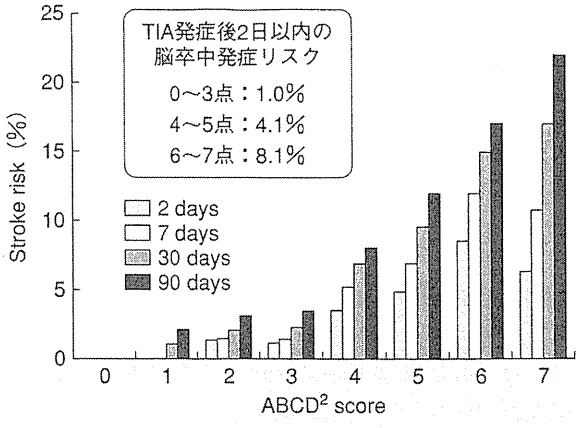


**図 2　TIA 後の脳卒中発症リスクの層別化**(Johnston ら[9]より)
ABCD²スコアが高いほど，TIA 発症後の脳卒中発症リスクは高くなる．

治療されなかった場合に比べ 79.2%も軽減されたとの報告もある[8]．

2．ABCD²スコアによるリスク層別化

TIA 後の脳梗塞発症の危険度予測には，ABCD²スコアを用いたリスク層別化が勧められている(図 2)．ABCD²スコアとは，TIA の臨床像や合併症の中から特定の項目を選んで点数を付け，その合計点で脳梗塞発症危険度を判断するものである．すなわち，年齢(age)≧60 歳(1 点)，血圧(blood pressure)＞140/90 mmHg(1 点)，臨床像(clinical feature)としての片麻痺(2 点)，麻痺を伴わない言語障害(1 点)，症状持続時間(duration of symptoms)≧60 分(2 点)，10〜59 分(1 点)，糖尿病(diabetes)あり(1 点)の各スコアの合計点である．ABCD²スコアの高得点，diffusion-weighted MRI 上の高信号は，TIA 発症後の脳卒中発症リスクが高いことを意味する[9,10]．なお，TIA に対する治療は，基本的に脳梗塞に対する治療と同様である．

## ガイドライン 2009 における「脳梗塞急性期治療」の主な改訂点

ガイドライン 2004 と比べた場合の主な改訂点は，rt-PA(アルテプラーゼ)静注療法の国内承認に伴う推奨文の改訂，開頭外減圧療法の適応の明記，「特殊な病態による脳梗塞の治療」の項への脳動脈解離，大動脈解離，脳静脈・静脈洞閉塞症の追記である．

rt-PA 静注療法は，わが国で行われたオープン試験(第Ⅲ相治験，J-ACT)の結果，海外での臨床治験と同等の有効性と安全性が得られたため[11]，2005 年 10 月に国内承認がなされた．2008 年 9 月，臨床試験 ECASS-Ⅲの結果が発表され，発症 3.0〜4.5 時間の脳梗塞患者に対する rt-PA 静注療法の有効性と安全性が証明された[12]．この成績も，今回のガイドラインの本文中で紹介されている．また，「特殊な病態による脳梗塞の治療」の中の「大動脈解離」の項で，「大動脈解離を合併する脳梗塞では rt-PA 静注療法は禁忌である(グレード D)」ことが明記された．「開頭外減圧療法」に関しては，中大脳動脈灌流域を含む一側大脳半球梗塞のうち進行する脳浮腫をきたす悪性中大脳動脈梗塞に対しては，3 つの大規模臨床研究，French DECIMAL[13]，German DESTINY[14]，Dutch trial HAMLET[15]の結果を受けて推奨文が改訂された．詳細は各論を参照して頂きたい．

## ガイドライン 2009 における「脳梗塞慢性期治療」の主な改訂点

「脳梗塞慢性期治療」には 11 項目の危険因子と 10 項目の治療が含まれている．危険因子のうちグレード A，B の推奨文を含むのは，「高血圧症」「糖尿病」「脂質異常症」「飲酒・喫煙」「心房細動」の 5 項目である．高血圧の降圧目標は「日本高血圧学会ガイドライン 2009」に準じている[16]．糖尿病例における脳梗塞再発防止に対するピオグリタゾンの有効性は，PROactive 研究のサブ解析により明らかにされた[17]．脂質異常症に関しては，SPARCL 研究により，高用量のスタチンが脳梗塞再発予防に有効であること[18]，わが国で行われた JELIS 研究のサブ解析より，低用量のスタチンが脳梗塞再発予防に有効であることが報告された[19]．心房細動での推奨文は前回のガイドラインと同様である．

慢性期治療の中で，「再発予防のための抗血小板療法」における「非心原性脳梗塞治療」の項に，新たにクロピドグレルが追記された．これは，ハイリスク患者を対象とした脳梗塞再発に関するアスピリンとチクロピジンのランダム化比較試験にてチクロピジンの方が有意に再発を抑制したこと(但し下痢等の副作用の出現は多い)[20]，Antithrombotic Trialists' Collaboration の報告でチクロピジンとクロピドグレルを一括した場合の血管イベント発生がアスピリンに比べて有意に低いこと[21]，動脈硬化疾患合併例を対象としたアスピリンとクロピドグレルの比較でクロピドグレルの方が血管イベントを抑制したこと(CAPRIE 試験)[22]，クロピドグレルとチクロピジンを比較したわが国の治験で両者の間で効果には差がなかったが安全性は有意にクロピドグレルが優れていたことなどを勘案した結果である[23,24]．心原性脳塞栓症を除く脳卒中再発に関する CSPS

研究において，シロスタゾールはプラセボに比べ有意な抑制効果を示した[25]．

「再発予防のための抗凝固療法」のグレードA，Bに該当する記載事項は，基本的に前回のガイドラインと同様である．今回，新たにワルファリンの休薬時の処置が追記された(グレードC1)．

脳外科的処置に関し，頸動脈内膜剥離術(CEA)の適応は前回のガイドラインと同様である．SAPPHIRE研究の結果を根拠に，CEAリスクを有する症候性内頸動脈狭窄に対する頸動脈ステント留置術(CAS)の推奨レベルが，C1からBに格上げされた[26,27]．詳細は各論を参照して頂きたい．

## むすび

脳梗塞の分野は，治療法，予防法の進歩が最も著しい領域の一つである．「脳卒中治療ガイドライン2009」の冒頭に，「治療ガイドラインは生き物であり，常に改訂をしなければならない性質をもち，完成と同時に次のステップが始まっている」と書かれている．次回のガイドライン改訂時には，本章の多くの項目が改訂，追記されるであろう．今後，わが国から，更にエビデンスレベルの高い臨床研究の結果が発信されることを期待したい．

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連載

# 脳循環障害の画像診断

## 急性心筋梗塞と一過性脳虚血発作を同時に発症した1例

国立循環器病研究センター脳血管内科，同 脳血管内科 医長*，同 副院長**

佐藤 和明 Kazuaki SATO　横田 千晶* Chiaki YOKOTA　冨井 康宏 Yasuhiro TOMII　峰松 一夫** Kazuo MINEMATSU

### はじめに

心臓と脳の両者に同時に血管イベントを生じる「心脳卒中」の報告が散見されるが，その発症機序には不明な点が多い．今回我々は，急性心筋梗塞と一過性脳虚血発作（transient ischemic attack：TIA）を同時に発症し，「心脳卒中」の発症機序を考える上で示唆に富む症例を経験した．

### 症 例

62歳，女性，右利き．

### 主 訴

意識障害，左手足の脱力，呂律が廻らない．

### 既往歴

23歳時に虫垂炎にて手術．

### 家族歴

特記すべきことなし．

### 生活歴

喫煙：20本/日×40年，飲酒：なし．

### 現病歴

某年7月1日18時頃，レストランからの帰りに車に乗り込んだときに，突然嘔吐し，助手席に倒れ込み，呂律が廻らなくなった．18時35分に当センターを救急受診した．この間，胸痛の訴えはなかった．

### 入院時現症

身長142cm，体重35kg，四肢動脈拍動は触知できず，血圧は測定不能であった．体温35.6℃．右頸部に血管雑音を聴取した．一般身体所見に特記事項はなかった．

### 入院時神経学的所見

意識レベルJCS Ⅰ-1，脳神経系では，右への共同偏視，軽度の構音障害，左中枢性顔面神経麻痺あり．運動系では左片麻痺，感覚系では左半身に感覚鈍麻を認め，高次脳機能は左半側空間無視があった．National Institutes of Health Stroke Scale（NIHSS）スコアは13であった．

### 入院時検査所見

血液検査：

血算；白血球 14,800/μL，赤血球 409万/μL，ヘモグロビン 12.8g/dL，血小板 30.6万/μL

生化学；TP 5.9g/dL，T-bil 0.2mg/dL，AST 16IU/L，ALT 14IU/L，T-CHO 211mg/dL，LDL-CHO 107mg/dL，HDL-CHO 31mg/dL，TG 508mg/dL，BUN 18mg/dL，CRE 0.71mg/dL，Na 133mEq/L，K 3.5mEq/L，CK 38IU/L，血糖 418mg/dL，$HbA_{1c}$ 10.3%

凝固系；PT-INR 0.85，APTT 24秒，D-dimer 1.0μg/mL

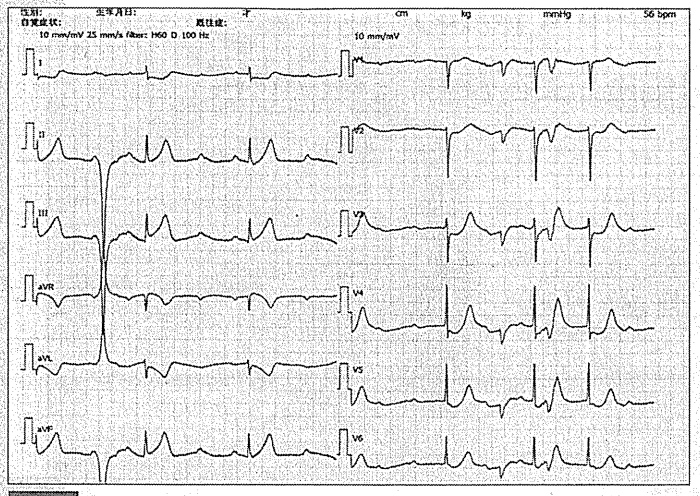

**図1** 入院時心電図

心拍数56回/分で完全房室ブロックあり．Ⅱ・Ⅲ・aVF でST上昇，Ⅰ・aVL でST低下を認めた．

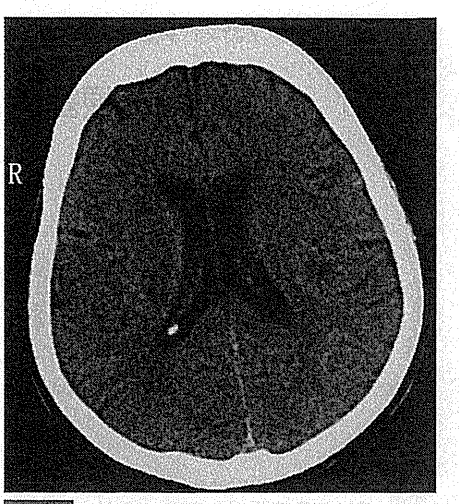


**図2** 入院時頭部 CT

異常所見を認めなかった．

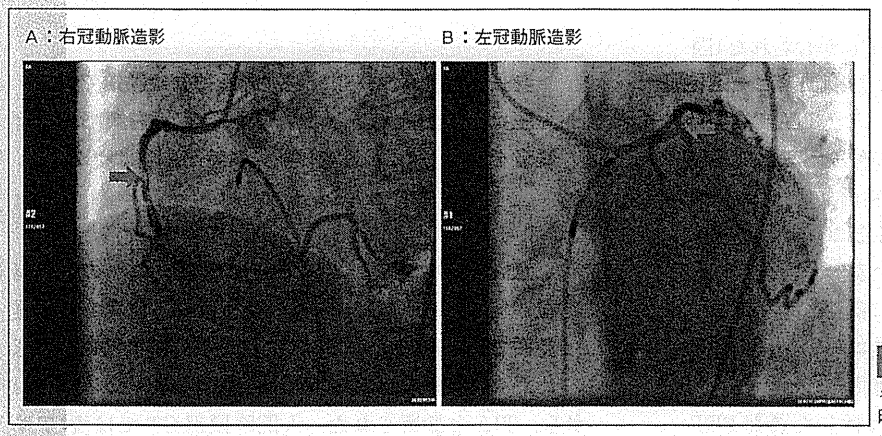


**図3** 心臓カテーテル検査

＃1：90%，＃6：75%狭窄を認めた（矢印）．

心電図：心拍数56回/分で完全房室ブロックあり．Ⅱ・Ⅲ・aVF でST上昇，Ⅰ・aVL でST低下がみられた（図1）．

胸部レントゲン写真：CTR 52%，肺うっ血なし，肺野に異常陰影なし．

経胸壁心エコー：下壁に壁運動低下あり．

頸部血管エコー：右内頸動脈起始部に高度の動脈狭窄あり．面積狭窄率96%，径狭窄率（NASCET 法）64%，収縮期最高血流速度（peak systolic flow velocity：PSV）は517cm/秒と著増していた．プラークの性状は，大部分が等輝度であったが，一部高輝度部位もあり，一部では可動性であった．

頭部 CT：異常所見はなかった（図2）．

## 入院後経過

入院後，著しい血圧低下に対して直ちに昇圧薬投与を開始した．入院時頭部 CT に異常所見がなかったため，アスピリン200mg と塩酸チクロピジン200mg の内服とヘパリン持続点滴が開始された．同日20時には神経学的異常所見は完全に消失した．その後，緊急心臓カテーテル検査が施行され，＃1：90%，＃6：75%の狭窄があり，＃1に対して経皮的冠動脈形成術（per-

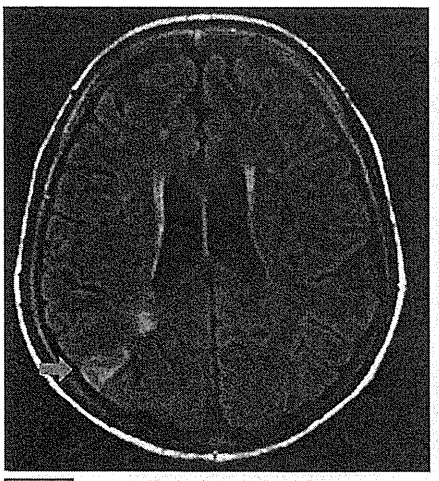

図4　第13病日の頭部 MRI FLAIR 法
右側頭後頭部に高信号域を認めた（矢印）.

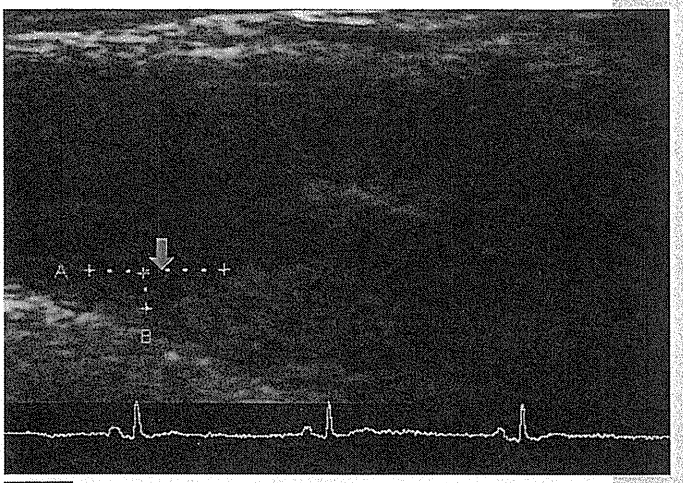

図5　頸部血管エコー
右内頸動脈プラーク部の潰瘍化を認めた（矢印）.

cutaneous coronary intervention：PCI）が行われた（図3）．＃6は冠動脈バイパス術の適応と判断され，カテーテル検査を終了した.

第13病日に入院後初の頭部 MRI 検査が行われた．FLAIR 法にて，右の側頭後頭部に高信号域を認め（図4），第16病日の頭部 CT でも同部位に低吸収域を検出した．第17病日になり循環動態が安定したため，脳血管系の精査・加療目的にて当科に転科となった.

第17病日に再検された頸部血管エコーでは，入院時に見られた可動性プラーク部が潰瘍化し，可動性は消失していた（図5）．第21病日に施行した頭部 PET 検査で，右前頭葉から頭頂葉にかけての脳灌流圧（CBF/CBV）の低下，脳血液量（CBV）の増加を認めたが，酸素摂取率（OEF）の増加はみられず，stage Ⅰと診断された（図6）．第28病日の CTA で，右内頸動脈高度狭窄（NASCET 75%）と診断した．第37病日の反転回復型 T1 強調法（Magnetization Prepared Rapid Acquisition with Gradient Echo：MPRAGE）を用いた頸部 MRI では，プラーク部は高信号であった（図7）．第44病日に，右内頸動脈高度狭窄（図8）に対する頸動脈ステント術（carotid artery stenting：CAS）が，さらに第91病日には，＃6に対する冠動脈バイパス術が施行された．患者は第115病日に自宅退院した.

## 考　察

本例は，TIA を発症し，同時に急性心筋梗塞（下壁），完全房室ブロックによる血圧低下を伴った「心脳卒中」症例である．本例では，症候性の右内頸動脈高度狭窄症を合併し，かつ冠動脈バイパス術の適応であったことから，右内頸動脈高度狭窄に対して CAS が施行された.

本症例は，発症時に広汎な右大脳半球症状を一過性に生じ，2時間以内に神経症候が完全に消失したことから，TIA と診断された．入院時頭部 CT では責任病巣は同定されなかった．急性心筋梗塞発症のため心臓内科に緊急入院となり，入院時に頭部 MRI の施行機会はなかったが，後日行われた MRI にて右側頭後頭部に新たな梗塞巣が検出された．同病変は，MRI とほぼ同時期に行われた頭部 CT でも確認された．同病変部位はいわゆる分水嶺には相当せず，かつ皮質梗塞の境界は明瞭であったことから，発症時の血圧低下により生じた病巣とは考えにくかった．受診時に右内頸動脈高度狭窄部位にみられた可動性プラークが第17病日の再検時には消失し，該当部位は潰瘍化していたことから，今回の TIA 発生機序には，血圧低下による脳灌流圧低下に加え，可動性プラークからの動脈原性塞栓（A-to-A embolism）も疑われた．初診時の症

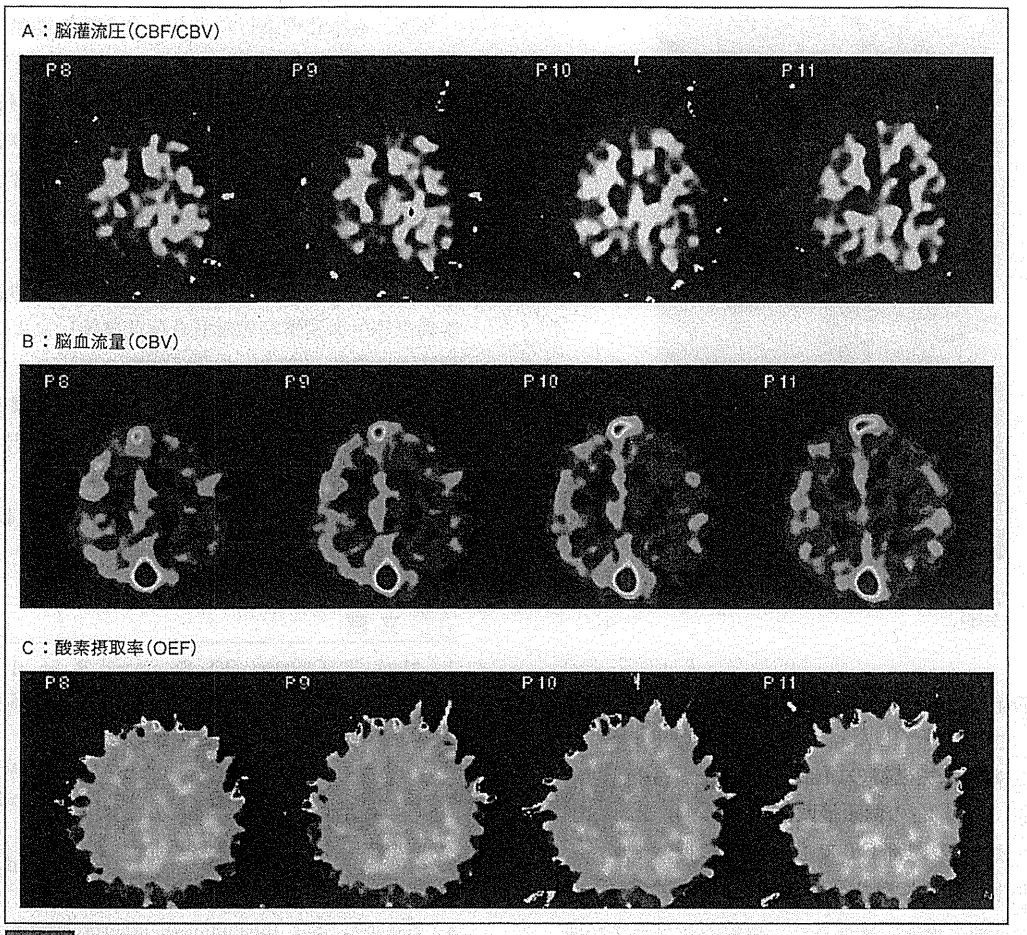


**図6** 頭部 PET

第21病日の PET．右前頭葉から頭頂葉にかけて脳灌流圧（CBF/CBV）の低下（A），脳血液量（CBV）の増加あり（B）．酸素摂取率（OEF）の増加はみられず（C），stage Ⅰと診断された．

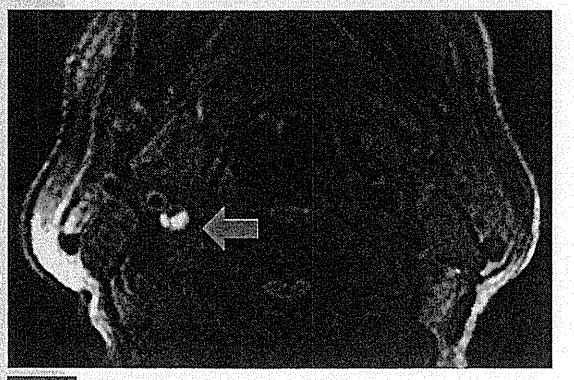

**図7** 頸動脈の MPRAGE

第37病日の頸部 MRI 反転回復型 T1 強調法（Magnetization Prepared Rapid Acquisition with Gradient Echo：MPRAGE）．右プラーク部に一致して，高信号域を認めた（矢印）．

候が右大脳半球の皮質症候を含むことから，右側頭後頭部の梗塞巣は両者の機序によって発症した虚血病巣の一部なのかもしれない．

心疾患と脳卒中を同時に発症する「心脳卒中」の発症機序の一つとして，広汎な前壁の急性心筋梗塞に伴う左室内血栓が考えられている．本症例は下壁梗塞であり，下壁に限局した壁運動低下のみが観察され，心腔内血栓の存在は確認されていない．Mooe ら[1]は，急性心筋梗塞発症後28日以内に初発脳梗塞を発症した103例の解析より，左室内血栓による発症機序で説明することが困難な脳梗塞例が多かったとしている．Bodenheimer ら[2]によると，2,446例の急性心筋梗塞発症例の12～52ヵ月追跡期間中，91例（3.7%）に脳

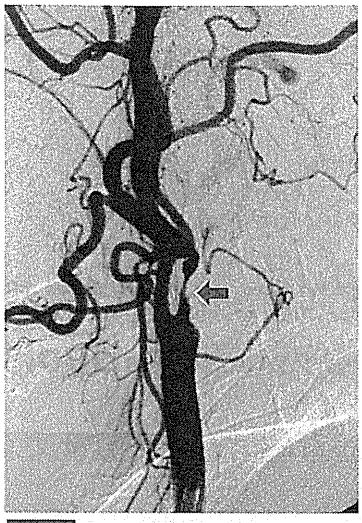

**図8** 脳血管造影
第44病日の右内頸動脈の脳血管造影．右内頸動脈起始部にNASCET 75%狭窄を認めた（矢印）．

梗塞が発症し，このうち前壁心筋梗塞例は23例のみであった．こうしたことから，「心脳卒中」発症機序における心原性脳塞栓症の割合は必ずしも高くないと推察される．一方，「心脳卒中」のもう一つの発症機序として，炎症反応により動脈硬化性病変が活性化され，活性化された動脈硬化性病変が液性因子を介してさらに全身的な炎症が促進され，複数のプラークが活性化されてプラーク破綻を引き起こすという仮説が，近年注目されている[3)4)]．動脈硬化の重症度の指標として，これまでは主に血管狭窄度が注目されてきたが，近年は動脈硬化病変の「質的」診断の重要性が指摘されている[5)]．Yamadaら[6)]は，後ろ向き研究より，MPRAGEを用いた頸部MRIにおいて高信号を呈する頸動脈プラークは，vulnerable plaqueである可能性を示した．本例でも，右内頸動脈高度狭窄部のプラークはMPRAGEで高信号であった．本症例では，右冠動脈と右内頸動脈に存在したvulnerable plaquesの同時破綻が，今回のイベントを引き起こした可能性もあると考えられた．

今後，高齢化の進行により，全身性の動脈硬化性病変合併の増加が懸念される．TIA例は，脳卒中のみならず重大な心血管イベント発症のリスクが高いと報告されている[7)]．こうした背景には，TIAの病態に，全身的な重症動脈硬化性病変が関連する場合が少なからず存在することを念頭に置かなければならない．

■本論文の一部は，厚生労働科学研究費補助金（循環器疾患等生活習慣病対策総合研究事業）による「一過性脳虚血発作（TIA）の診断基準の再検討，ならびにわが国の医療環境に則した適切な診断・治療システムの確立に関する研究（H21-循環器（生習）-一般-017）」，ならびに循環器病研究委託費20公-1「無症候性頸動脈狭窄症に対する治療方針の確立に関する研究」の援助による．

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連載

# 脳循環障害の画像診断

## —過性脳虚血発作患者の心血管病変の多様性

国立循環器病研究センター脳血管内科，同 副院長*

藤並　潤　Jun FUJINAMI
峰松 一夫* Kazuo MINEMATSU

### はじめに

一過性脳虚血発作（transient ischemic attack：TIA）の発症後早期の脳梗塞発症リスクが予想以上に高いこと，また早期からの治療介入により著しい脳梗塞予防効果が期待できることなどが報告され，TIA早期診療の重要性が再認識されている[1]．脳梗塞患者においては，発症機序に応じた適切な再発予防を行うことが重要である．脳梗塞もTIAも発症機序に本質的な差はないことから，TIAにおいても発症機序の同定と，治療介入を迅速に行うことが非常に重要である．日常診療の中でも，TIAの発症機序の多様性に驚かされることが少なくない．今回，我々が経験したTIA症例の発症機序と治療について紹介する．

### 症例

【症　例】72歳，男性．

【主　訴】左手足が動いていない，呼びかけに反応が弱い．

【既往歴】高血圧，脂質異常症，脳血管障害の既往なし．

【嗜好・生活歴】喫煙：20本/日，飲酒：焼酎5合/日．

【家族歴】特記事項なし．

【現病歴】某年2月5日19時に入浴した．20時になっても浴室から出てこないため，家人が様子をみにいくと浴槽にもたれるようにして倒れていた．呼びかけへの反応が弱く，左手足を動かさないため，救急要請．20時40分に当院救急外来に到着した．

【入院時現症】身長171cm，体重62kg，血圧172／90 mmHg，脈拍69bpm 整．

一般身体所見：右頸部に血管雑音を聴取，その他特記事項なし．

神経学的所見：意識清明，右共同偏視，左上肢の重度運動麻痺，左下肢の軽度運動麻痺あり，その他特記事項なし．

【入院時検査所見】総コレステロール186mg/dL，中性脂肪196mg/dL，LDLコレステロール92mg/dL，HDLコレステロール59mg/dL，$HbA_{1c}$ 6.8%，D-dimer 0.8 μg/mL，凝固・肝腎機能・血糖は正常．

【入院後経過】来院時の頭部MRIでは明らかな病巣は認めなかった．MRI撮像後に症状が著明に改善し，左下肢のわずかな運動麻痺を残すのみとなった．翌朝には症状が消失しており，TIAと診断した（ABCD²スコア＝6点）．頸動脈超音波検査では面積狭窄度95%，PSV 392cm/秒で，頭部MRA所見（図1）とあわせて右内頸動脈高度狭窄と診断した．外科的治療の適応と判断した．術前検査で冠動脈狭窄が発見されたため，心臓内科でステント治療を行った後に頸動脈内膜剥離術（CEA）を行った．

### 症例

【症　例】80歳，女性．

【主　訴】右手足に力が入りにくい，しゃべりにくい．

【既往歴】子宮筋腫，高血圧，狭心症，脳血管障害の

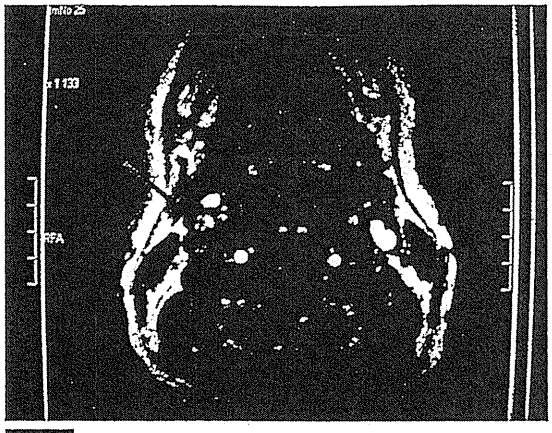

**図1** 頸部 MRA
右内頸動脈に高度狭窄を認める（矢印）.

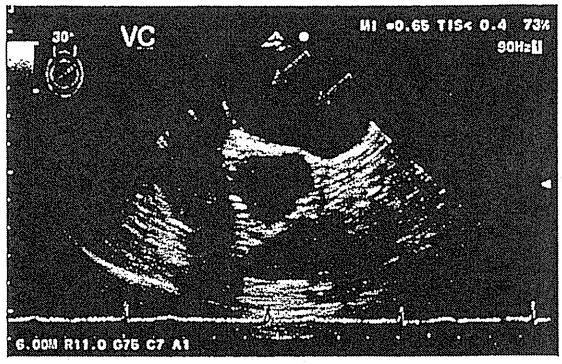


**図2** 経食道心臓超音波検査
コントラスト造影法．右房内に充満したバブルの一部がバルサルバ負荷解除直後に左房内に検出された（矢印）.

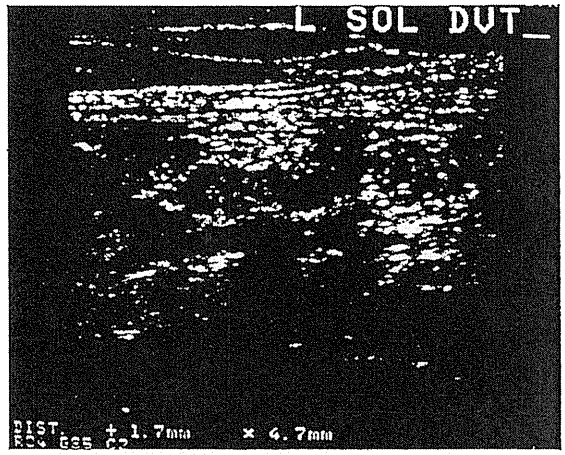


**図3** 下肢静脈超音波検査
右ヒラメ静脈を観察したところ，静脈内に血栓形成を認めた.

既往はない.

【嗜好・生活歴】喫煙：なし，飲酒：なし.

【家族歴】父：肝細胞癌，母：高血圧，妹：高血圧・大腸癌.

【現病歴】某年2月6日朝7時に起床した際は普段どおりであった．その直後に，カーテンを開けようとしたところ，突然右手足に力が入らなくなった．しばらく座って様子をみていたが，夫に声をかけられて返事をすると呂律が回らなかった．症状持続するため救急要請した．その後，症状改善傾向となり，8時7分に当院救急外来到着時には症状消失していた（ABCD$^2$スコア＝6点）.

【入院時現症】身長155cm，体重58kg，血圧200／96 mmHg，脈拍59bpm 整

一般身体所見：特記事項なし.

神経学的所見：意識清明，明らかな運動麻痺は認めず，その他特記事項なし.

【入院時検査所見】総コレステロール236mg/dL，中性脂肪107mg/dL，LDL コレステロール147mg/dL，$HbA_{1c}$ 5.2%，D-dimer 3.4$\mu$g/mL，肝腎機能・血糖は正常.

【入院後経過】来院時の頭部 MRI で明らかな責任病巣は認めなかった．TIA と診断し，ヘパリン持続点滴を開始した．原因精査を行ったところ，主幹動脈の有意狭窄や心房細動は検出されなかった．経食道心臓超音波検査では，卵円孔開存による右左シャントを認めた（図2）．下肢静脈超音波検査で，右ヒラメ静脈内に血栓形成を認めた（図3）．奇異性脳塞栓症と同様の機序で発症した TIA と考え，ワルファリンの投与を開始した.

## 症例 8

【症　例】42歳，女性.

【主　訴】後頭部の頭痛，右手足に力が入りにくい.

【既往歴】急性虫垂炎，脳血管障害の既往なし.

【嗜好・生活歴】喫煙：なし，飲酒：なし.

【家族歴】特記事項なし.

【現病歴】某年5月10日17時頃から後頭部痛を自覚

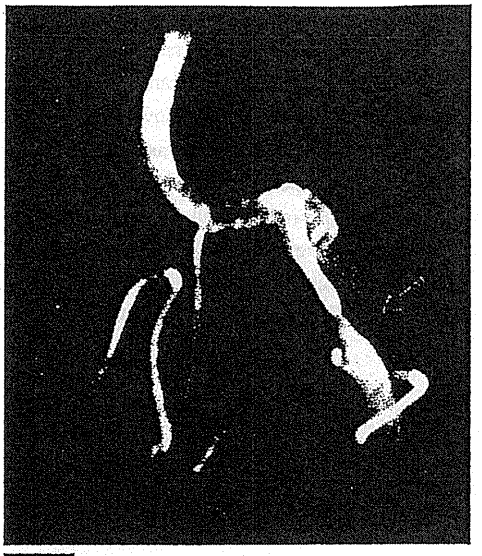

**図4** 頭部 MRA
左椎骨動脈の後下小脳動脈（PICA）分岐部付近に狭窄（矢印）と，末梢側の拡張所見を認めた．

**図5** 脳血管造影検査
左椎骨動脈の PICA 分岐部より末梢側に瘤状の拡張所見を認めた．

し，気分が悪くなった．市販の頭痛薬を内服して様子をみたが，症状改善しなかった．22時頃に起き上がったところ，右手足に力が入りにくかったため救急要請した．22時30分に当院救急外来に到着した．

【入院時現症】身長154cm，体重68kg，血圧153／105 mmHg，脈拍85bpm 整．

一般身体所見：右下腹部に手術痕あり．

神経学的所見：意識清明，右上肢は挙上保持可能だが回内あり，右下肢は膝立て可能だが十分な挙上が不可能，その他特記事項なし．

【入院時検査所見】総コレステロール211mg/dL，中性脂肪91mg/dL，LDL コレステロール142mg/dL，HDL コレステロール49mg/dL，D-dimer 0.5μg/mL，凝固・肝腎機能・血糖は正常であった．

【入院後経過】来院時の頭部 MRI で明らかな病巣を認めなかった．翌朝には軽度の後頸部～頭部痛は残存していたが，右上下肢の運動麻痺は消失していたため，TIA と診断した（ABCD²スコア＝5点）．原因精査を行ったところ，頭部 MRA で左椎骨動脈の狭窄と狭窄後拡張所見を認めた（図4）．脳動脈解離を疑い血管造影検査を行ったところ，左椎骨動脈の PICA 分岐部より末梢側に瘤状の拡張所見を認め，左椎骨動脈解離と診断した（図5）．診断後は血圧管理などの保存的治療を行い，その後症状増悪することなく経過した．

TIA の発症機序としては，アテローム血栓性機序が多いことが過去に報告されている[3]．実際に，今回報告した症例1では右内頸動脈に高度狭窄病変が存在した．アテローム血栓性梗塞と同様の機序で TIA を発症したものと考え，最終的に CEA を行った．一方で，症例2や3のように精査を行うことで，急性期治療や脳梗塞発症予防法の選択が変わることも稀ではない．TIA は症状が軽微であっても，基本的には脳梗塞の場合と同様に，その発症機序の早期同定に努める必要がある．

現在，国内外で TIA 臨床的意義や診断基準の見直しが始まっている．国内の厚生労働省科学研究費補助金による「TIA の診断基準の再検討，ならびにわが国の医療環境に則した適切な診断・治療システムの確立に関する研究」班では，多施設共同後ろ向き登録研究が開始されている．近年のわが国での TIA の動向を知るためにも，その結果が待たれるところである．いずれにせよ，TIA を疑った場合には，心電図や各種超音波検査，画像検査などを駆使し，その発症機序

を同定し，より適切な脳梗塞発症予防を行うことが必要である．

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# Early Hospital Arrival Improves Outcome at Discharge in Ischemic but Not Hemorrhagic Stroke: A Prospective Multicenter Study

Masaki Naganuma[a] Kazunori Toyoda[a] Hiroshi Nonogi[b] Chiaki Yokota[a]
Masatoshi Koga[a] Hiroyuki Yokoyama[b] Akira Okayama[c] Hiroaki Naritomi[a]
Kazuo Minematsu[a]

[a]Cerebrovascular Division and [b]Division of Cardiology, Department of Medicine, and
[c]Department of Preventive Medicine, National Cardiovascular Center, Suita, Japan

**Key Words**
Infarction · Intracerebral hemorrhage · Cohort studies · Outcome, stroke

**Abstract**
***Background:*** Our purpose was to determine whether the onset-to-arrival time affects the outcome of stroke patients. ***Methods:*** We carried out a prospective multicenter study involving 1,817 patients with ischemic stroke and 1,226 with intracerebral hemorrhage who presented to hospitals within 24 h of symptom onset. The primary outcome was independent activity of daily living corresponding to a modified Rankin Scale (mRS) score ≤2 at discharge approximately 3 weeks after stroke. ***Results:*** In ischemic stroke patients, the initial NIH Stroke Scale (NIHSS) score decreased as the onset-to-arrival time increased: 9 (median) in the earliest tertile group (<3 h), 5 in the second tertile group (3–8 h) and 4 in the latest tertile group (≥8 h, $p < 0.001$). The median mRS scores at discharge in these groups were 3, 2 and 2, respectively ($p < 0.001$). After adjustment for underlying features and the initial NIHSS score, the independent activity of daily living at discharge was 1.73 times more common in patients in the earliest group than in the latest group (95% CI = 1.24–2.42, $p = 0.001$). A similar tendency was shown in the subanalysis for large-artery atherosclerosis and cardioembolic stroke. In intracerebral hemorrhage patients, both the initial NIHSS score and the mRS score at discharge decreased as the onset-to-arrival time increased. After multivariate adjustment, the independent activity of daily living was 2.33 times ($p < 0.001$) and 1.69 times ($p = 0.006$) less common in patients in the earliest (<1.2 h) and second tertile groups (1.2–3.5 h), respectively, than in the latest tertile group (≥3.5 h). ***Conclusions:*** Early hospital arrival improved the clinical outcome in ischemic stroke patients but not in patients with intracerebral hemorrhage.


## Introduction

Since it is said that 'time is brain', rapid diagnosis and treatment of stroke are thought to give stroke victims better recovery. For this strategy, the American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care [1] focused on the initial prehospital assessment, including rapid recognition and reaction to stroke warning signs and rapid emergency medical services system transport to hospitals. In particular, the establishment of intravenous (IV) recombinant tissue plasminogen activator (rt-PA) as standard therapy for hyperacute stroke has increased the impor-

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Kazunori Toyoda, MD
Cerebrovascular Division, Department of Medicine
National Cardiovascular Center
Fujishirodai 5-7-1, Suita 565-8565 (Japan)
Tel. +81 6 6833 5012, Fax +81 6 6872 7486, E-Mail toyoda@hsp.ncvc.go.jp

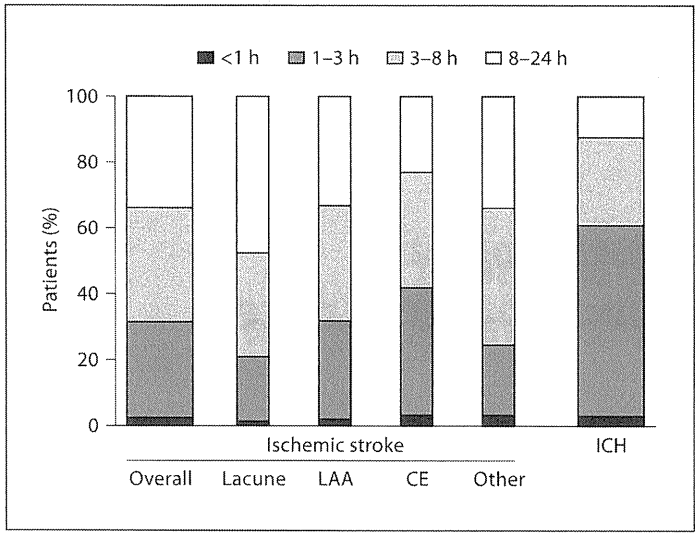


**Fig. 1.** Onset-to-arrival time for each stroke type. LAA = Large-artery atherosclerosis; CE = cardioembolism.

tance of rapid initiation of stroke therapy within 3 h of symptom onset [2–4]. However, previous studies have generally shown that patients who arrived at a hospital early after ischemic stroke onset had a worse functional outcome and higher mortality than those who arrived later [5, 6]. Major causes of this discouraging result might be that stroke patients with severer initial disability have a tendency to visit a hospital earlier [5–12], as well as the fact that previous studies did not adjust patient outcome for initial neurological severity. Although intracerebral hemorrhage (ICH) is associated with a poorer outcome than ischemic stroke, the positive relationship between early hospital visit and initial severity was reported only in studies based on relatively small numbers of patients [13, 14].

A prospective, multicenter, observational study was conducted in Japan to assess clinical evaluation indicators for stroke and acute coronary syndrome. In the present study, using the data of the stroke patients, we investigated whether early hospital arrival affected the patient outcome after adjustment for the initial severity.

## Patients and Methods

The Cooperative Study on the Clinical Evaluation Indicator for Cardiovascular Diseases in Japan was conducted between January 2005 and May 2007 at 27 hospitals in Japan. The medical ethics review boards of the participating institutes approved the study protocol. To revise the study protocol in response to a new Japanese law dealing with protection of personal information, the study had a 6-month-long pause in patient registration between April and September 2005.

Consecutive patients who were admitted to our hospitals within 24 h after the onset of ischemic stroke or ICH detectable on MRI or CT were enrolled. The patients with transient ischemic attack were excluded from this study; transient ischemic attack was defined as a brief episode of neurologic dysfunction caused by focal brain ischemia, with clinical symptoms typically lasting <1 h, and without evidence of acute infarction [15]. The following data were prospectively collected using common work sheets: age, sex, hypertension (use of antihypertensive agents, or systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg before onset), diabetes mellitus (use of oral hypoglycemic agents or insulin, or fasting blood glucose levels ≥126 mg/dl), hyperlipidemia (use of antihyperlipidemic agents or serum cholesterol level ≥220 mg/dl), atrial fibrillation identified on electrocardiogram, current smoking, alcohol abuse >60 g/day, time interval between symptom onset and hospital arrival (onset-to-arrival time), baseline neurological impairment according to the National Institutes of Health Stroke Scale (NIHSS) score, subtypes of ischemic stroke according to the Trial of Org 10172 in Acute Stroke Treatment classification [small-vessel occlusion (lacune), large-artery atherosclerosis, cardioembolism and stroke of other determined or undetermined etiology] [16], site of infarcts (infratentorial or supratentorial) and activity of daily living at hospital discharge according to the modified Rankin Scale (mRS) score.

The primary outcome was independent activity of daily living at discharge, corresponding to an mRS score ≤2. The secondary outcomes included an mRS score ≤1 at discharge and in-hospital death.

*Statistics*

The patients with ischemic stroke were classified into 3 groups by tertiles based on the onset-to-arrival time. The patients with ICH were classified in the same manner. Among the 3 groups, baseline clinical characteristics and stroke features were compared using the $\chi^2$ test, 1-way factorial analysis of variance or the Kruskal-Wallis test, as appropriate. To identify factors associated with the primary and secondary outcomes, multivariate logistic regression model analyses were performed using baseline clinical characteristics and stroke features. Statistical test results were considered significant with a p value <0.05. All analyses were performed using JMP version 6.0.3 statistical software (SAS Institute Inc., Cary, N.C., USA).

## Results

Of a total of 3,058 patients registered, 15 were ineligible for analyses due to missing data. Thus, 3,043 patients were studied; 1,817 had ischemic stroke, and 1,226 had ICH. The ischemic stroke patients visited hospitals at a median of 4.5 h after onset [interquartile range (IQR) = 3.0–8.0 h; fig. 1]. The onset-to-arrival time differed among patients with different subtypes of ischemic stroke

**Table 1.** Characteristics of ischemic and hemorrhagic stroke patients

| | Ischemic stroke | | | | ICH | | | |
|---|---|---|---|---|---|---|---|---|
| | <3 h (574 cases) | 3–8 h (632 cases) | ≥8 h (611 cases) | p value | <1.2 h (473 cases) | 1.2–3.5 h (424 cases) | ≥3.5 h (329 cases) | p value |
| Age, years | 72.1 ± 11.0 | 73.2 ± 12.0 | 72.6 ± 11.6 | 0.242 | 63.8 ± 14.1 | 67.7 ± 14.2 | 67.8 ± 13.9 | <0.001 |
| Male | 338 (58.9) | 385 (60.9) | 369 (60.4) | 0.759 | 252 (53.3) | 219 (51.7) | 166 (50.5) | 0.725 |
| Hypertension | 356 (62.0) | 382 (60.5) | 388 (63.5) | 0.561 | 322 (68.1) | 281 (66.6) | 210 (63.8) | 0.455 |
| Diabetes mellitus | 128 (22.3) | 140 (22.2) | 151 (24.8) | 0.491 | 40 (8.5) | 41 (9.7) | 31 (9.4) | 0.792 |
| Hyperlipidemia | 115 (20.1) | 127 (20.2) | 151 (24.8) | 0.079 | 40 (8.5) | 49 (11.6) | 36 (11.0) | 0.256 |
| Atrial fibrillation | 234 (40.8) | 205 (32.4) | 148 (24.2) | <0.001 | 21 (4.4) | 19 (4.5) | 20 (6.1) | 0.510 |
| Smoking | 124 (22.4) | 129 (21.6) | 155 (26.9) | 0.053 | 123 (27.0) | 59 (14.8) | 54 (17.7) | <0.001 |
| Alcohol abuse | 24 (4.2) | 32 (5.1) | 23 (3.8) | 0.514 | 30 (6.7) | 18 (4.3) | 18 (5.5) | 0.389 |
| Infratentorial infarct | 84 (14.9) | 101 (16.3) | 145 (23.9) | <0.001 | | | | |
| Stroke subtype | | | | | | | | |
| Lacune | 94 (16.4) | 143 (22.6) | 218 (35.7) | <0.001 | | | | |
| Large-artery atherosclerosis | 189 (32.9) | 210 (33.2) | 196 (32.1) | | | | | |
| Cardioembolism | 248 (43.2) | 206 (32.6) | 138 (22.6) | | | | | |
| Other | 43 (7.5) | 73 (11.6) | 59 (9.7) | | | | | |
| Initial NIHSS score | 9 (4–17) | 5 (2.25–11) | 4 (2–7) | <0.001 | 8 (4–21) | 8 (4–19) | 6 (3–15) | 0.001 |
| mRS score at discharge | 3 (1–5) | 2 (1–4) | 2 (1–4) | <0.001 | 4 (2–6) | 4 (2–5) | 3 (1–5) | <0.001 |
| In-hospital death | 61 (10.6) | 38 (6.0) | 31 (5.1) | <0.001 | 139 (29.5) | 104 (24.8) | 52 (16.0) | <0.001 |

Data are numbers of patients (percent), mean ± SD for age, or median (IQR) for NIHSS score and mRS score.

(p = 0.001). The median onset-to-arrival time for the ICH patients was 2.0 h (IQR = 1.2–3.5). The median duration of hospitalization was 22 days (IQR = 14–36) in the ischemic stroke patients and 24 days (IQR = 13–42) in the ICH patients.

In the ischemic stroke patients, atrial fibrillation was less common (p < 0.001) and infratentorial infarcts were more common (p < 0.001) as the onset-to-arrival time increased (table 1). Cardioembolism was the leading subtype in the earliest tertile group visiting hospitals within <3.0 h, while lacune was the leading subtype in the latest group visiting hospitals within ≥8.0 h (p < 0.001). The initial NIHSS score, the discharge mRS score and the in-hospital mortality rate decreased as the onset-to-arrival time increased (p < 0.001 for each). After multivariate adjustment, early hospital arrival within <3.0 h was independently predictive of an mRS score ≤2 at discharge compared to arrival within ≥8.0 h as the reference [odds ratio (OR) = 1.73, 95% CI = 1.24–2.42; table 2]. In addition, advanced age (OR = 0.96, 95% CI = 0.95–0.97 per 1-year increase, p < 0.001), diabetes mellitus (OR = 0.85, 95% CI = 0.73–0.98, p = 0.026), a higher NIHSS score (OR = 0.74, 95% CI = 0.72–0.77 per 1-point increase, p < 0.001) and large-artery atherosclerosis (OR = 0.52, 95% CI = 0.38–0.73, p = 0.001 compared with lacune as the reference) were inversely predictive of an mRS score ≤2. In a similar multivariate adjustment for patients of each ischemic stroke subtype, early arrival within <3.0 h was independently related to an mRS score ≤2 at discharge for the patients with large-artery atherosclerosis (OR = 2.07, 95% CI = 1.21–3.62) and for those with cardioembolism (OR = 1.87, 95% CI = 1.01–3.49; table 3). As secondary outcomes, early hospital arrival within <3.0 h was independently predictive of an mRS score ≤1 at discharge (OR = 1.66, 95% CI = 1.21–2.28), but it was not predictive of in-hospital death (OR = 0.90, 95% CI = 0.53–1.52).

In the ICH patients, age (p < 0.001) and smoking habit (p < 0.001) differed among the 3 groups with different onset-to-arrival times (table 1). The initial NIHSS score (p = 0.001), the discharge mRS score (p < 0.001) and the in-hospital mortality rate (p < 0.001) decreased as the onset-to-arrival time increased. After multivariate adjustment, the earliest (<1.2 h) and the second (1.2–3.5 h) tertiles of onset-to-arrival time were inversely predictive of an mRS score ≤2 at discharge compared to arrival within ≥3.5 h as the reference (OR = 0.43, 95% CI = 0.30–0.63, and OR = 0.59, 95% = CI 0.40–0.86, respectively; table 2). Even when the ICH patients were divided into 3 groups using the same onset-to-arrival time points as for ischemic stroke, early arrival within <3.0 h (747 patients) was

**Table 2.** Effect of onset-to-arrival time on the primary and secondary outcomes

| | mRS ≤2 at discharge | | | mRS ≤1 at discharge | | | In-hospital death | | |
|---|---|---|---|---|---|---|---|---|---|
| | OR | 95% CI | p value | OR | 95% CI | p value | OR | 95% CI | p value |
| Ischemic stroke | | | | | | | | | |
| <3 | 1.73 | 1.24–2.42 | 0.001 | 1.66 | 1.21–2.28 | 0.002 | 0.90 | 0.53–1.52 | 0.685 |
| 3–8 h | 0.98 | 0.73–1.32 | 0.916 | 1.15 | 0.87–1.53 | 0.325 | 0.83 | 0.48–1.44 | 0.503 |
| ≥8 h | 1.00 | (reference) | – | 1.00 | (reference) | – | 1.00 | (reference) | – |
| ICH | | | | | | | | | |
| <1.2 h | 0.43 | 0.30–0.63 | <0.001 | 0.46 | 0.30–0.68 | <0.001 | 2.41 | 1.62–3.64 | <0.001 |
| 1.2–3.5 h | 0.59 | 0.40–0.86 | 0.006 | 0.50 | 0.33–0.75 | <0.001 | 1.59 | 1.05–2.43 | 0.030 |
| ≥3.5 h | 1.00 | (reference) | – | 1.00 | (reference) | – | 1.00 | (reference) | – |

Adjusted for age, sex, hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, initial NIHSS score, infratentorial infarction and stroke subtype (the latter 2 confounders were used for ischemic stroke patients only).

**Table 3.** Effect of onset-to-arrival time on the primary outcome (mRS ≤2 at discharge) for each ischemic stroke subtype

| | Patients | OR | 95% CI | p value |
|---|---|---|---|---|
| Large-artery atherosclerosis | | | | |
| <3 h | 189 | 2.07 | 1.21–3.62 | 0.009 |
| 3–8 h | 210 | 0.81 | 0.50–1.31 | 0.389 |
| ≥8 h | 196 | 1.00 | (reference) | – |
| Cardioembolism | | | | |
| <3 h | 248 | 1.87 | 1.01–3.49 | 0.047 |
| 3–8 h | 206 | 1.17 | 0.65–2.15 | 0.599 |
| ≥8 h | 138 | 1.00 | (reference) | – |
| Lacune | | | | |
| <3 h | 94 | 1.27 | 0.62–2.75 | 0.524 |
| 3–8 h | 143 | 1.03 | 0.56–1.91 | 0.932 |
| ≥8 h | 218 | 1.00 | (reference) | – |
| Other | | | | |
| <3 h | 43 | 1.20 | 0.37–4.03 | 0.767 |
| 3–8 h | 73 | 2.03 | 0.41–2.58 | 0.952 |
| ≥8 h | 59 | 1.00 | (reference) | – |

Adjusted for age, sex, hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation and initial NIHSS score.

inversely predictive of an mRS score ≤2 compared to arrival within ≥8.0 h as the reference (149 patients, OR = 0.49, 95% CI = 0.31–0.78). As secondary outcomes, the earliest and second tertiles were inversely predictive of an mRS score ≤1 (OR = 0.46, 95% CI = 0.30–0.68, and OR = 0.50, 95% CI = 0.33–0.75, respectively) and positively predictive of in-hospital death (OR = 2.41, 95% CI = 1.62–3.64, and OR = 1.59, 95% CI = 1.05–2.43, respectively).

## Discussion

In the present study, we determined the effect of the time interval between stroke onset and hospital arrival on the outcome at discharge. The first major finding was that, after adjustment for confounders including the initial neurological severity, early hospital arrival was related to a favorable functional outcome corresponding to an mRS score ≤1 or ≤2 in the ischemic stroke patients, in particular among those with large-artery atherosclerosis and cardioembolism. The second major finding was that, after multivariate adjustment, early hospital arrival was related to an unfavorable functional outcome and in-hospital death in the ICH patients.

Ischemic stroke patients with severer initial disability have a tendency to visit hospitals earlier [5–12], and severe initial disability is a known predictor of a poor chronic outcome [17–21]. Thus, patients with earlier hospital arrival were reported to have a poorer outcome [5, 6], as was shown in the present unadjusted results. To minimize the influence of initial severity on the outcome, multivariate adjustment was incorporated into the analyses. Our adjusted results suggest that early hospital arrival contributes to better stroke recovery. A previous study using logistic regression analyses showed that early contact with a neurologist, but not early visit to the emergency department, after onset of stroke (mostly ischemic) was related to a good outcome on discharge [7]. This result suggests the limited acute stroke management capabilities of the emergency department when the study was conducted in the early 1990s.

Spontaneous or thrombolysis-induced improvement of the clinical features within minutes to hours of isch-

emic stroke onset is seen in some patients. In particular, a spontaneous dramatic improvement was called a spectacular shrinking deficit by Mohr and Barnett [22], and it was thought to be caused by rapid migration of an embolus initially lodged in a large artery to its distal branches [23]. In our previous studies, 12% of the ischemic stroke patients with an initial major hemispheric syndrome who did not receive thrombolysis showed spectacular shrinking deficit, and most of these patients visited our hospital within 4 h of stroke onset [24, 25]. Thus, this syndrome may be responsible for the association between early hospital arrival and a favorable outcome. Although IV rt-PA for hyperacute ischemic stroke can improve the patient outcome [2–4], this therapy might have affected our results less than previous studies from Western countries [5]. In Japan, IV rt-PA for stroke was approved just during the time of the present study (in October 2005); hence, the percentage of stroke patients receiving rt-PA during this period was not high. In fact, a postmarketing surveillance study estimated the rate to be approximately 2% between October 2005 and May 2007. In the present study, conventional management for ischemic stroke, including general supportive care, early initiation of oral aspirin and prevention of acute complications, may have contributed to the good outcome for the patients who arrived at the hospital early. In particular, the early initiation of management might be effective for atherothrombotic and cardioembolic strokes, which have a much higher risk of early clinical progression and recurrence than lacunar stroke [26–31].

Active bleeding of ICH is generally thought to cease within the first few hours; the Factor Seven for Acute Hemorrhagic Stroke Treatment trial indicated that little active bleeding occurs between the third and fourth hours after ICH onset [32]. The frequency of hematoma growth significantly decreased with time [33–36]. A previous study from our institute showed that the frequency was 36% when the initial CT was taken within 3 h from onset, 16% when the timing was 3–6 h, 15% when it was 6–12 h and 6% for 12–24 h [34]. In addition, hematoma growth is an established cause of clinical deterioration [34, 37, 38]. Thus, a potent reason for the poor outcome after ICH for early visitors after adjustment for initial severity appears to be that early hospital arrival increases the opportunity for continued active bleeding after arrival, which causes hematoma growth and clinical deterioration. The International Surgical Trial in Intracerebral Haemorrhage [39] failed to show an overall benefit from early surgery for ICH patients when compared with initial conservative treatment. These findings resulted in a relative increase in the role of medical therapies for acute ICH. Although the trial of efficacy and safety of recombinant activated factor VII for acute ICH failed [40], in the near future, new thrombostatic strategies may suppress active bleeding during the initial hours and be beneficial for early visitors.

Certain limitations need to be considered prior to the interpretation of the present study results. First, the data on acute therapies, including IV rt-PA, intra-arterial thrombolysis, antithrombotics, statins, surgery and the type of wards, were incomplete and could not be used for analysis. Second, unknown prehospital mortality might systematically bias the patient characteristics, especially in cases after ICH. Third, information on stroke recurrence or hematoma growth was not available. Fourth, the chronic outcome at 3 months was not evaluated. Although the outcome was assessed at hospital discharge, this timing might depend on the availability of secondary care facilities, such as rehabilitation centers or nursing homes. Fifth, we did not assess the data on NIHSS sub-items as an indicator for baseline neurological impairment.

In conclusion, early hospital arrival improved the patient outcome after ischemic stroke, even before rt-PA use had become routine. In Japan, given rt-PA approval in 2005, the setting for acute stroke management, including IV rt-PA and stroke care unit equipment, has been drastically improved. This improvement will further strengthen the clinical significance of early hospital arrival. Meanwhile, early hospital arrival was associated with a poorer outcome after ICH; this suggests the lack of efficient emergent management for ICH at this time point compared with ischemic stroke.


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# Albuminuria, but not metabolic syndrome, is a significant predictor of stroke recurrence in ischemic stroke

Chiaki Yokota *, Kazuo Minematsu, Atsushi Ito, Kazunori Toyoda, Hikaru Nagasawa, Takenori Yamaguchi

*Cerebrovascular Division, Department of Medicine, National Cardiovascular Center Suita, Osaka, Japan*

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ABSTRACT

The aim of this study is to determine if there was an association of stroke recurrence with metabolic syndrome (MetS), defined by the National Cholesterol Education Program's Adult Treatment Panel III (NCEP-III) report or the International Diabetes Federation (IDF), as well as with other risk factors, including albuminuria. From February 1, 2004 to February 5, 2006, 523 patients were admitted to our Stroke Care Unit within 7 days of stroke onset. After excluding 22 patients who died in hospital and 27 patients who did not provide consent, 474 survivors (M/F=313/161, median age, 71 years) were enrolled. End-point events were fatal or nonfatal stroke. Diagnosis of MetS by NCEP-III criteria was made in 33% of patients, and by IDF criteria in 26%. During follow-up (505.4 person-years), 2 patients dropped out. Forty-nine patients among 370 with ischemic stroke and 5 patients among 102 patients with brain hemorrhage had stroke recurrence, being fatal in 3. A significant predictor of recurrence was albuminuria (HR: 1.835, 95% CI: 1.005–3.350) in ischemic stroke. There were no significant predictors of stroke recurrence in patients with brain hemorrhage. In conclusion, albuminuria, but not MetS, was a significant predictor of stroke recurrence in ischemic stroke.



## 1. Introduction

Stroke is not only a major cause of death but also a leading cause of disability worldwide. Abdominal obesity, regarded as crucial in the pathogenesis of metabolic syndrome (MetS), has been shown to induce hypoadiponectinemia together with increases in tumor necrosis factor and plasminogen activator inhibitor type 1, leading to vascular changes and metabolic disorders, including insulin resistance [1]. Since MetS was reported to be a significant predictor of future stroke [2–5] as well as of coronary heart disease in the general population [6–12], therapeutic lifestyle changes, with emphasis on body weight reduction, have been considered to be important. Several studies also have shown MetS to be associated with carotid atherosclerosis [13–16]. Kurl et al. [2] demonstrated that the risk of stroke was increased in men with MetS, as defined by the National Cholesterol Education Program's Adult Treatment Panel Third (NCEP-III) report [17] and World Health Organization (WHO) [18] criteria, in the absence of stroke, diabetes and cardiovascular diseases at baseline. MetS has been speculated to be associated with the development of atherosclerosis, a leading cause of future cardiovascular diseases, including stroke. However, the impact of MetS on stroke recurrence has not been clarified.

In the present study, we aimed to clarify whether there was an association between stroke recurrence and MetS as defined either by the NCEP-III or International Diabetes Federation (IDF) [19] or between stroke recurrence and risk factors such as albuminuria, hypertension (HT), diabetes mellitus (DM), and hypercholesterolemia (HCL).

## 2. Methods

### 2.1. Patients

This is a single-center hospital-based prospective study that was approved by our Institutional Research and Ethics Committee. Subjects were 523 patients who were admitted to our Stroke Care Unit within 7 days of stroke onset from February 1, 2004 to February 5, 2006. After excluding 22 patients who died during the hospital stay and 27 patients who did not provide consent for this research, 474 stroke survivors who did provide consent (men/women=313/161, median age, 71 years (range 22–94)) were enrolled (Table 1). All patients with subarachnoid hemorrhage of a ruptured aneurysm were admitted to the Neurosurgical Care Unit and were not included in the study.

### 2.2. Baseline assessment

Baseline clinical characteristics, including age, sex, presence of HT, HCL, DM, and ischemic heart disease (IHD), and past history of stroke at the time of admission, were recorded. Information on risk factors and

* Corresponding author. Cerebrovascular Division, Department of Medicine, National Cardiovascular Center 5-7-1, Fujishirodai, Suita, Oaka, 565-8565 Japan. Tel.: +81 6 6872 7486, +81 6 6833 5012; fax: +81 6 6872 7486.
*E-mail address:* cyokota@hsp.ncvc.go.jp (C. Yokota).

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**Table 1**
Baseline characteristics of all study subjects

| | |
|---|---|
| Sex (M/F) | 313/161 |
| Age (years, mean±SD) | 70±11 |
| Ischemic heart disease | 72 (15) |
| Past history of stroke | 145 (31) |
| Hypertension | 397 (84) |
| Diabetes mellitus | 145 (31) |
| Hypercholesterolemia | 112 (24) |
| Atrial fibrillation | 122 (26) |
| MetS (NCEP-III) | 157 (33) |
| MetS (IDF) | 122 (26) |
| Albuminuria | 165 (35) |
| Microalbuminuria | 133 (28) |
| Macroalbuminuria | 32 (7) |
| Body mass index (kg/m$^2$) | 23.0±3.3 |

MetS (NCEP-III): metabolic syndrome as diagnosed by NCEP-III criteria, MetS (IDF): metabolic syndrome as diagnosed by IDF criteria, (): %.

past medical history was inferred from a self-reported medical history or prescribed medication by home doctors. We defined HCL as a total cholesterol level of ≥220 mg/dl or the use of statins. HT was indicated by systolic blood pressure (BP) ≥140 mm Hg or diastolic BP ≥90 mm Hg at 2 independent measurements 2 weeks after stroke onset or the use of anti-hypertensive drugs. DM was defined as a fasting blood glucose level ≥126 mg/dl or an ambient blood glucose value ≥200 mg/dl. Patients who had been treated with insulin or oral hypoglycemic agents were also diagnosed as having DM. Information on medications prescribed at discharge were obtained from medical records.

Brain CT, carotid ultrasonography, and ECG were always performed on admission. To evaluate cervico-cephalic arteries, magnetic resonance angiography or conventional digital subtraction cerebral angiography was performed in addition to carotid ultrasonography. Two-dimensional echocardiography was done to investigate a potential embolic source if the patient had possible cardioembolic infarction. Morning blood samples after an overnight fast for measurement of glucose and lipid levels and morning urine samples for screening for albuminuria, including microalbuminuria and macroalbuminuria, were obtained 2 weeks after stroke onset to avoid contamination by acute effects of stroke. Plasma glucose levels were examined by the glucose-oxidase method, and triglyceride, total cholesterol, low density lipoprotein (LDL) cholesterol, and high density lipoprotein (HDL) cholesterol levels were measured enzymatically. Microalbuminuria was defined as an albumin-to-creatinine ratio between 20 and 300 mg/g creatinine, and macroalbuminuria was defined by a value above 300 mg/g creatinine in a morning urine sample. BP on the day of discharge and waist circumference on an average of 18 days after stroke onset were measured in all patients. Diagnosis of MetS was determined according to the criteria of NCEP-III [17] and that of IDF [19]. The waist circumference cutoff selected as indicating abdominal obesity was the same as that used by the Japan Society of Internal Medicine (men≥85 cm, women≥90 cm) [20].

Stroke subtypes, such as atherothrombotic brain infarction ($n$=61), lacunar infarction ($n$=64), cardioembolic infarction ($n$=100), other types of infarction ($n$=103), transient ischemic attack ($n$=43), and brain hemorrhage ($n$=103), were diagnosed as previously described [21], mainly according to the criteria in the Classification of Cerebrovascular Disease III [22].

**Table 2**
Comparison of medications prescribed at discharge between subjects with and without stroke recurrence

| | Recurrence (−) $n$=418 | Recurrence (+) $n$=54 | $p$ value |
|---|---|---|---|
| Angiotensin converting enzyme inhibitors | 86 (21) | 11 (20) | 1.00 |
| Angiotensin II receptor blockers | 97 (23) | 10 (19) | 0.494 |
| Calcium antagonists | 134 (32) | 20 (37) | 0.645 |
| Statins | 77 (18) | 9 (17) | 0.853 |
| Pioglitazone | 3 (0.7) | 1 (2) | 0.386 |
| Aspirin | 205 (49) | 33 (61) | 0.112 |
| Warfarin | 138 (33) | 20 (37) | 0.544 |

(): %.

**Table 3**
Comparison of characteristics of ischemic stroke patients with and without stroke recurrence

| Characteristics | | Recurrence (−) $n$=322 | Recurrence (+) $n$=49 | $p$ |
|---|---|---|---|---|
| Male | | 207 (64) | 39 (80) | 0.036 |
| Age (years) | | 70±12 | 71±10 | 0.690 |
| Body mass index (kg/m$^2$) | | 23.1±3.2 | 22.6±3.0 | 0.416 |
| Hypertension | | 258 (80) | 44 (90) | 0.118 |
| Diabetes mellitus | | 95 (30) | 25 (51) | 0.005 |
| Hypercholesterolemia | | 78 (24) | 12 (24) | 1.000 |
| Atrial fibrillation | | 98 (30) | 14 (29) | 0.868 |
| Ischemic heart disease | | 55 (17) | 8 (16) | 1.000 |
| History of stroke | | 105 (33) | 15 (31) | 0.870 |
| Albuminuria | | 114 (35) | 25 (51) | 0.035 |
| Abdominal obesity | | 106 (33) | 16 (33) | 1.000 |
| Low HDL-cholesterol | | 149 (46) | 26 (53) | 0.443 |
| High triglyceride | | 51 (16) | 7 (14) | 1.000 |
| High fasting blood glucose (I*) | | 150 (47) | 30 (61) | 0.066 |
| High fasting blood glucose (N**) | | 79 (25) | 16 (33) | 0.224 |
| High blood pressure (N**) | | 236 (73) | 43 (88) | 0.032 |
| MetS (I*) | | 85 (26) | 13 (27) | 1.000 |
| MetS (N**) | | 108 (34) | 20 (41) | 0.336 |
| No. components | | | | 0.413 |
| (NCEP-III) | 0 | 24 | 1 | |
| | 1 | 79 | 10 | |
| | 2 | 111 | 18 | |
| | ≥3 | 108 | 20 | |

MetS: metabolic syndrome, I*: by the IDF definition, N**: by the NCEP-III definition, No. components: no. of MetS components of the NCEP-III criteria, (): %.

### 2.3. Patient follow-up

Every effort was made to have in-person follow-up until June 2006. Primary end points were fatal or nonfatal stroke recurrence. Recurrent stroke was defined as a new neurological deficit fitting the definitions of ischemic (including TIA) or hemorrhagic stroke and that was assessed and recorded by experienced stroke physicians. Information obtained at outpatient clinic ($n$=303), by telephone interviews ($n$=157), or from postal surveys ($n$=14) were conducted to identify occurrence of or death from cardiovascular diseases.

### 2.4. Statistical analysis

Statistical analyses were performed using the SPSS 16.0J statistical package (SPSS, Inc., 2007). Patients with ischemic stroke and those with brain hemorrhage were analyzed separately. To determine the differences in clinical characteristics among patients with and without endpoint events, the $\chi^2$ test or Student's $t$ test was used as appropriate.

Event-free survival time for stroke survivors was calculated from the date of stroke onset. Patients who died of a non-stroke cause or

**Table 4**
Results of multivariate Cox regression analysis of stroke recurrence in patients with ischemic stroke

| Variables | Hazard ratio | 95% CI | $p$ |
|---|---|---|---|
| Male | 1.959 | 0.955–4.017 | 0.066 |
| Diabetes mellitus | 1.803 | 0.681–4.778 | 0.236 |
| Albuminuria | 1.835 | 1.005–3.350 | 0.048 |
| High fasting blood glucose (I*) | 0.868 | 0.319–2.364 | 0.782 |
| High blood pressure (N**) | 1.992 | 0.832–4.773 | 0.122 |

I*: by the IDF definition, N**: by the NCEP-III definition.

had a non-stroke cardiovascular event or cardiovascular surgery were censored at the date of death or the event. We estimated the independent contribution of each factor to stroke recurrence by Cox proportional hazards models. Clinical covariates with a univariate probability value <0.05 were entered into the Cox proportional hazards models to adjust for potential confounders. A value of $p<0.05$ was considered to indicate a significant difference.

## 3. Results

Baseline characteristics in the present study are shown in Table 1. Using NCEP-III criteria and IDF criteria, 33% and 26% of patients, respectively, were diagnosed as having MetS. Medications prescribed at discharge did not differ significantly between those with and without stroke recurrence (Table 2). Medications at discharge in each stroke subtype (ischemic and hemorrhagic stroke) also did not differ between those with and without stroke recurrence (data not shown). During the follow-up period (505.4 person-years), one patient with ischemic stroke and one patient with brain hemorrhage dropped out of the study. Forty-nine patients among the 370 with ischemic stroke and 5 patients among the 102 patients with brain hemorrhage had stroke recurrence 122 days on average after the index stroke, which was fatal in 3 (2 hemorrhagic and a stroke of undetermined subtype). In 51 patients with non-fatal recurrence, 11 patients had hemorrhagic and 40 patients had ischemic stroke recurrence. In the patients with brain hemorrhage, all who had recurrence had hemorrhagic stroke recurrence. Patients having ischemic strokes with recurrence more frequently had DM (51% vs. 30%, $p=0.005$), albuminuria (51% vs. 35%, $p=0.035$), and high BP by the NCEP-III definition (88% vs. 73%, $p=0.032$) compared to those without recurrence (Table 3). By multivariable Cox regression analysis of individual risk factors, albuminuria (HR: 1.835, 95% CI: 1.005–3.350) alone was a significant predictor (Table 4). There were no significant predictors of stroke recurrence in patients with brain hemorrhage as the index stroke.

## 4. Discussion

The present study demonstrated that albuminuria was a significant predictor of stroke recurrence in those with ischemic stroke. Albuminuria, including micro- and macroalbuminuria, is known to be an independent risk factor for cardiovascular disease and increased all-cause mortality in individuals with or without DM [23]. It is uncertain whether albuminuria is an independent risk factor for recurrence of stroke in stroke survivors. In the present study, albuminuria was an independent risk factor for stroke recurrence in patients with ischemic stroke, taking into account high BP by the NCEP-III definition and DM. Albuminuria, considered to be a marker of endothelial dysfunction [24], was reported to be a risk factor for cerebral small vessel disease in elderly subjects [25]. Even very low levels of microalbuminuria were associated with increased risk of coronary heart disease and death in a population study [26]. Patients with ischemic stroke and albuminuria might have underlying macrovascular as well as microvascular diseases, indicating a condition that places them at high-risk for stroke recurrence. Although significant predictors of stroke recurrence were not determined in persons with brain hemorrhage, all patients with recurrence of brain hemorrhage had hemorrhagic stroke recurrence, indicating that control of blood pressure would be important after the onset of brain hemorrhage.

In the present study, MetS, as defined by either NCEP-III or IDF criteria, was not a significant predictor of stroke recurrence. Ovbiagele et al. [27] reported that MetS was not a significant risk factor for major vascular events in patients with symptomatic intracranial atherostenosis. After the establishment of atherosclerotic conditions, severity of micro- as well as macrovascular diseases rather than MetS might be responsible for bringing about cardiovascular diseases. The relatively short time period after the index stroke in this study would also favor severity of micro- and macrovascular diseases rather than individual risk factors as significant predictors of stroke recurrence. Other factors possibly influencing stroke recurrence are medications such as angiotensin converting enzyme inhibitors [28], angiotensin II receptor antagonists and statins [29]. However, medications prescribed at discharge in the present study did not differ significantly between those with and without stroke recurrence.

A limitation of this study is the relatively small sample size of subjects for detection of significant predictors, especially in patients with brain hemorrhage. Although albuminuria was demonstrated to be a determinant of stroke recurrence in patients with ischemic stroke, larger studies with more subjects would be needed to achieve more precise estimates. This study was a single-hospital based study design performed at the National Cardiovascular Center, which allowed for a high follow-up rate of 99%. A large proportion of subjects had severe atherosclerotic diseases, which would be expected from a patient population at such a Center; however, this could influence the results. A second limitation is how the diagnosis of MetS was made. Blood and urine samples for that purpose were obtained 2 weeks after stroke onset but before discharge. This time point was chosen to avoid contamination by the acute effects of stroke. Restricted dietary intake during hospitalization may have led to underestimation of serum lipid and glucose levels. The proportion of patients with low HDL cholesterol levels (men; <40 mg/dl, women; <50 mg/dl) was relatively high (271/474 patients, 57%). Also, the proportion of patients with high BP was high (338/474, NCEP-III criteria; 426/474, IDF criteria). We do not think that this limitation would profoundly influence the proportion of subjects with MetS in the present study.

In conclusion, albuminuria, but not MetS, was a significant predictor of stroke recurrence in patients with ischemic stroke. Screening of albuminuria would be a simple and practical examination for predicting stroke recurrence. Further research is required to determine whether implementing a decrease in albuminuria would be a promising strategy for preventing stroke recurrence.

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