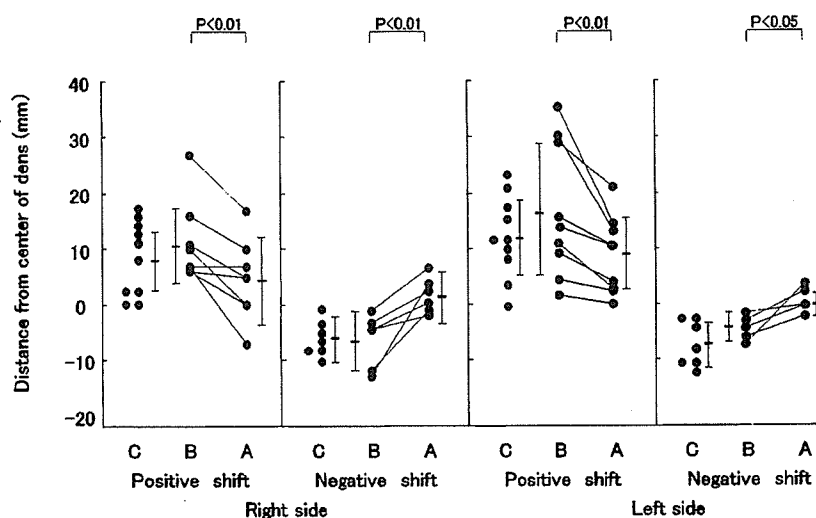


Fig. 3. The actual distance from the maxillary occlusal plane to the center of the dense.

The vertical bar indicates the actual distance from the maxillary occlusal plane to the center of the dens. Data were obtained from patients without dental adjustment treatment (C), those from patients with dental adjustment treatment before (B) and after treatment (A) in either right or left side. A connected line means that the data corresponds to the same patient before and after treatment. Mean \pm s.d. are indicated by the bold horizontal bars and thin vertical bars, respectively. There was no significant difference between group C and B. There were significant differences between B and A ($p < 0.01$ or $p < 0.05$) as shown in this figure.

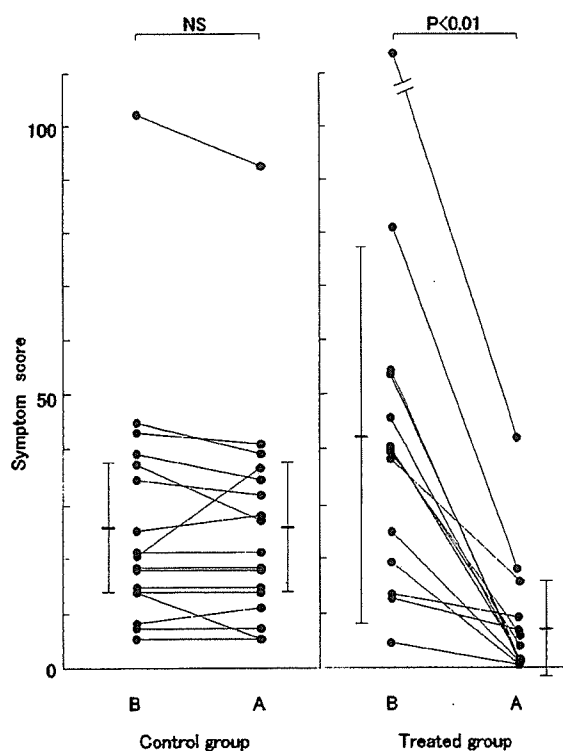


Fig. 4. Symptom scores in the control group and in the treated group, before and after dental treatment.

Symptom scores are shown in patients with only caries treatment (Control group) and with both dental caries and adjustment treatments (Treated group) before (B) and after (A) treatment. A connected line means that the data corresponds to the same patient. There was no significant difference between symptom scores obtained before and after treatment in the control group ($p = 0.86$). Symptom scores after treatment were significantly decreased compared with those before treatment in the treated group ($p < 0.01$). The highest score before treatment in the treated group was 142 points, and this decreased to 42 points after treatment.

maxillary occlusal plane. It is suggested that for elderly people with dentures it should also be determined if they have an adequate MOP passing through the center of the DAV.

In conclusion, our results suggest that correction of the maxillary occlusal plane passing through the near center of the dens of the cervical vertebrae might be effective in relieving clinical symptoms associated with dental deformities.

Acknowledgments

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Cognitive Decline in Patients with Long-Term Domiciliary Oxygen Therapy

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OHROI, 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 $66.0 \pm 7.5\%$ 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 ($-0.524/\text{year}$, $R^2 = 0.426$ vs $-0.120/\text{year}$, $R^2 = 0.027$, $p < 0.0001$), while there was no significant difference between male patients and male controls ($-0.156/\text{year}$, $R^2 = 0.054$, vs $-0.077/\text{year}$, $R^2 = 0.016$, $p = 0.231$). 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

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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 ageing 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 Hogg 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