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 18 年度　総括研究報告書

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平成 19(2007)年 3 月

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平成18年度厚生労働科学研究費補助金（長寿科学総合研究事業）

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

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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。

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A.　研究目的

わが国の超高齢化社会において、介護を必要とする認知症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。それら認知症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り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 ACE 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。

B. 研究方法

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。

（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 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。

D. 考察

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－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 ACE 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。

E. 結論

脳移行性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。

F. 健康危険情報

特になし。

G. 研究発表

1. 論文発表

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H. 知的財産権の出願

特になし。

平成18年度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

アルツハイマー病における統合医療の試み

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研究要旨：アルツハイマー病(AD)治療薬としてのcholinesterase阻害剤（塩酸ドネペジル）の効果を高める目的で、漢方薬加味温胆湯との併用効果を検討した。38名のAD患者をランダムに2群に分け、ドネペジル単独治療(n=20)と、ドネペジル・加味温胆湯併用治療(n=18)を12週間行い、治療前後の認知機能（MMSE, ADAS-cog）及び^{123}I-IMP-SPECTによる脳血流量を評価した。MMSE($p=.001$; -4.17＜95% C.I＜-1.28), ADAS-cog($p<.0001$; 2.54 ＜ 95% C.I ＜ 5.80)、脳血流($p<0.05$)とも併用治療群のみ有意な改善を示した。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され、認知症の治療に有益であることが示唆された。

A. 研究目的

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）を抑制する可能性も指摘されており、この酵素の機能を高める薬剤とのコンビネーションはCE-Iにとって望ましい治療法となりうる。漢方方剤加味温胆湯（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、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

38名の臨床的に診断基準を充たすAD患者をランダムに2群に分け、ドネペジル単独治療(n=20, 74.6 ± 3.9 in age, M:F=4:16)と、ドネペジル・加味温胆湯併用治療(n=18, 73.7 ± 5.6 in age, M:F=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。

（倫理面への配慮）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

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な差がないことを確認した。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)とも併用治療群のみ有意な改善を示し、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。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

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明らかにし得た。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

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. 発表論文

1．論文発表

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G. 知的財産権の出願・登録状況

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
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Maruyama M, Tomita N, Iwasaki K,	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*	*869-872*	*2006*

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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

To the Editor: Although many attempts have been made to demonstrate its cognitive benefits in Alzheimer's disease (AD),[1] donepezil, one of the cholinesterase (ChE) inhibitors, is still a standard therapeutic agent. Because of a limited benefit of a single drug alone, several clinical trials of combination regimen have been reported.[2] One study demonstrated that an inhibition of ChE leads to a marked reduction of choline acetyltransferase (ChAT) levels in the rat brain.[3] A negative feedback mechanism may explain this finding, supporting the use of a ChAT activator in combination with donepezil in AD. Kami-Untan-To (KUT), a traditional Japanese herbal medicine, is known to upregulate the expression of ChAT at the messenger ribonucleic acid level.[4] It also increases acetylcholine levels and the number of ChAT-positive neurons in aged mice.[5] Finally, Suzuki et al. conducted a clinical trial of KUT to evaluate safety and efficacy in patients with mild to moderate AD.[6] Therefore, we designed an observer-blind, donepezil monotherapy controlled clinical trial of a combination of donepezil plus KUT. A 12-week, observer-blind, donepezil monotherapy controlled clinical trial was conducted at the Tohoku University hospital outpatient clinic for dementia from October 2003 through January 2005. Thirty-eight eligible AD patients (National Institute of Neurological and Communicative Disorders and Stroke—Alzheimer's Disease and Related Disorders Association criteria[7]) were randomly assigned to receive donepezil alone (n = 20, mean age ± standard deviation 74.6 ± 3.9; men, n = 4; women n = 16) or a combination of donepezil and KUT (n = 18, aged 73.7 ± 5.6; men, n = 4; women n = 14). In both groups, patients received a 3-mg daily dose of donepezil for the first 14 days followed by an escalation to 5 mg thereafter. The 13 herbs of KUT[6] were purchased from Tsumura Co. Ltd, Tokyo, Japan. The quality of the herbs was standardized based on the Good Manufacturing Practice defined by the Ministry of Health and Welfare of Japan. Cognitive function was measured using the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog)[8] and Mini-Mental State Examination (MMSE), as well as regional cerebral blood flow (rCBF) using ^{123}I-IMP-ARG single photon emission computed tomography, with SPM99 software package (Wellcome Department of Imaging Neuroscience, London, UK) implemented in MATLAB 5.3 system (Mathworks Inc., Natick, MA).

At baseline, there was no significant difference in age, sex distribution, MMSE score (19.6 ± 4.1 vs 18.9 ± 4.9 points), ADAS-cog score (19.5 ± 6.8 vs 21.0 ± 7.6 points), prevalence of silent brain infarction (38% vs 44%), or grade for deep white matter lesions (0.9 ± 0.6 vs 1.1 ± 0.2) and for periventricular hyperintensity (0.7 ± 0.8 vs 0.7 ± 0.8) (as previously defined[9]) between the treatment groups (chi-square test, $P > .05$). Two patients in the donepezil monotherapy group had intractable diarrhea, conceivably due to cholinergic adverse effects by donepezil. No such event was observed in the combination group. Analyses were performed using the last observation carried forward method. Differences in the MMSE and ADAS-cog scores between baseline and posttreatment were analyzed using a paired *t* test and repeated measure analysis of variance.

As shown in Figure 1A, relative to baseline, posttreatment MMSE scores significantly improved only in the combination group (from 18.9 ± 4.9 to 21.6 ± 4.2 points, $P = .001$; $-4.17 < 95\%$ confidence interval (CI) < -1.28) but not in the donepezil monotherapy group (from 19.6 ± 4.1 to 20.4 ± 4.5). As shown in Figure 1B, ADAS-cog scores also improved significantly in the combination group (from 21.0 ± 7.6 to 16.8 ± 7.1, $P < .001$; $2.54 < 95\%$ CI < 5.80) but not in the monotherapy group (from 19.5 ± 6.8 to 18.2 ± 7.0). Furthermore, as shown in Figure 1C, the rCBF in frontal regions significantly increased in the combination group alone ($P < .05$ corrected: Brodmann's area (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; $k_E = 6{,}029$).

Despite a small sample size and a short observation period, we demonstrated that the combined use of donepezil plus KUT was more beneficial than donepezil alone in cognition and brain perfusion. Although cholinergic-related adverse effects might be expected, such events did not occur in the combination group. Therefore, it is likely that donepezil and KUT worked synergistically in a safe fashion to enhance availability of acetylcholine. In our study, the prevalence of silent brain infarction was 38% in the donepezil monotherapy group and 44% in the combination group. This was comparable with results of studies with serially enrolled autopsy-confirmed AD cases by Heyman et al. (30.2%).[10] Therefore, it should be noted that our study was conducted in a mixed population of pure AD and AD with cerebrovascular diseases. In summary, KUT might be used as a complementary regimen to enhance treatment success of current cholinergic therapy for AD.

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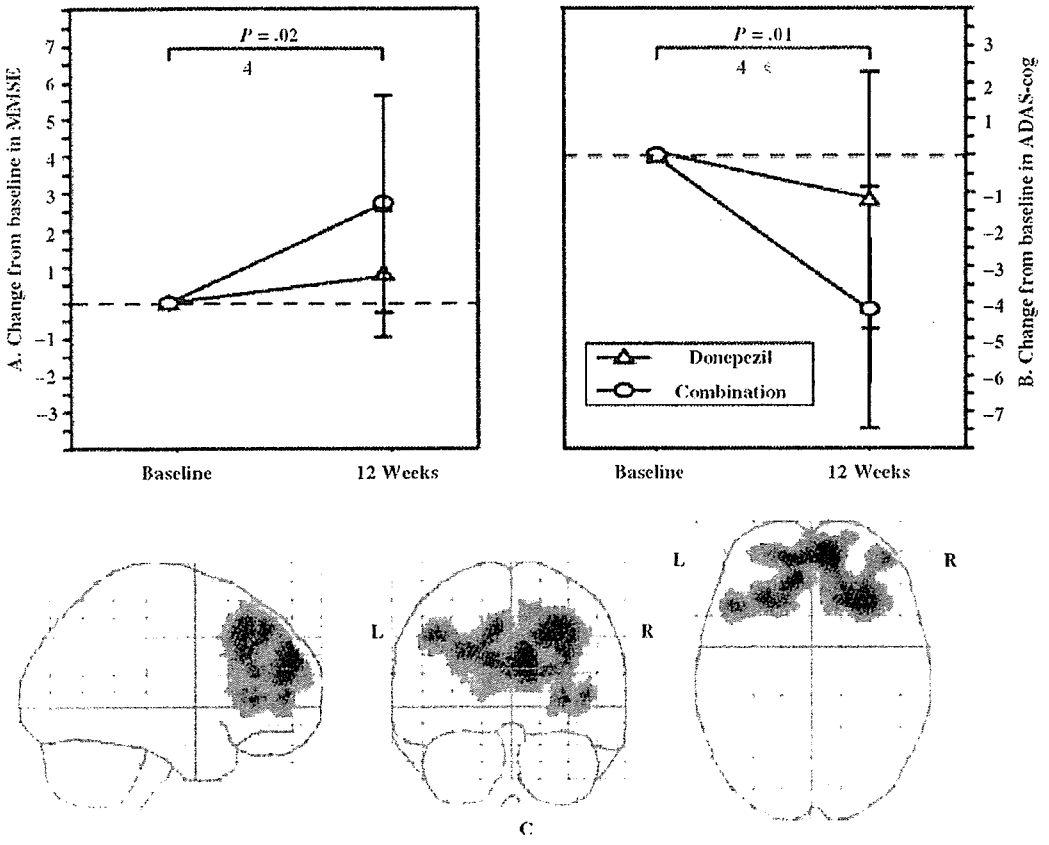

Figure 1. Mean change from baseline ± standard deviation in (A) Mini-Mental State Examination (MMSE) and (B) Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) scores at the 12-week treatment point in donepezil-treated and donepezil plus KUT (combination)-treated groups. ADAS-cog scores below baseline indicate improvement in cognitive function. (C) Z map of increased regional cerebral blood flow on repeated single photon emission computed tomography examination compared with baseline examination in the combination group. Significant areas are found in prefrontal cortices ($P<.05$ corrected: Brodmann's area (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; $k_E = 6,029$).

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ACKNOWLEDGMENTS

Financial Disclosures: Masahiro Maruyama and Hiroyuki Arai, Japanese patent no. 2004–341921.

Author Contributions: Koh Iwasaki and Hiroyuki Arai: study concept and design. Masahiro Maruyama, Naoki Tomita, Mari Ootsuki, Toshifumi Matsui, Miyako Nemoto, and Miho Tsutsui: acquisition of subjects and data. Nobuyuki Okamura, Makoto Higuchi, Tomoko Suzuki, Takashi Seki, and Tomohiro Kaneta: analysis and interpretation of data. Masahiro Maruyama and Koh Iwasaki: preparation of manuscript.

Sponsor's Role: None.

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GATIFLOXACIN-INDUCED DELIRIUM AND PSYCHOSIS IN AN ELDERLY DEMENTED WOMAN

To the Editor: Fluoroquinolone antibiotics are being used with increasing frequency. We present a case of gatifloxacin-induced delirium and psychosis.

Ms. G, an 89-year-old woman, was admitted with increased falls and confusion. She was noted to have pneumonia on chest x-ray and was started on gatifloxacin 400 mg orally every other day for a total of eight doses. (Her baseline creatinine was approximately 130 μmol/L.) Computed tomography of her head revealed no acute processes. Her other medications included nifedipine, enteric-coated acetylsalicylic acid, latanoprost eye drops, and donepezil. She had seen a psychiatrist 1.5 months earlier, who found her to have mild cognitive impairment. (Her Folstein Mini-Mental State Examination (MMSE) score at that time was 26/30.)

Two days after initiation of gatifloxacin, her MMSE score was noted to be 17 of 29. She was prescribed risperidone 0.5 mg daily 5 days after gatifloxacin treatment began, which was then titrated up to 2 mg daily. On Day 6 of antibiotic treatment, she was noted to be throwing items at staff and was delusional. Three days after the antibiotic course, she was noted to be concerned and agitated about a fire at a local hotel (which did not occur), and at 4 days after the antibiotic treatment had ended, she was convinced that she was on the street looking for an acquaintance. Throughout these episodes, her laboratory values did not explain her behavior. Psychiatry was consulted when such delusional themes persisted 7 days after the antibiotic treatment had ended. On examination, her MMSE score was 23 of 30, and there was no evidence of delusions. The recommendations were that the risperidone be discontinued and that the patient be observed for lingering effects of the gatifloxacin. Two days later, the patient was noted to no longer speak of delusions to the treating team.

Because of change in medical responsibility and recurrence of sepsis, the patient was inadvertently given gatifloxacin. After an initial intravenous dose, she received six daily oral doses of 400 mg and was noted to be hallucinating and paranoid as early as the evening of the first dose. The paranoia resolved with antibiotic cessation.

To our knowledge, there is only one previously reported case of gatifloxacin-induced psychosis[1] and one case of gatifloxacin-induced delirium.[2] Fluoroquinolone antibiotics are known to have significant central nervous system effects, including psychosis.[3,4] With their increased use for urinary and respiratory illness, it is important for physicians to be aware of the potential for antibiotic-related psychosis.

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ACKNOWLEDGMENTS

Financial Disclosures: None.

Author Contributions: Satyendra Satyanarayana and Barry Campbell participated in the clinical work described and participated equally in the preparation of the manuscript.

Sponsor's Role: There was no sponsor for this report.

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RECTAL SHEATH HEMATOMA IN AN ELDERLY WOMAN AFTER ANTICOAGULATION TREATMENT

To the Editor: An 85-year-old woman with new-onset atrial fibrillation was started on warfarin and abdominal subcutaneous injection of enoxaparin 40 mg every 12 hours. On the third day, she complained of severe left lower quadrant abdominal pain that increased upon sitting up. Physical examination revealed a firm, tender left lower quadrant mass. Carnett's test was positive. Blood tests showed a drop in hemoglobin of 2 g/dL and mild leukocytosis. A computed tomography of the abdomen and pelvis showed a left rectus sheath hematoma (RSH) (Figure 1). Anticoagulation was held, and two units of fresh frozen plasma and two units of packed red blood cells were transfused. The hematoma stabilized, and hemoglobin rose to baseline levels. At 2-month follow-up, the patient was still doing fine.

RSH is a rare cause of acute abdomen. It is due to a tear of the epigastric vessels (A. epigastrica superficialis) usually in the lower quadrant muscles.[1] It has been associated with anticoagulation,[2] abdominal trauma, pregnancy, subcutaneous abdominal injections of medications (low-molecular-weight heparin, insulin, and goserelin), severe bouts of coughing (causing sudden increase of intra-abdominal pressure), hemodialysis (anticoagulation with heparin during dialysis) or peritoneal dialysis (cannula insertion), laparoscopic procedures such as cholecystectomy, connective tissue diseases (such as Ehlers-Danlos), and hematological

Discussion. Our patient improved with each course of IVMP, supporting the contention that GAD65 ataxia is an immune-mediated disorder. IVMP also reduced serum and CSF GAD65 antibody titers. In contrast, plasma exchange produced no immediate clinical benefit or reduction in CSF GAD65 antibody levels (although serum titers predictably decreased). These data suggest that CSF GAD65 antibody titers may correlate better with clinical response.

We also found an elevated CSF GAD65 specific index, indicative of intrathecal antibody production.[3] The association of elevated CSF GAD65 specific index and GAD65 antibody titers with disease severity suggests that intrathecal antibody production may be pathogenic. Moreover, the absence of cerebellar atrophy on MRI and marked clinical response to immunotherapy, with return of near-normal cerebellar function, argue against a destructive, cytotoxic process in our patient. A predominant humoral mechanism for GAD65 ataxia contrasts with that seen in paraneoplastic cerebellar degeneration in which $CD8^+$ cytotoxic T lymphocytes are likely pathogenic and autoantibodies are probably insufficient to cause disease.[7] If antibodies are primarily pathogenic, it remains unclear whether GAD65-specific or other antibodies are causative.

Our case is also notable because of the response to azathioprine, as evidenced by the patient's clinical remission. Azathioprine should be considered alongside IV corticosteroids in the management of GAD65 ataxia.

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Disclosure: The authors report no conflicts of interest.

Received March 21, 2006. Accepted in final form June 16, 2006.

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Acknowledgment

The authors thank Vanda Lennon, MD, PhD, for help with GAD antibody assays.

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ACE activity in CSF of patients with mild cognitive impairment and Alzheimer disease

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There is increasing evidence of angiotensin-converting enzyme (ACE) in the development of Alzheimer disease (AD).[1-5] However, little is known about the ACE activity in the CNS in living patients with AD. We therefore measured ACE activity in CSF in patients with mild cognitive impairment (MCI) and mild to moderate AD and compared the values with those of age-matched healthy control subjects. We also examined whether treatment with a brain-penetrating ACE inhibitor[3] can alter CSF ACE activity in patients with mild to moderate AD.

Methods. We registered 90 patients (mean age 72.6 ± 1.8 [SE] years) who had undergone evaluations for memory disturbance at the Tohoku University Hospital Outpatient Clinic on Dementia in January 2003. Clinical assessments by geriatricians and neuropsychological examinations, including Mini-Mental State Examination (MMSE) and Wechsler Memory Scale–Revised, were performed for all subjects, as described previously.[4] Our established criteria[4] based on the current consensus[5] were used for a diagnosis of progressive MCI and AD-converted MCI. In detail, 28 individuals fulfilled the criteria for a diagnosis of amnestic MCI[5] at the time of the CSF examination. Fourteen of 28 patients (male/female ratio, 6:8) progressed over time. They lived independently during a 2-year follow-up and were considered as having progressive MCI.[4] Six of 28 subjects (male/female ratio, 3:3) showed clinical progression that warranted a diagnosis of dementia and ultimately met the National Institute for Neurological and Communication Disorders and Stroke/Alzheimer's Disease and Related Disorders (NINCDS-ADRDA) diagnostic criteria for AD[6] and were categorized as having AD-converted MCI.[4] In the current study, we enrolled both patients with progressive MCI and those with AD-converted MCI as the MCI group. A diagnosis of AD was made in accordance with the NINCDS-ADRDA criteria.[6] As a consequence, 20 patients (mean age 72.9 ± 1.2 years, 9 men) fulfilled the diagnostic criteria for progressive MCI and AD-converted MCI (MCI group), 34 patients (mean age 73.7 ± 1.2 years, 14 men) were diagnosed as having AD (AD group), and 20 subjects (mean age 71.4 ± 1.7 years, 9 men) were found to be cognitively normal (normal group). Four (20%) of the 20 patients in the MCI group and 6 (18%) in the AD group received a 5-mg daily dose of donepezil hydrochloride at study entry.

We collected CFS samples from each subject at baseline investigation. CSF samples were obtained by lumbar puncture before lunch between 1:00 PM and 2:00 PM in all subjects and were kept at −80 °C. ACE activity in the CSF was measured by the colorimetric method, which is based upon colorimetry of the quinoneimine dye produced from the substrate *p*-hydroxyhippuryl-L-histidyl-L-leucine by action of this enzyme, as described in detail previously.[7] CSF ACE assay was performed in duplicate in all samples. As there was no significant difference between the measurements, the mean value was adopted in the following analysis.

In 7 of 34 patients with AD who had hypertension, CSF was collected again after oral administration of a brain-penetrating ACE inhibitor, perindopril (2 mg/day)[3] for 1 month, and measurement of ACE activity in the CSF was repeated in these subjects. CSF collection was performed 5 hours after taking the last dose of perindopril in seven patients in the perindopril study. This study was approved by the Tohoku University Ethical Committee, and informed consent was obtained from participants and their caregivers before the study.

For group comparisons of clinical and biochemical variables, one-way analysis of variance (ANOVA) was done, followed by Tukey–Kramer multiple comparison test. Relationships between CSF ACE activity and MMSE scores were examined using a linear regression analysis. Correlations between two variables were tested by the *t* statistic. Significance was taken as $p < 0.05$.

Results. The mean baseline MMSE value was 18.9 ± 0.7 (SE) in the AD group, 25.0 ± 0.4 in the MCI group, and 28.5 ± 0.3 in the normal group. CSF ACE activity was elevated in the MCI group (0.32 [mean] ± 0.03 [SE] IU/L, n = 20) vs the control group (0.17 ± 0.02 IU/L, n = 20, $p < 0.0001$). There was also an increase in the mean CSF ACE activity in the AD group (0.24 ± 0.01 IU/L,

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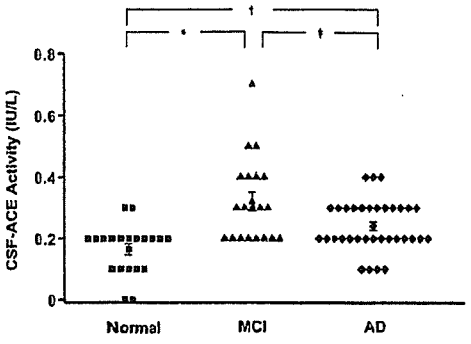

*Figure. Individual CSF angiotensin-converting enzyme (ACE) activity (IU/L) in cognitively normal subjects (n = 20) and patients with mild cognitive impairment (MCI; n = 20) or Alzheimer disease (AD; n = 34). A significant increase in CSF ACE activity was observed in patients with MCI (filled triangle) and AD (filled diamond) vs normal subjects (filled square). A difference in CSF ACE activity was also found between patients with MCI vs AD. *$p < 0.0001$, †$p = 0.0219$, ‡$p = 0.0170$.*

n = 34, $p = 0.0219$) vs the control group (figure). Furthermore, CSF ACE activity in the MCI group was elevated vs the AD group ($p = 0.0170$) (figure). There was no significant difference in the CSF ACE activity between the patients with and those without cholinesterase inhibitors. Elevated CSF ACE levels were significantly associated with lower baseline MMSE scores when normal subjects and patients with MCI were combined for analysis and also when normal subjects and patients with AD were combined for analysis. However, in all subjects, there was no significant correlation between CSF ACE levels and baseline MMSE scores (figure E-1 on the *Neurology* Web site at www.neurology.org).

The brain-penetrating ACE inhibitor perindopril inhibited CSF ACE activity in patients with AD after 1 month of treatment (0.24 ± 0.02 [before] vs 0.13 ± 0.03 IU/L [after], n = 7, $p = 0.038$). The mean 1-year decline in MMSE scores during a 2-year follow-up in patients with AD treated with perindopril was lower vs patients with AD without perindopril treatment (−0.7/year in patients with perindopril vs −2.2/year in those without perindopril, $p < 0.01$).

Discussion. In the current study, we have shown a substantial elevation in CSF ACE activity in patients with progressive and AD-converted MCI and mild to moderate AD as compared with age-matched healthy control subjects. MCI is a transitional state between the cognitive changes of normal aging and early AD.[5] A previous neuropathologic study described that ACE is overexpressed in the hippocampus, frontal cortex, and caudate nucleus in patients with AD.[2] The increased ACE activity in CSF in this study might reflect an increase in the brain regional ACE activity in MCI and AD, especially in MCI.

The role of ACE in the pathophysiology of AD remains controversial. Some researchers reported that ACE degrades amyloid β-protein in vitro, whereas others reported an ACE inhibitor has no effect on the degradation of amyloid β-protein in vivo.[1,3] There is also a possibility that increased CNS ACE activity might be involved in the cerebrovascular pathology in AD. It is reported that the enhanced formation of angiotensin II by increased ACE activity would result in an increased inhibitory effect of angiotensin II on acetylcholine release.[2] We have previously shown that brain-penetrating ACE inhibitors can reduce the incidence of AD in elderly hypertensive patients and also shown that a brain-penetrating ACE inhibitor inhibits the decline of cognitive function in patients with mild to moderate AD.[3] Furthermore, in this study, we showed that a brain-penetrating ACE inhibitor can significantly inhibit CSF ACE activity in patients with mild to moderate AD. We therefore assume that an increased CNS ACE activity might be involved in the progression of AD, although the precise mechanism remains unknown.

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Disclosure: The authors report no conflicts of interest.

Supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture (No.17590591) of the Japanese government.

Received November 1, 2005. Accepted in final form June 16, 2006.

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Acknowledgment

The authors thank Mr. Grant Crittenden for the English correction of this manuscript.

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VIDEO Action myoclonus–renal failure syndrome: A cause for worsening tremor in young adults

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Action myoclonus–renal failure syndrome (AMRF) is an autosomal recessive disorder first described in 4 French Canadian patients, followed by a recent description of 15 cases from various countries.[1,2] The condition independently affects the kidney, with focal glomerulosclerosis causing renal failure and the brain causing progressive myoclonus epilepsy (PME) or progressive myoclonic ataxia (PMA).[3,4] Tremor is often an early feature. The diagnosis of tremor and myoclonus in patients with severe renal disease is challenging. Here we highlight the evolution of tremor in this syndrome in two new cases and emphasize problems in early diagnosis.

Case reports. Case 1. Case 1 is an Australian man of English ancestry with unrelated parents (figure). He was well until age 20 when end-stage renal failure developed, after a 3-month history of anorexia, nausea, and lethargy. Renal ultrasound demonstrated small kidneys; the etiology of renal failure was not established and renal biopsy not performed. He was treated with dialysis.

At age 22 he reported a mild, intermittent upper limb tremor occurring only with action and exacerbated by stress that had been present for 2.5 years. A very mild fine upper limb postural

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