の比率はほぼ同等であったが，mRS 6(死亡)の比率は，全脳卒中で3分の1，脳梗塞で2分の1，脳出血で4分の1と低率であり，特に脳出血での比率が大きく解離していた．

考　察

2006年4月の診療報酬改訂において，SCU加算が新設されたが，脳卒中専門病棟(病床)と多職種からなる専任の脳卒中チームが配置されているSCUの国内における普及率は低く，SCU加算を申請している施設は勿論のこと，SCUを標榜している施設も増加していない．また，SCUを標榜している施設の中には，SCU加算の施設要件を満たさないもののSCUの機能を十分備えている施設から，単にICUに脳卒中患者のベッドを数床確保しただけのものをSCUと呼ぶ施設があるなど，その機能は標準化されておらず，提供されている診療の質を評価する方法すら確立していないのが現状である．2005年10月のアルテプラーゼ静注療法承認後，脳卒中専門病棟(病床)を運営する施設は，8.3%から17.4%に倍増したと推定されている[8]が，専属の脳卒中チームの人員配置基準が厳しいためにSCU加算を実際に申請している施設は限定され，アルテプラーゼ静注療法の実施施設の本格的な整備と普及を念頭に入れた医療政策的取り組み(SCU加算の導入)は必ずしも進展していない．SCUの普及率を上げるためには，施設要件(人員基準)の緩和が必要と考えられる．

2006年に峰松らの研究班によって行われたアンケート調査によれば[9]，急性期脳卒中患者を受け入れていると回答した1,480施設の脳卒中急性期診療体制は，SU(急性期集中治療)型：0.9%，SU(急性期治療)＋リハビリテーション型：7.4%，神経疾患一般の診療とリハビリテーション型：20.5%，移動脳卒中チーム型：4.7%，一般病棟混在型：63.8%，その他：2.7%に分類され，SUを設置していた施設は8.3%に留まっていた．63.8%の施設が一般病棟で脳卒中の急性期治療を行い，専属の脳卒中チームを持たない一般病棟混在型の体制をとっていた．また，夜間・休日には脳卒中を専門としない医師が初期対応する施設が78.4%にも及んだとしている．アルテプラーゼ静注療法が保険診療として承認されている現在においては，夜間・休日を含めて，脳卒中に精通した専門の医師が初診時から対応する脳卒中診療体制を一刻も早く構築する必要がある．また，脳卒中の転帰を改善する急性期リハビリテーションが十分に実施できる体制を整備することも重要な課題である．

欧米とは異なる医療体制下にあるわが国のSCUが有効に機能しているかどうかに関しては，これまで全くデータが無かったが，同研究班が行った多施設共同前向き観察研究ではじめてSCUの有用性が確認された．すなわち，全国117施設から登録された症例のうち，3カ月目の追跡調査が終了した2,585例を対象として，SU治療(急性期型および急性期＋リハビリ型)とそれ以外に分けて，28日目と3カ月目の転帰をlogistic regression modelを用いて解析したところ，SU治療は，年齢，男性，入院前mRS，入院時NIHSSとともに，3カ月目の転帰良好(mRS：0-2)と有意に関連していたとされている．

当院のSCUに入室した患者の入院時NIHSSは，全体では6.3 ± 7.0と比較的軽症で，脳梗塞では5.4 ± 6.4と軽症例が多く，脳出血では9.8 ± 7.6と比較的中等症が多かった．当院のSCUでは比較的軽症/中等症の脳卒中患者が診療されていた．SCU在室日数は，SCU入室患者全体，脳梗塞，脳出血とも平均8日間であったが，在院日数は，前半(2007年7月まで)では61.1 ± 68.6日，後半(2007年8月から)では52.5 ± 51.8日と後半で短縮傾向が見られ，早期に自立できる患者が増えた可能性が考えられる．SCUへの入室継続日数は最大14日とされているが，当院でのSCU在室日数は，在院日数に比較して短期間であることが明らかであった．当院で治療を受ける急性期の全脳卒中患者のうち，SCUで加療される症例が約半数で，平均在室日数が8日間と比較的短いことからSCUの適切な病床数については再検討する余地があるかもしれない．しかしながら，SCUの適切な病床数に関してはSCUが各施設での脳卒中診療においてどのような役割を果たしているかを考慮して設定する必要がある．当院では，ICUとSCUとを一体的に運用し，SCUの機能を急性期リハビリテーションにより特化させており，急性期リハビリテーションの効果が期待されない軽症例や遷延性意識障害を伴う重症例はほとんどSCUに入室していないのが現状である．当院でのSCUの病床数についてはSCU加算の施設要件に加えて急性期リハビリテーションの必要度を考慮する必要がある．

当院のSCUに入室した患者の転帰は，同一期間に入院した全脳卒中患者の転帰に比較して，全脳卒中，脳梗塞，脳出血のいずれもmRS 0-2の比率はほ

ぼ同等であったが，mRS 6(死亡)の比率は，全脳卒中で3分の1，脳梗塞で2分の1，脳出血で4分の1と低率で，脳梗塞と脳出血で著しく異なっていた．このような比較データからは，SCUに入室した患者の退院時の転帰が改善したかどうかは正しく判定できないが，急性期リハビリテーションが期待されない軽症例や遷延性意識障害を伴う重症例はほとんどSCUに入室していない状況を考慮すれば，SCUに入室した患者の退院時mRS 0-2が脳梗塞で60%，脳出血で40%に達したことは，自立レベルとなる脳梗塞，脳出血が軽症例並みに増えているとも考えられる．このことから，急性期リハビリテーションが患者の転帰に一定の効果を上げていることが示唆される．一方，SCUに入室した患者の退院時のmRS 6(死亡)は脳梗塞で4%，脳出血で5%にとどまり，脳梗塞では同一期間に入院した脳梗塞のmRS 6(死亡)の頻度の2分の1まで減少し，脳出血では同一期間に入院した脳出血のmRS 6(死亡)の4分の1まで減少していた．このことは，発症早期に多くの重症脳卒中患者がSCUでの管理に至らずに死亡していること反映し，特に脳出血で顕著であることを示唆している．

アルテプラーゼ静注療法が保険診療として承認されて4年目に入ったが，その実施件数は急性期脳梗塞の2-3%にとどまっており[10]，国内における脳卒中の救急医療体制が十分機能していない現実が明らかになっている．脳卒中の医療体制の構築は，2008年度から開始された都道府県の医療計画でも重点事業の一つとされ，前方連携(救急医療としてのネットワーク構築)，および後方連携(地域完結的医療としてのネットワーク構築)からなる地域連携医療のモデルとして取り組まれているが，必ずしも進展していない．特に，前方連携では，脳卒中救急医療を24時間担うことのできる施設を脳卒中センターとして各地域に整備することが必要である．また，脳卒中センターの施設機能として，SCUが必要であることは言うまでもないが，都道府県地域医療計画や地域連携医療の進展の観点から，施設要件(人員基準)の緩和を含めて，早急に対応する必要がある．脳卒中の転帰に及ぼすSCUの効果に関しては，今後も多施設共同の臨床研究が必要と考えられる．

結　論

中村記念病院では，ICUとSCUが一体的に運用され，急性期病棟内のSCUでは比較的軽症/中等症の脳卒中患者が診療されていた．SCU導入後，脳卒中患者の在院日数は短縮傾向にあり，その転帰は改善していると考えられた．国内におけるSCUの普及と脳卒中センターの整備は極めて重要な政策課題であり都道府県地域医療計画や地域連携医療の進展の観点から，施設要件(人員基準)の緩和を含めて，早急に対応する必要がある．脳卒中の転帰に及ぼすSCUの効果に関しては，今後も多施設共同の臨床研究が必要と考えられる．

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Abstract

Present state of stroke care unit in stroke center of Nakamura Memorial Hospital

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Stroke unit (SU) with both stroke patient's ward (or beds) and stroke team could significantly improve the outcome by decreasing mortality and increasing patients back to home with independent life in former clinical studies. In Japan, an additional payment to stroke care unit (SCU) which has the same definition as SU was introduced in public health insurance system from May, 2006. In our hospital, SCU with 6 beds and specific stroke team were organized in 2 acute patients wards composed with total 41 beds and registered from Jun, 2006. SCU was integrated with a special ward such as intensive care unit (ICU) with 14 beds for managing stroke patients with conscious disturbance or respiratory distress, IV thrombolytic therapy, and perioperative management of acute surgical or endovascular treatments. Main function of SCU was set up for acute physical rehabilitation, prevention of complications such as pneumonia, and pharmacotherapy for secondary prevention. From May, 2006 to Nov, 2008, 1,166 patients were managed in SCU. NIHSS of patients at admission was 6.3 ± 7.0 in all stroke patients, 5.4 ± 6.4 in patients with cerebral infarction, and 9.8 ± 7.6 in patients with cerebral hemorrhage. Admitted period in SCU was 8.1 ± 3.5 days in all patients, 8.1 ± 3.6 days in patients with cerebral infarction, 8.3 ± 3.2 days in patients with cerebral hemorrhage. Total admitted periods in hospital was 61.1 ± 68.6 days in the first half of the investigation period (to July, 2007) and 52.5 ± 51.8 days in the second half of the investigation period (from Aug, 2007). The outcome (mRS) at discharge was 56% in mRS 0–2, 40% in mRS 3–5, 4% in mRS 6 (death). In our stroke center, patients with mild to moderate severity were managed in SCU. After the introduction of SCU, shortening of total admitted periods in hospital and improving tendency of the outcome was observed. Stroke center equipped with SCU should be promptly organized nationwide corresponding to stroke emergency.

(Jpn J Stroke 31: 461–466, 2009)

Key words：stroke care unit, stroke patient's ward, stroke team, stroke center, outcome

連載

知って得するワンポイントアドバイス

一過性脳虚血発作患者における拡散強調画像の意義と落とし穴

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はじめに

一過性脳虚血発作（transient ischemic attack：TIA）は脳梗塞の前兆として広く知られているが，その診断要素として，従来から唱えられている症状持続時間に加え，MRI拡散強調画像でとらえられる新鮮脳梗塞巣の有無が，重要な意味をもつようになってきた．本稿においては，TIA患者におけるMRI拡散強調画像の意義とピットフォールについて述べる．

TIA診断における拡散強調画像の意義

TIAは，1990年に発表されたNINDS（National Institute of Neurological Disorders and Stroke）のCVD-Ⅲ分類[1]では，「虚血が原因と考えられる局在性脳機能障害による発作が24時間以内に消失するもの」と定義されているが，頭部CT，MRIでの病巣の有無については言及されていなかった．近年，MRIにおける拡散強調画像（diffusion weighted image：DWI）により，新鮮梗塞巣が発症早期から正確に診断されるようになり，2002年に米国のTIA Working Groupが，脳局所症状が1時間以内に消失し，画像上梗塞巣がないものをTIAの新たな定義として発表した[2]．以後，従来の定義に基づいた24時間以内に症状が消失した症例においても，症状の持続時間に比例して拡散強調画像での新鮮梗塞の陽性率が高まり，梗塞巣を有する場合，脳梗塞発症のリスクが高まるとした報告が散見される[3)4)]．その後，2009年にAHA（American Heart Association）/ASA（American Stroke Association）Stroke Councilは，TIAの定義を「局在性の脳，脊髄，網膜の虚血が原因で生じる一過性の神経機能障害で新鮮脳梗塞のないもの」としており，症状の持続時間を問わないものとなっている[4]．TIAの定義は今なお混沌としているが，TIA診断における拡散強調画像を用いた新鮮梗塞巣検出の重要性は，もはや論を俟たない．

TIAにおけるMRI拡散強調画像のピットフォール

徳島大学脳卒中センターにおいては，1999年の開設以来一貫して，脳卒中の初期診断として3テスラMRIを用いてきた．3テスラMRIの使用により，短時間での診断が可能となり，微小な新鮮脳梗塞をより鋭敏にとらえることができるようになった．さらに，従来の定義に当てはまる24時間以内に脳虚血症状が消失するTIA症例においても，新鮮梗塞を有する例が多く存在することが経験され，これらを脳梗塞とみなして治療してきた．一方，初回のMRI拡散強調画像で新鮮

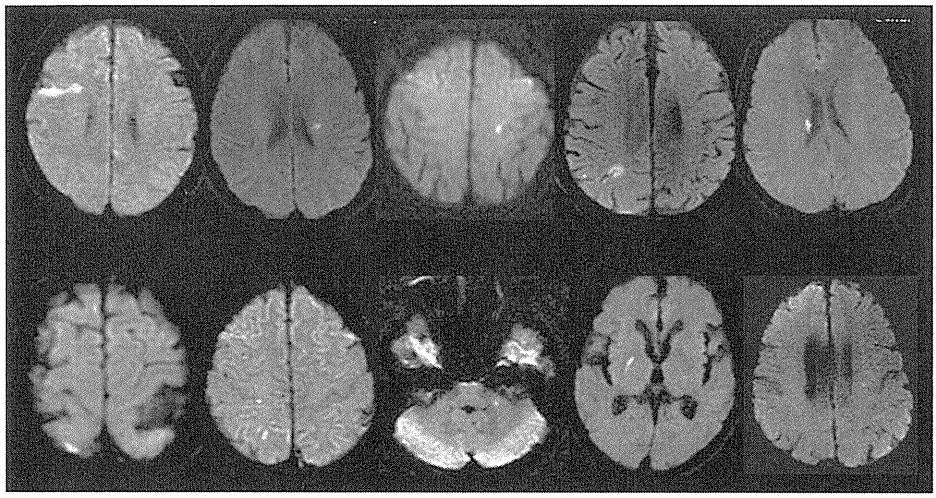

図1　再検査MRIにより脳梗塞が検出された症例の拡散強調画像

梗塞巣がみられないTIA症例についても，入院の上，経時的にMRI検査を行うと，新たに新鮮梗塞巣が出現する症例に遭遇するようになり，初回のみのMRIではとらえられない，より完成型脳卒中に近いTIAサブグループが存在することが明らかとなってきた．

徳島大学脳卒中センターにおいて，2009年8月から2010年6月にTIAと診断され，拡散強調画像を含めた頭部MRIが撮像された症例のうち，初回拡散強調画像にて明らかな異常信号域を認めなかった症例は27例であった．いずれの症例も24時間前後でMRIの再検査を行ったところ，うち10例で新鮮梗塞巣が拡散強調画像で検出された．再検査での梗塞はおしなべて小さなサイズであったが，出現部位はさまざまであり，病因は単一ではないと考えられる（図1）．これらは，再検査で新鮮梗塞巣が出現しなかった群と比較し，発症時のABCD²スコアが優位に高かった（表1）．また，TIAの症状持続時間が1時間を超えるものは，1時間以内のものに比べ，拡散強調画像での陽性率が優位に高かった（図2）．TIAのリスク評価，症状持続時間は拡散強調画像陽性率と相関しており，TIA初診時の予後予測の指標となり得ると考えられる．

TIAにおける初診時MRI拡散強調画像が陰性であったものが，追跡のMRIで梗塞巣が検出される理由としていくつか考えられる．ラクナ梗塞，微小塞栓など小さな梗塞体積によるもの，脳幹梗塞にみられる梗塞出現の遅延，発症から初回MRIまでの時間が短いもの，TIAの再発，MRI装置に起因するもの（磁化率効果，スライスギャップ厚，インプラントなどによるアーチファクト）などである．

表1　再検査MRIでの拡散強調画像陽性の有無とABCD²スコアの患者分布

ABCD²スコア	DWI（＋）（n＝10）	DWI（－）（n＝17）
7	0　(0%)	0　(0%)
6	5　(50.0%)	1　(5.9%)
5	1　(10.0%)	3　(17.6%)
4	2　(20.0%)	8　(47.1%)
3	2　(20.0%)	4　(23.5%)
2	0　(0%)	1　(5.9%)
1	0　(0%)	0　(0%)
0	0　(0%)	0　(0%)

これらの結果を踏まえ，徳島大学脳卒中センターにおいては，たとえMRI拡散強調画像で梗塞巣が出現していなくとも，症状からTIAが強く疑われる場合は，原則入院の上，24時間前後の間隔を空けてMRI再検査を行っている．

Diffusion negative TIAの中に脳梗塞が潜んでいるかもしれないことを，常に明記する必要がある．

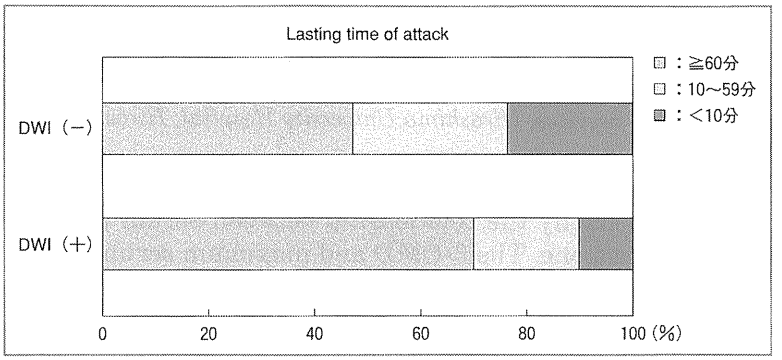

図2　再検査 MRI での拡散強調画像陽性の有無と症状持続時間

まとめ

TIA 患者の MRI 拡散強調画像は，初回検査時に陰性であったとしても，経過の MRI で新鮮梗塞巣がとらえられることがある．繰り返し MRI 検査を行うことにより，脳梗塞へ移行しやすい high risk TIA を見逃さないことが大事である．

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Relationship Between 3-O-methyldopa and the Clinical Effects of Entacapone in Advanced Parkinson's Disease

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ABSTRACT

The aim of this study is to clarify the relationship between serum 3-O-methyldopa (3-OMD) and the clinical effects of entacapone. The 3-OMD and maximum serum concentration (Cmax) of levodopa were measured in 21 Parkinson's Disease patients who took 100 mg levodopa / dopa decarboxylase inhibitor. After the administration of entacapone, the 3-OMD concentration and percentage of "on" time during waking hours (% of "on" time) were studied for 8 weeks. The 3-OMD concentration was reduced by 34%, and the increase in % of "on" time was 28% at the 8th week compared with baseline. We defined the COMT-index as [baseline 3-OMD concentration] / [levodopa Cmax when 100 mg levodopa was administered alone]. The COMT-index was significantly correlated with the increase in % of "on" time at the 8th week. In conclusion, the measurement of baseline 3-OMD and levodopa pharmacokinetics is useful for predicting the clinical effects of entacapone.

Key words: *Parkinson's disease, 3-OMD, Entacapone, Levodopa AUC*

Parkinson's disease (PD) is caused by the degeneration of nigrostriatal neurons, resulting in a deficiency of dopamine in the central nervous system (CNS). As dopamine does not readily cross the blood-brain barrier, the dopamine prodrug levodopa and dopamine agonists are mainly used to treat PD. Despite the development of dopamine agonists, levodopa is still the most effective treatment for PD[15)]. However, long-term levodopa treatment causes motor complications such as wearing-off and dyskinesia[4)]. These motor complications occur with an annual incidence of about 10% among PD patients[1)]. Furthermore, the wearing-off phenomenon impairs the quality of life of Parkinson's disease patients[6)]. Therefore, it is important that it is managed.

Levodopa is metabolized to dopamine by dopa decarboxylase and to 3-O-methyldopa (3-OMD) by catechol-O-methyltransferase (COMT) in the periphery. When levodopa is administered together with dopa decarboxylase inhibitor (DCI), levodopa availability in the CNS is increased[3)], and the COMT pathway of levodopa metabolism becomes predominant in the periphery[4)]. While the half-life of levodopa is approximately 1 hr, the half-life of 3-OMD is about 15 hr, which leads to the accumulation of 3-OMD in the plasma and brain under chronic levodopa treatment[10)]. Like levodopa, 3-OMD is transported across the blood-brain barrier by the large neutral amino acid (LNAA) transporter and consequently competes with levodopa for uptake into the brain[14)]. Moreover, a recent study indicated that 3-OMD damages neuronal cells[11)]. Thus, it is assumed that the serum concentration of 3-OMD plays an important role in levodopa-treated PD patients. Entacapone, a peripheral COMT inhibitor, prolongs the retention time of levodopa in the plasma[14)] and is used in PD patients with the wearing-off phenomenon. However, the determinants of serum 3-OMD concentration and the relationship between motor symptoms and serum 3-OMD concentration are not fully understood. Since entacapone was approved for use in Japan in April 2007, there is little data about its clinical effects and the relationship between its clinical effects and serum 3-OMD concentration in Japanese patients. Furthermore, there is no study about predictive factors for its clinical effect. The aims of this study are: first, to clarify the factors that determine the serum 3-OMD concentration; second, to investigate the change in serum 3-OMD concentration that occurs in Japanese PD patients administered

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entacapone; and third, to clarify the relationship between serum 3-OMD concentration and the clinical effects of entacapone.

METHODS

Patients

The study subjects were PD patients who visited our hospital from August 2007 to September 2008. The study was conducted according to the Declaration of Helsinki. The patients were given oral and written information about the study and gave their written consent.

All patients fulfilled the clinical diagnostic criteria of the UK Brain Bank for PD[8] and exhibited signs of wearing-off motor fluctuations. All patients were taking levodopa and had shown a positive response to levodopa treatment. Patients who had previously received entacapone or were suffering from dementia were excluded.

The clinical data collected included age, sex, disease duration, duration of therapy, duration of wearing-off, antiparkinsonian drug doses, and levodopa equivalent daily dose (LEDD). LEDD was calculated according to a previous report[9].

Study Design

1. First study (pharmacokinetics of the first administration of entacapone)

In order to assess the pharmacokinetics of levodopa, the patients took a tablet orally containing 100 mg levodopa and DCI (10 mg carbidopa or 25 mg benserazide) in the morning following an overnight fast. Blood specimens were then collected through an intravenous catheter at 0, 15, 30, 45, 60, 90, 120, and 180 min after the levodopa/DCI administration. The serum levodopa and 3-OMD concentrations were measured. The area under the concentration-time curve (AUC) of levodopa was calculated by the trapezoid method up to 180 min, and the maximum serum concentration (Cmax) of levodopa was calculated using the one compartment model.

The pharmacokinetic evaluation was performed the next day using the same method, but 100 mg of entacapone was now added to the regimen.

2. Second study (clinical effects and pharmacokinetics during long term entacapone therapy)

After the first study, the same patients were administered one 100 mg entacapone tablet orally with each dose of their levodopa/DCI preparation for 8 weeks. The patients completed an "on/off" self-rating diary on a daily basis at the baseline and during the 2nd, 4th, 6th, and 8th weeks. For each 30-min period between 05:00 and 24:00, the patients rated their motor physical condition by choosing: "on" (good mobility), "off" (worse to bad mobility), or asleep. The mean "on" time duration of at least 3 days was calculated from the self-rating diary. When the "on" time duration was not prolonged by more than 30 min at the 4th week, 200 mg entacapone was administered with each dose of their levodopa/DCI preparation. The doses of other antiparkinsonian drugs were not changed throughout the study. The levodopa dose was reduced when a patient's symptoms necessitated it. Unified Parkinson's Disease Rating Scale (UPDRS) motor scores were assessed, and serum 3-OMD concentrations were measured at the baseline and in the 2nd, 4th, 6th, and 8th weeks.

Serum analysis

The serum levodopa and 3-OMD concentrations were determined by the high-performance liquid chromatography-electrochemical detection method[2] with minor modifications. In brief, 100 μl aliquot serum samples were processed by adding 100 μl of 1 M perchloric acid and 20 μl of 50 μM dihydroxybenzylamine hydrobromide as an internal standard. Then, the precipitated proteins were removed by centrifugation at 13,000 rpm for 5 min. The resultant supernatants were applied to the chromatographic system.

The chromatographic system consisted of a LC-10AT pump, a CTO-10A column oven, and a DGU-14A degasser (Shimadzu, Kyoto, Japan). The system was connected to an ECD-100 electrochemical detector (Eicom, Kyoto, Japan). The voltage was set at 750 mV vs Ag/AgCl, and chromatographic separation was performed using an EICOMPAK SC-5ODS column (Eicom, Kyoto, Japan) with a PC-03 guard column (Eicom, Kyoto, Japan) in a column oven. The mobile phase (per liter) contained 150 ml of methanol, 850 ml of citrate-acetate buffer, 400 mg of sodium octane sulfate, and 20 mg of EDTA-2Na, pumped at a fixed flow rate of 0.5 ml/min. The citrate-acetate buffer consisted of 0.017 M of sodium acetate and 0.083 M of citric acid monohydrate, and the pH of the buffer was adjusted to 2.8 with perchloric acid. Levodopa, 3-OMD, and dihydroxybenzylamine were eluted at 5.2, 11.8, and 7.2 min, respectively.

Statistical Methods

Statistical analysis was performed using a nonparametric method (Wilcoxon signed-rank test, Spearman's rank correlation and Friedman test), and statistical significance was set at $p < 0.05$. Calculations were performed using the JMP 5.0.1J software (SAS Institute Inc., Cary, N.C., USA) and SPSS 16.0J for Windows (SPSS Inc, Chicago).

RESULTS

Patients

Twenty-one advanced PD patients, comprising 9 men and 12 women, were recruited. The characteristics of the patients are shown in Table. At the baseline, 16 patients took levodopa/carbidopa and

5 patients took levodopa/benserazide preparation. The concomitant antiparkinsonian medications included anticholinergics (n = 6), selegiline (n = 13), dopamine agonists (n = 19), amantadine (n = 6), and droxidopa (n = 3). The median "on" time duration of these patients was 7.7 hr and the median percentage of "on" time during waking hours (% of "on" time) was 48%.

Table: Patient baseline characteristics (n=21)

Age (yrs)	68	(52 - 80)
Sex (n)		
Men	9	
Women	12	
Duration of PD (yrs)	12	(5 - 19)
Duration of wearing-off (yrs)	2	(1 - 10)
Duration of antiparkinsonian medication (yrs)	11	(3 - 18)
"on" time duration (hrs)	7.7	(2.2 - 10.3)
% of "on" time during waking hours (%)	48	(12 - 61)
Hoehn and Yahr stage at "on" phase	3	(1 - 5)
UPDRS motor score at "on" phase	24.5	(9 - 42)
Daily dose of levodopa/DCI (mg)	400	(250 - 625)
Dosing frequency of levodopa/DCI	4	(3 - 8)
Total LEDD (mg)	840	(467.5 - 1346)

All data are shown as median (minimum - maximum).
UPDRS : unified Parkinson's disease rating scale
DCI : dopa decarboxylase inhibitor
LEDD : levodopa equivalent daily dosage

First study

The baseline serum 3-OMD concentration was positively correlated with duration of therapy (p = 0.045), levodopa AUC (p = 0.001) and levodopa Cmax (p = 0.002) in the absence of entacapone (Fig. 1). However, the baseline serum 3-OMD concentration was not correlated with age, sex, duration of wearing-off, the daily levodopa dosage, LEDD, Hoehn & Yahr stage, UPDRS motor score, the "on" time duration, nor % of "on" time at the baseline.

The AUC of levodopa was significantly increased by 22% (median) after the first entacapone administration compared with the control value for levodopa/DCI alone (p < 0.001).

Second study

After the initiation of entacapone administration, 3 patients withdrew from the study due to study protocol deviation (2 patients did not complete the "on/off" self-rating diary, and another patient stopped taking entacapone of her own volition because of dyskinesia). The remaining 18 patients completed the study. The daily levodopa dose was not changed at any point during the study period. In 1 patient (5.6%), the dose of entacapone was increased to 200 mg because the "on" time duration was not prolonged by more than 0.5 hr at the 4th week.

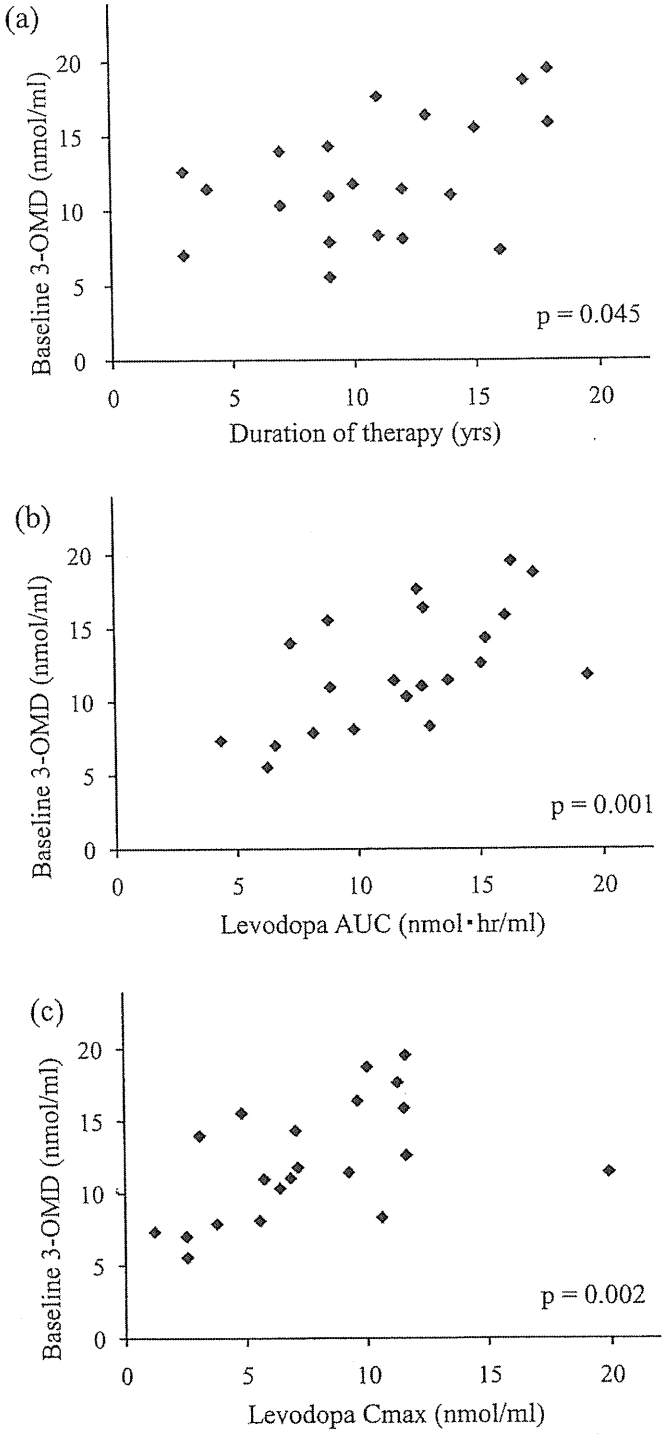

Fig. 1. The baseline serum 3-OMD concentration was positively correlated with (a) the duration of therapy (p = 0.045), (b) levodopa AUC (p = 0.001), and (c) levodopa Cmax (p = 0.002). (Spearman's rank correlation)

The median serum 3-OMD concentration, the UPDRS motor score and median % of "on" time was significantly decreased with entacapone (Friedman test, p <0.001, respectively). The median serum 3-OMD concentration was significantly decreased from the 2nd week to the 8th week and was decreased by 3.5 nmol/ml (34%) at the 8th week (Wilcoxon's signed rank test, p < 0.001) (Fig. 2a). The UPDRS motor score was also

significantly decreased by 7 points (median) at the 8th week (Wilcoxon's signed rank test, $p < 0.001$) (Fig. 2b) compared with the baseline. The median "on" time duration was significantly improved by 4.4 hr at the 8th week (Wilcoxon's signed rank test, $p < 0.001$) and the median % of "on" time was also significantly improved by 28% at the 8th week (Wilcoxon's signed rank test, $p < 0.001$) (Fig. 2c) compared with the baseline.

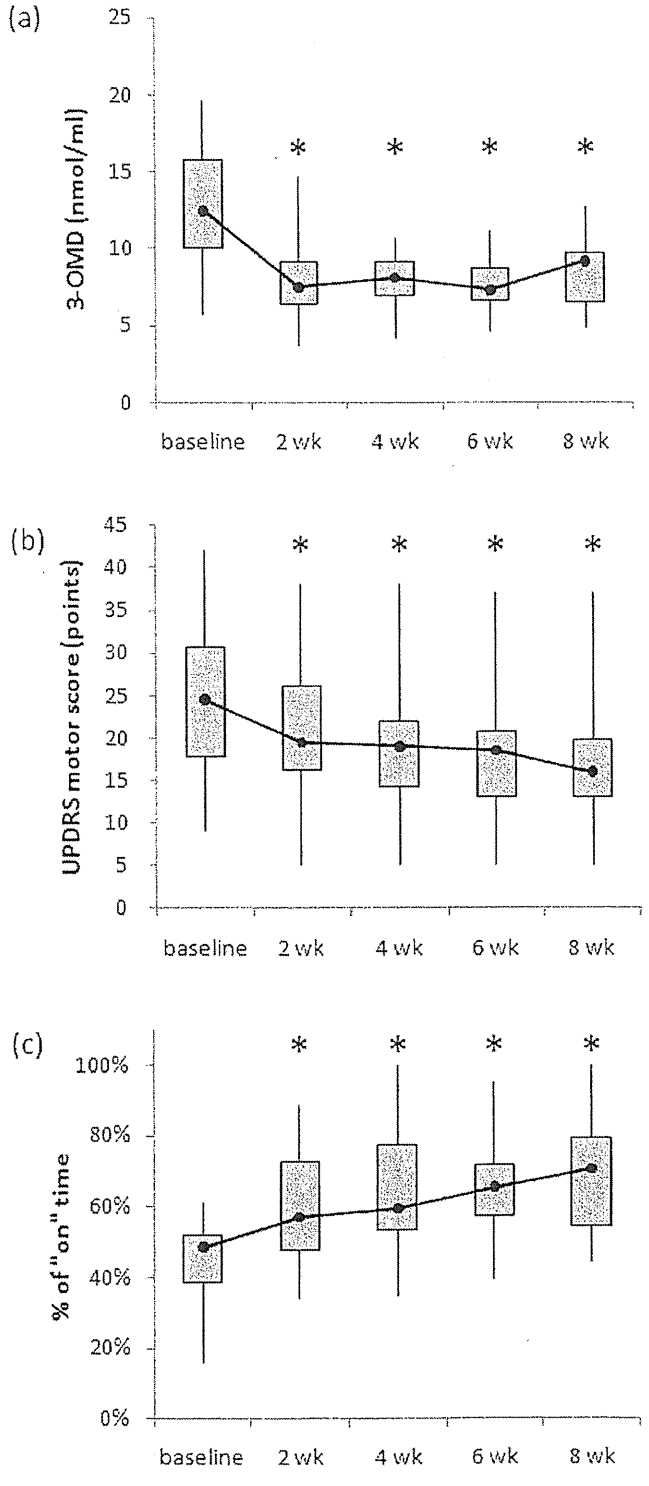

Fig. 2. Changes in (a) serum 3-OMD, (b) UPDRS motor score, and (c) % of "on" time from the baseline to the 8th week after entacapone therapy (n=18).
* Wilcoxon's signed rank test, $p < 0.001$, compared with the baseline.

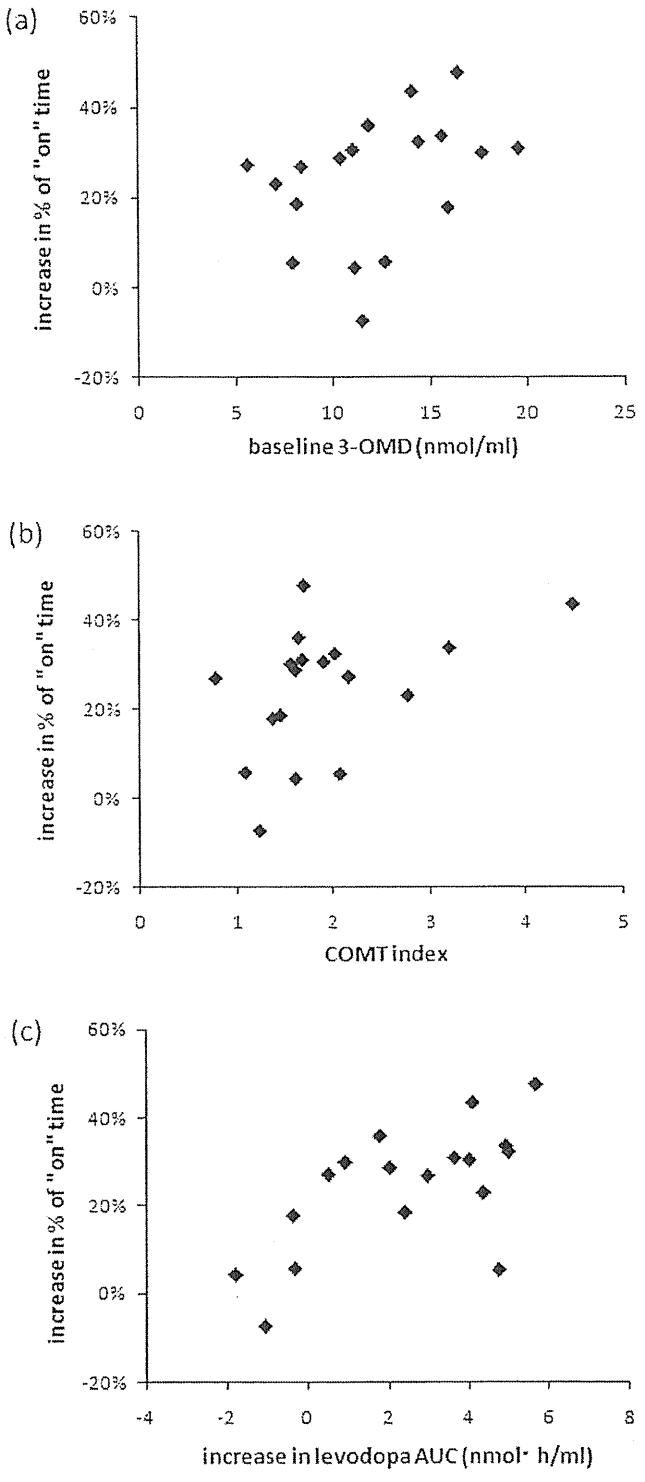

Fig. 3. (a) Association between the increase in % of "on" time and serum 3-OMD concentration. (p=0.053)
(b) Association between the increase in % of "on" time and COMT index. (p=0.027)
(c) Association between the increase in % of "on" time and the change in levodopa AUC. (p=0.006)
Evaluation at the 8th week (n=18).
(Spearman's rank correlation)

The baseline serum 3-OMD concentration tended to be correlated with the increase in % of "on" time at the 8th week ($p = 0.053$) (Fig. 3a). Neither the rate of decline in the serum 3-OMD concentration nor the reduction in the serum 3-OMD concentration was correlated with the increase in % of "on" time. None of age, sex, disease duration, duration of therapy, duration of wearing-off, LEDD, Hoehn & Yahr stage, or UPDRS motor score was correlated with the increase in % of "on" time.

Since levodopa is metabolized to 3-OMD by COMT, the concentration of 3-OMD is determined by COMT activity and the amount of levodopa absorbed. The ratio of the serum 3-OMD concentration to the levodopa concentration might reflect COMT activity more correctly than serum 3-OMD concentration. Thus, we defined the COMT-index as [baseline 3-OMD concentration] / [levodopa Cmax when 100 mg levodopa was administered alone]. The COMT-index was significantly correlated with the increase in % of "on" time at the 8th week ($p = 0.027$) (Fig. 3b).

The increase in levodopa AUC after the first entacapone administration was positively correlated with the increase in % of "on" time at the 8th week ($p = 0.006$) (Fig. 3c).

DISCUSSION

We prospectively studied the association between the 3-OMD, a levodopa metabolite, concentration and the effects of entacapone in Japanese advanced PD patients.

We clarified that the baseline serum 3-OMD concentration was associated with the duration of therapy. Our study suggested that long-term levodopa therapy increases COMT activity. Serum 3-OMD concentration was associated with the AUC and Cmax of levodopa, but not with the daily levodopa dosage. The rationale for this was that most patients (15 of 21 patients) took a daily dosage of 300 - 400 mg levodopa, but each of them would have had a different levodopa absorption rate. Because the AUC and Cmax of levodopa reflect the amount of levodopa absorption, serum 3-OMD, a levodopa metabolite, concentration was associated with the AUC and Cmax of levodopa.

Our study showed that the 3-OMD concentration was decreased by about 30% and the UPDRS motor score at the "on" phase was also decreased by 7 points by treatment with entacapone in Japanese patients. As entacapone generally does not increase the Cmax of levodopa after a single coadministration of levodopa[16], motor function is not improved by a single administration of entacapone. However, repeated administration of entacapone may increase the overall levodopa concentration and improve the motor function of patients. Moreover, a recent study[11] showed that 3-OMD impaired the locomotor activity of rats and that 3-OMD can damage neuronal cells. In another study[12], when treatment with controlled-release carbidopa and levodopa was compared with treatment with a combination of carbidopa, levodopa and entacapone, the mean pharmacokinetic values of levodopa were similar, but the "off" time duration was shorter for the entacapone group than the controlled-release levodopa group. As it is assumed that the 3-OMD concentration was decreased in the entacapone group, the difference between the clinical effects observed in the 2 groups might have been due to differences in the 3-OMD concentration.

Therefore, we assumed that PD patients benefit from entacapone for the following reasons: first, entacapone increases the overall serum levodopa concentration; second, the amount of levodopa crossing the blood-brain barrier might be increased due to reduced competition with 3-OMD for the LNAA transporter; and finally, neuronal cell damage caused by 3-OMD also might be reduced.

In a previous study of Japanese Parkinson's disease patients with wearing-off motor fluctuations, the mean "on" time duration improvement was 1.4 hr for the entacapone group[13]. The reason why patients obtained a longer "on" time duration in our study may be attributable to differences in the categories in the self-rating diary. In a previous study[13], "on" was defined as good to excellent mobility and "off" as bad mobility. On the other hand, our diary defined "on" as good mobility and "off" as worse to bad mobility (partial to complete "off"). Partial "off" is a condition in between "off" and "on" [7]; thus, partial "off" might be easily converted to the "on" state by entacapone. In addition, open-label study also contributed to the longer "on" time. We defined the COMT-index as an index of COMT activity. The COMT-index was significantly correlated with the increase in the % of "on" time, in other words, patients with high COMT activity would show increased clinical effects of entacapone. We considered that patients with low COMT activity would show poor clinical effects of entacapone because there might be other factors for the wearing-off phenomenon in those patients. Therefore, the COMT-index could predict the clinical effect of entacapone before the administration of entacapone.

The increase in levodopa AUC after the first entacapone administration was also correlated with the increase in % of "on" time at the 8th week. We considered that patients with a good pharmacological response on first entacapone administration would have a good clinical response and that the increase in levodopa AUC could also predict the clinical effect of entacapone.

However, a two-day blood study is necessary to calculate the increase in levodopa AUC after the first entacapone administration. On the other hand, the COMT-index can be calculated with only a one-day blood study and might be more clinically useful than the increase in levodopa AUC.

The limitations of this study were as follows. The sample size was small, and we conducted an open-label study. We excluded patients with dementia because the "on" time parameter was designed so that it could be recorded by the patients themselves. Therefore, selection bias could not be avoided and might have interfered with the collection of accurate information.

In conclusion, our study showed that the measurement of serum 3-OMD concentration and levodopa pharmacokinetics and the calculation of COMT index are useful for predicting the clinical effects of entacapone. A further large study will be needed to confirm our conclusion.

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ORIGINAL ARTICLE

Cancer-associated ischemic stroke is associated with elevated D-dimer and fibrin degradation product levels in acute ischemic stroke with advanced cancer

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Aim: Although several studies have reported various causes of ischemic stroke in patients with cancer, only a few have evaluated the clinical relevance of ischemic stroke pathogenesis to cancer. The aim of the present study was to elucidate the clinical characteristics of cancer-associated ischemic stroke.

Methods: We evaluated 154 ischemic stroke patients without cancer and 57 ischemic stroke patients with cancer who had either received continuous treatment for cancer within 5 years before to the onset of ischemic stroke, or who had been diagnosed with cancer within 1 year after the onset of ischemic stroke. Cancer patients were grouped into "cancer-associated ischemic stroke," the "conventional ischemic stroke," or "other."

Results: A total of 15 patients (26%) were classified into the cancer-associated ischemic stroke in cancer patients. In univariate analysis of the cancer-associated ischemic stroke and the others, there were significant differences in the prevalence of hypertension, hyperlipidemia and advanced cancer (clinical stage IV), and the levels of D-dimer, fibrin degradation product and hemoglobin. With multivariate regression analysis of those factors, the prevalence of hypertension, hyperlipidemia and advanced cancer (clinical stage IV), and the levels of D-dimer and fibrin degradation product remained as statistically independent factors, which were associated with cancer-associated ischemic stroke ($n = 111$, $\chi^2 = 67.21$, $P < 0.0001$).

Conclusion: In acute ischemic stroke, the cancer-associated ischemic stroke is associated with elevated D-dimer and fibrin degradation products, even after controlling hypertension, hyperlipidemia and advanced cancer (clinical stage IV). **Geriatr Gerontol Int 2012; ••: ••–••.**

Keywords: cancer, D-dimer, fibrin degradation product, ischemic stroke.

Introduction

Systemic thromboembolism associated with cancer was first described by Armand Trousseau and colleagues in 1865. In a more recent autopsy study of 3426 cancer cases, excluding primary brain tumors, 15% of the cases examined had experienced cerebrovascular events.[1] The

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causes of ischemic stroke in patients with cancer might differ from those in patients without cancer. Cancer can predispose patients to hypercoagulable states and might cause the development of deep vein thrombosis (DVT) and non-bacterial thrombotic endocarditis (NBTE).[2] NBTE is one of the most common causes of ischemic stroke in cancer patients,[3] and it has been found in 27% of cancer patients with ischemic stroke on post-mortem analysis.[1]

A number of previous studies have evaluated the characteristics of ischemic stroke patients with cancer. Cestari *et al.* classified the subtypes of ischemic stroke with cancer and found conventional ischemic stroke in just 35 of 96 patients (36%).[4] In addition, there were 36 of 52 patients (69%) with NBTE or embolism of an undetermined source in the subtype of embolic stroke.[4] In another study, embolic signals were detected with transcranial Doppler (TCD) in 45.9% of ischemic stroke patients with cancer.[5] In embolic stroke patients with cancer, a hypercoagulable state attributable to the cancer might have been one of the major causes of ischemic stroke.

However, these studies included a large number of elderly cancer patients, and it is possible that there was a certain proportion of these elderly patients in whom conventional ischemic stroke might have been attributable to atrial fibrillation (Af), atherosclerotic disease or other causes. This highlights the possibility that the causes of ischemic stroke in cancer patients are more complex than previously anticipated. To effectively detect and prevent ischemic stroke in cancer patients, it is necessary to define the causal relationship between ischemic stroke and cancer. However, the characteristics of ischemic stroke attributable to cancer that might allow its discrimination from conventional ischemic stroke remain undetermined.

The aim of the present study was to elucidate the clinical characteristics of cancer-associated ischemic stroke to differentiate it from the other type of ischemic stroke.

Methods

Design

This was a retrospective study of acute ischemic stroke patients admitted to Hiroshima University Hospital, Hiroshima, Japan, between January 2006 and August 2010. Ischemic stroke was confirmed by computed tomography (CT) and/or magnetic resonance imaging (MRI). We classified the patients as with cancer if they had active cancer or had been diagnosed with any cancer within 1 year after the onset of ischemic stroke, excluding primary intracranial tumors. Active cancer was defined by the presence of any continuous treatment for cancer within 5 years before the onset of ischemic stroke. The patients were classified as non-cancer patients if they had never been diagnosed with cancer, had undergone surgical removal of cancer more than 5 years before stroke onset and had shown no recurrence of cancer until their stroke onset, or had no clinical information regarding their cancer.

Data collection

Patients were classified as hypertensive when they had been diagnosed with hypertension before stroke onset, and/or were taking antihypertensive medication. Patients were classified as having diabetes mellitus (DM) if they had glycated hemoglobin (HbA_{1c}) ≥ 6.5% and fasting blood glucose ≥126 mg/dL, and/or were taking oral hypoglycemic agents or insulin. Patients were classified as hyperlipidemic if they had total cholesterol ≥220 mg/dL, low-density lipoprotein cholesterol ≥140 mg/dL and triglyceride level ≥150 mg/dL, and/or were taking antihyperlipidemic medication. Af was diagnosed with a standard electrocardiogram (ECG), 24-h ECG recording or 14-day ambulatory ECG monitoring.[6] The clinical stage of cancer was evaluated at the onset of ischemic stroke based on the tumor–node–metastasis (TNM) classification (for solid cancer) or the modified Ann Arbor (Cotswold's) staging (for malignant lymphoma).[7] In cases with an onset of ischemic stroke before cancer diagnosis, the clinical stage of cancer was evaluated at the time of cancer diagnosis. When a patient had multiple primary cancers, we evaluated the most advanced cancer.

Blood cell counts and blood coagulation factors (e.g. prothrombin time [PT; s], PT international normalized ratio [PT–INR], activated partial thromboplastin time [APTT; s], fibrinogen [mg/dL], D-dimer [μg/mL], fibrin degradation product [FDP; μg/mL], and antithrombin 3 [AT3; %]) were evaluated within 24 h of admission. D-dimer levels were measured by the latex agglutination method using a Sysmex XE7000 and the RIAS AUTO D-dimer NEO reagent (Kobe, Japan).

Ischemic stroke subtypes were classified by two stroke neurologists using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria and imaging examinations (e.g. brain MRI, carotid ultrasonography, transthoracic echocardiography [TTE]), which were carried out within 1 week after hospitalization.[8] In addition, patients with the cancer-associated ischemic stroke were further categorized in accordance with the patients for whom no causes of stroke other than cancer could be identified in the subtype of undetermined etiology, despite extensive evaluations including brain MRI, carotid ultrasonography and TTE. Patients were classified as conventional ischemic stroke if their ischemic stroke was a lacunar infarction or if they had Af, myocardial infarction, rheumatic valvular disease, valvular replacement, cardiomyopathy, severe stenosis

(>50%) of the infarct-related artery, arterial dissection or aortitis.

Statistical analysis

Medians (minimum to maximum) were used to describe continuous data, and frequency and percentage were used for categorical data. Univariate analyses were carried out to evaluate differences among the groups with regards to baseline characteristics, risk factors and laboratory data. Statistical analysis was carried out using JMP software version 9.0 for Windows (SAS Institute, Cary, NC, USA). Values were compared between patient groups using Fisher's exact test for categorical variables. Differences in continuous variables among the groups were examined using the Kruskal–Wallis test. When there was a statistically significant difference, the Wilcoxson signed rank test was applied to examine the difference between each group. Multivariate logistic regression was utilized to assess the relative importance of variables found to be related to the cancer-associated ischemic stroke, in initial univariate analyses. All analyses were two-tailed, and a value of $P < 0.05$ was considered statistically significant.

Results

A total of 211 consecutive acute ischemic stroke patients (79 women and 132 men) were identified between January 2006 and October 2010. The median age was 73 years (range 25–92). The patients' baseline characteristics are listed in Table 1. With our classifications, 15 patients (26%) were in the cancer-associated ischemic stroke group, 39 (68%) were in the conventional ischemic stroke group and three (6%) were not assigned to either classification among the cancer patients. No patient in the present study was assigned to both classifications. Of the three patients not assigned to either classification, one was classified as having a stroke of an undetermined etiology, because the general condition of the patient deteriorated before further evaluation. The two other patients in this group showed disseminated intravascular coagulation (DIC). There were no significant differences in prevalence of vascular risk factors in the cancer patients compared with that in the non-cancer patients. The most common vascular risk factor in the cancer patients was hypertension. It was similar to non-cancer patients. Ischemic stroke onset preceded cancer diagnosis in eight patients. The median duration from cancer diagnosis to stroke onset was 8 months (range –11 to 120) in the cancer patients. The patients in the cancer-associated ischemic stroke group had a lower rate of hypertension and hyperlipidemia than those in the conventional ischemic stroke group ($P < 0.05$).

Table 1 Baseline characteristics

		Non-cancer ($n = 154$)	Cancer ($n = 57$)	CAIS ($n = 15$)	CIS ($n = 39$)	Other ($n = 3$)
Age, years median (range)		73 (25, 92)	75 (50, 91)	74 (50, 87)	76 (56, 91)	67 (56, 86)
Sex	Female, *n* (%)	65 (42)	14 (25)	6 (40)	7 (20)	1 (33)
Risk factors	Hypertension, *n* (%)	100 (65)	33 (58)	5 (33)	26 (67)	2 (67)
	DM, *n* (%)	54 (35)	19 (33)	3 (20)	16 (41)	0 (0)
	Hyperlipidemia, *n* (%)	74 (48)	17 (30)	1 (7)	16 (41)	0 (0)
	Af, *n* (%)	55 (36)	19 (33)	0 (0)	19 (49)	0 (0)
Ischemic stroke subtypes	Small-vessel disease, *n* (%)	22 (14)	5 (9)	0 (0)	5 (13)	0 (0)
	Large artery atherosclerosis, *n* (%)	30 (20)	12 (21)	0 (0)	12 (31)	0 (0)
	Cardioembolism, *n* (%)	62 (40)	18 (32)	0 (0)	18 (46)	0 (0)
	Other determined etiology, *n* (%)	16 (10)	6 (10)	0 (0)	4 (10)	2 (67)
	Undetermined etiology, *n* (%)	24 (16)	16 (23)	15 (100)	0 (0)	1 (33)
Duration from cancer diagnosis to ischemic stroke onset, month median (range).		NA	8 (–11, 120)	13 (0, 69)	7 (–11, 120)	7 (0, 11)

Af, atrial fibrillation; CAIS, cancer-associated ischemic stroke; CIS, conventional ischemic stroke; DM, diabetes mellitus; NA, not assessed.

Table 2 Distributions of primary cancers

	Cancer ($n = 57$)	CAIS ($n = 15$)	CIS ($n = 39$)	Other ($n = 3$)
Lung	8	2	6	0
Stomach	7	1	6	0
Liver	6	2	4	0
Colon	5	0	5	0
Prostate	4	0	4	0
Malignant lymphoma	4	1	3	0
Pancreas	3	2	0	1
Gall bladder	3	2	1	0
Kidney	3	2	1	0
Esophagus	3	0	2	1
Pharynx	2	0	1	1
Breast	3	1	2	0
Others	6	2†	4‡	0

†These two patients had uterus cancer and malignant melanoma. ‡These four patients had thyroid cancer, gastrointestinal stromal tumor, bladder cancer or soft tissue tumor of the elbow. CAIS, cancer-associated ischemic stroke; CIS, conventional ischemic stroke.

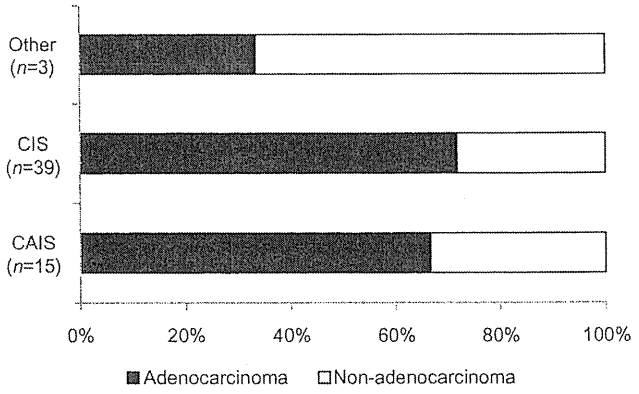

Figure 1 Histological types of primary cancer in the ischemic stroke classification in association with cancer. The difference in the distribution of adenocarcinoma between the cancer-associated ischemic stroke (CAIS) group and the conventional ischemic stroke (CIS) group was not significant.

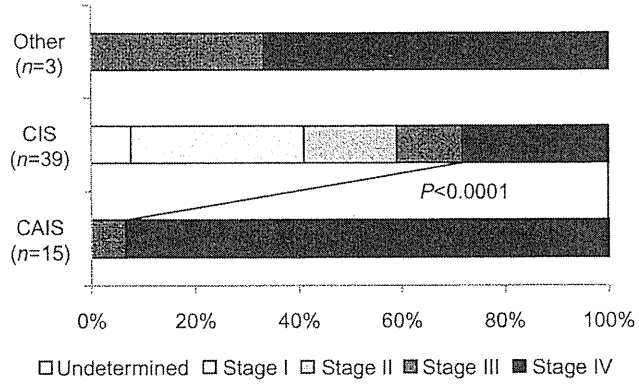

Figure 2 Clinical stage of primary cancer in the cancer-associated ischemic stroke group. There was a higher prevalence of advanced cancer (clinical stage IV) in patients with cancer-associated ischemic stroke (CAIS) compared with patients with conventional ischemic stroke (CIS).

The distributions of the primary cancers are shown in Table 2. Primary cancers were located in the lung in eight patients (14%) and in the stomach in seven patients (12.2%). Through histological classification, it was determined that 39 patients (68%) had adenocarcinoma. There was no significant difference in the distribution of adenocarcinoma between the cancer-associated ischemic stroke and the conventional ischemic stroke groups (Fig. 1). There was a higher prevalence of advanced cancer (clinical stage IV) in the cancer-associated ischemic stroke group than in the conventional ischemic stroke group ($P < 0.0001$; Fig. 2).

Blood cell counts, including hemoglobin and platelet counts, were evaluated in all patients. D-dimer and FDP levels were evaluated in 177 (84%) and 118 patients (56%), respectively. There was no significant difference in platelet counts among the groups. Hemoglobin was low in both cancer groups compared with that of the non-cancer group. D-dimer and FDP levels were significantly higher in the cancer-associated ischemic stroke group than in the non-cancer group and conventional ischemic stroke group ($P < 0.05$; Fig. 3). To assess the association between blood coagulation and clinical stage of primary cancer, differences between D-dimer and FDP levels were evaluated in the different clinical stages. Levels of D-dimer and FDP in the patients with cancer of clinical stage IV were significantly higher than those in patients of clinical stages I–III (D-dimer: 1.3 μg/mL [0.1–29.0] in stages I–III and 8.3 μg/mL [0.4–81.5] in stage IV and FDP: 3.1 μg/mL [0.8–50.5] in stages I–III and 15.1 μg/mL [1.2–100.2] in stage IV, $P < 0.05$, respectively).

In univariate analysis on the cancer-associated ischemic stroke and the other groups, there were significant differences in the prevalence of hypertension, hyperlipidemia, and advanced cancer (clinical stage IV) and the levels of D-dimer, FDP and hemoglobin. Then, we carried out multivariate logistic regression analysis on the cancer-associated ischemic stroke and the others with those factors. As a result, the prevalence of hypertension, hyperlipidemia, and advanced cancer (clinical stage IV), and the levels of D-dimer and fibrin degradation product remained as statistically independent factors, which associated with cancer-associated ischemic stroke ($n = 111$, $\chi^2 = 67.21$, $P < 0.0001$; Table 3).

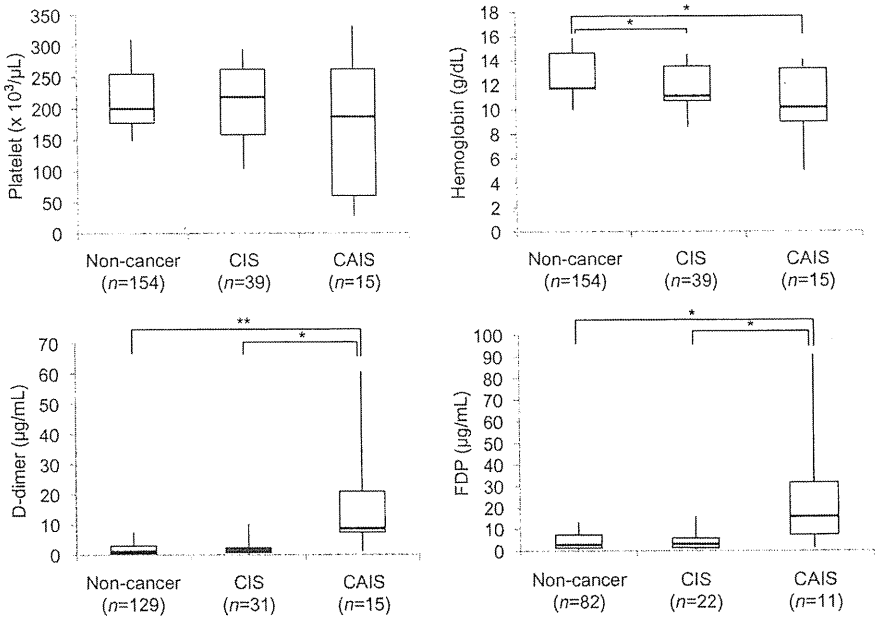

Figure 3 Blood cell counts and coagulation factors in the cancer-associated ischemic stroke group. There was no significant difference in platelet counts between the cancer-associated ischemic stroke (CAIS) and the conventional ischemic stroke (CIS) groups. Although hemoglobin level was low in both cancer patient groups compared with that of the non-cancer patients, there was no significant difference between the patients with CAIS and those with CIS. D-dimer and fibrin degradation product (FDP) levels were significantly higher in the CAIS group than the other groups. Boxplot graph was made with median, 10th, 25th, 75th and 90th values. Significant differences among groups: $*P < 0.05$, $**P < 0.0001$.

Table 3 Multivariate logistic regression analysis on the cancer-associated ischemic stroke and the others

Factors	χ^2	*P*-value
Hypertension	11.13	0.0008
Hyperlipidemia	4.16	0.0414
Advanced cancer	48.47	<0.0001
D-dimer	12.60	0.0004
FDP	9.24	0.0024
Hemoglobin	2.15	0.9988

$n = 111$, $\chi^2 = 67.21$, $P < 0.0001$. FDP, fibrin degradation product.

Discussion

In the present study, we evaluated the clinical characteristics of ischemic stroke patients with cancer. Of the 58 patients examined, 16 (28%) were classified as having cancer-associated ischemic stroke. The characteristics of cancer-associated ischemic stroke were evaluated by comparison with the non-cancer group and conventional ischemic stroke group. There was no significant difference in the prevalence of adenocarcinoma between the cancer-associated ischemic stroke and the conventional ischemic stroke groups. However, there was a higher prevalence of advanced cancer (clinical stage IV) in patients with cancer-associated ischemic stroke than in patients with conventional ischemic stroke. There was a lower prevalence of hypertension and hyperlipidemia in patients with the cancer-associated ischemic stroke than in patients with the conventional ischemic stroke. There were no significant differences between the two groups in hemoglobin and platelet counts. FDP and D-dimer levels were significantly higher in patients with the cancer-associated ischemic stroke than in the non-cancer group and the conventional ischemic stroke group. In acute ischemic stroke, cancer-associated ischemic stroke was associated with elevated D-dimer and fibrin degradation products, even after controlling hypertension, hyperlipidemia and advanced cancer (clinical stage IV).

In the present study, we attempted to select the patients with cancer-associated ischemic stroke using the TOAST criteria. Kim *et al.* have also tried to classify ischemic stroke patients with cancer using conventional and cryptogenic stroke mechanisms.[9] In their classification, ischemic stroke patients with undetermined etiologies according to the TOAST criteria were categorized solely with reference to cryptogenic stroke mechanisms. Although their classification method is almost equal to our method, they classified five NBTE patients as a conventional ischemic stroke mechanism. NBTE is widely recognized as a unique cause of cardioembolism frequently observed in cancer patients, as has been reported in a post-mortem series.[1] Although transesophageal echocardiography (TEE) is the most appropriate method to diagnose cardiac sources of embolism, such as NBTE,[10] it is difficult to carry out TEE in all cancer patients, as TEE is an invasive examination. In the present study, we carried out TEE in just 37% of the patients who were suspected to have had a cardioembolic stroke from the results of imaging analysis and who could tolerate esophageal intubation. Although our execution rate of TEE was higher than that in previous reports,[4,11] it is quite likely that there is a selection bias. Therefore, we tried to classify cancer-associated ischemic stroke without using the finding of TEE. As a

result, three patients with NBTE in the cancer-associated ischemic stroke group were included, because there were not embolic sources, despite extensive examination without TEE. From this result, this classification method could be adequate in a clinical site.

D-dimer is a plasmin-derived degradation product of cross-linked fibrin that is elevated in patients with hypercoagulability. D-dimer levels were elevated in a wide variety of conditions with intravascular clotting, including ischemic stroke itself. Previous studies have reported that D-dimer is higher in stroke patients with cancer than in stroke patients without cancer.[4] In the present study, we have shown that, among ischemic stroke patients, D-dimer levels were more elevated in patients with cancer-associated ischemic stroke than non-cancer and conventional ischemic stroke. The patients with NBTE showed high D-dimer levels. There were three patients with NBTE found with TEE in the cancer-associated ischemic stroke group. Their D-dimer levels were 8.7 μg/mL, 23.1 μg/mL and 55.5 μg/mL; these values were markedly higher than those of the other patients in this group. It might be because NBTE can result from a hypercoagulable stage. Furthermore, we investigated the possibility that patients with advanced cancer show high levels of D-dimer. Interestingly, the levels of D-dimer were higher in the patients with stage IV cancer than in those with clinical stages I–III. From the present results, D-dimer and FDP remained as independently significant, even after controlling the prevalence of hypertension, hyperlipidemia and advanced cancer (clinical stage IV). Therefore, although the elevation of blood coagulation factors in the patients with the cancer-associated ischemic stroke might be attributable to a higher clinical stage of primary cancer, it was independently associated with the cancer-associated ischemic stroke.

Uemura *et al.* reported that hemoglobin levels were reduced in cancer patients compared with patients with no malignancy.[12] Their explanation for the reduced hemoglobin levels in cancer patients was the general condition of these patients as a result of cancer cachexia or gastrointestinal bleeding in gastrointestinal cancer patients. The present results support those of Uemura *et al.*; hemoglobin levels in the cancer groups were lower than the non-cancer group in the present study. However, there was no significant difference in hemoglobin levels between the patients with cancer-associated ischemic stroke and those with conventional ischemic stroke. The present results suggested that hemoglobin levels cannot be a marker used to distinguish between cancer-associated ischemic stroke and conventional ischemic stroke in cancer patients.

Circulating mucinous material has been reported in embolic stroke patients with mucin-producing adenocarcinomas.[13–15] Seok *et al.* reported that embolic signal was observed in patients with metastasis or adenocarcinoma.[5] Of the patients in the present study, 68% were adenocarcinoma patients. However, there was no significant difference in histological types between the cancer-associated ischemic stroke and the conventional ischemic stroke patients. These results require confirmation in a larger number of patients.

In the present results, there was a significant difference in the clinical stage of cancer, but not the histological type between the patients with cancer-associated ischemic stroke and those with conventional ischemic stroke. A few previous reports have evaluated the relationship between cancer-associated ischemic stroke and its clinical stage. Kim *et al.* showed a high prevalence of distant metastasis in cryptogenic stroke mechanisms.[9] This report supports the present results in that there was a high prevalence of advanced cancer in the patients with cancer-associated ischemic stroke.

The present study has some limitations. First, this was a single-center retrospective study. Our hospital functions as both a regional cancer center and an advanced emergency center. The proportion of ischemic stroke patients with cancer might differ between our hospital and the general population. Therefore, there might be a selection bias for ischemic stroke patients with cancer. Second, the method of classifying cancer-associated ischemic stroke is not generalized. With our classification system, all of the ischemic stroke patients with Af were classified as having cardioembolism in conventional ischemic stroke. However, there is a possibility that some of these stroke cases might have been attributable to a hypercoagulable state as a result of cancer rather than to Af. Further selection criteria are necessary to select the Af patients in whom the ischemic stroke was a result of hypercoagulability as a result of cancer. Therefore, further research investigating the association between ischemic stroke and cancer is needed. Finally, although TEE is necessary to diagnose NBTE, TEE cannot be carried out in all cases because of patients' general conditions, anatomical reasons (e.g. esophageal or gastric cancer and esophageal varix) and/or lack of patient cooperation.

In conclusion, 26% of the patients studied were classified as having cancer-associated ischemic stroke. Based on our results, elevated D-dimer and FDP levels can be associated with cancer-associated ischemic stroke, even after controlling hypertension, hyperlipidemia and advanced cancer (clinical stage IV).

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Disclosure statement

None.

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ORIGINAL ARTICLE

Blood pressure variability and prognosis in acute ischemic stroke with vascular compression on the rostral ventrolateral medulla (RVLM)

Shiro Aoki, Toshiho Ohtsuki, Naohisa Hosomi, Yoshimasa Sueda, Tomoyuki Kono, Takemori Yamawaki and Masayasu Matsumoto

One of the known causes of hypertension is vascular compression on the rostral ventrolateral medulla (RVLM). However, it remains unknown whether RVLM vascular compression causes the significant variability in blood pressure observed during acute ischemic stroke. The purpose of this study was to evaluate differences in blood pressure variability and prognosis in acute ischemic stroke patients based on the presence or absence of RVLM vascular compression. We evaluated 56 patients with acute ischemic stroke. Blood pressure was measured every 6 h for 72 h after admission and evaluated with successive variation (SV). The presence of RVLM vascular compression was evaluated using time-of-flight 3D magnetic resonance imaging. Neurological severity was evaluated using the National Institutes of Health Stroke Scale (NIHSS) at admission and 14 days after admission, and clinical improvement was determined by taking the difference in the NIHSS scores between admission and at 14 days. Patient clinical outcome was evaluated with the modified Rankin scale on discharge. Vascular compression of the RVLM was identified in 15 patients (26.8%). The proportion of patients showing clinical improvement was significantly higher in the non-compression group (odds ratio, 0.21 (95% CI=0.06–0.78); P=0.01). The SV value for systolic blood pressure was significantly higher in the compression group (P<0.0001). We found that patients with RVLM vascular compression had a greater variability in blood pressure during the acute ischemic stroke phase, which may be related to poorer prognosis.
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Keywords: acute ischemic stroke; blood pressure; rostral ventrolateral medulla

INTRODUCTION

Regardless of nationality or ethnicity, hypertension is a lifestyle-related disease afflicting patients throughout the world and is a major risk factor for stroke. Hypertension is a multifactorial disease. It has been reported that a large population of patients with vascular compression on the rostral ventrolateral medulla (RVLM) have hypertension.[1–4] Surgical decompression of the RVLM reduced sympathetic nerve activity and normalized systemic blood pressure.[5,6] Therefore, it is suggested that vascular compression on the RVLM influences the development or maintenance of hypertension. The RVLM has been experimentally shown to be a site of cardiac and vasomotor regulation. The mechanism of increased blood pressure in patients with vascular compression on the RVLM remains to be completely elucidated. It is currently hypothesized that chronic stimulation of this region with vascular compression can cause constitutive activation of the sympathetic nervous system and the development of hypertension.[7,8]

More than 80% of acute stroke patients have elevated blood pressure. Several days following the incidence of stroke, however, the blood pressure in these patients returns to baseline levels.[9] This blood pressure elevation varies depending on the subtype of ischemic stroke and on the patient's medical history.[10] In general, the cause of elevated blood pressure during the acute phase of ischemic stroke is presumed to be an increase in sympathetic nerve activity and stress from the ischemic insult that disrupts intracerebral autoregulation to maintain cerebral blood flow.[11] During acute ischemic stroke, the rapid decrease in blood pressure reduces cerebral blood flow in parallel to a decrease in the perfusion pressure that is sufficiently large to expand infarct volumes and worsen neurologic symptoms. Therefore, such an excessive lowering of blood pressure during acute ischemic stroke is not desirable. Even in studies examining the correlation between blood pressure and prognosis in the acute ischemic stroke phase, the variability in blood pressure has been shown to be an independent prognostic factor for a poor outcome.[12,13]

RVLM vascular compression may cause significant variability in blood pressure during acute ischemic stroke by sympathetic nerve activation.[14] However, to our knowledge, it remains unclear whether RVLM vascular compression influences blood pressure during acute ischemic stroke. Therefore, the purpose of this study was to evaluate differences in blood pressure variability and prognosis during acute ischemic stroke in the presence or absence of RVLM vascular

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