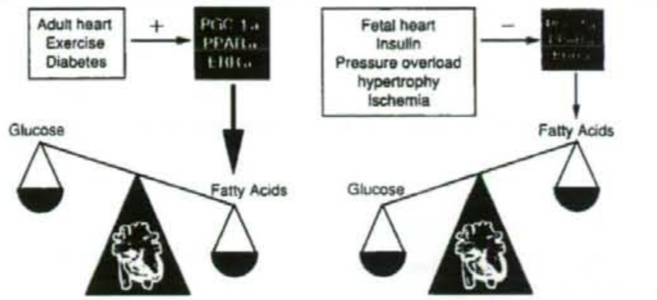
図❶　心筋エネルギー基質利用の動的な調節（代謝シフト）の存在（文献1より）



核受容体（PPAR α，ERR α）とリガンド（PGC-1 α）の発現ならびに活性の変化によって，図のような種々の条件下で代謝シフトが出現する。

ることに起因するが，二次的に心機能維持にとって重要な細胞処理の調節不全を助長する。そして，それはエネルギー需要を高める結果となり，機能をさらに低下させる下降スパイラルを導く。したがって臨床的には，このような代謝調節の変動をモニターすることは，心不全の病態把握・重症度評価に極めて重要であり，近年急速に進歩する心不全治療の分野で，その効果判定に有益な情報を提供すると期待されている。

Ⅱ．代謝イメージング技術の概要

1．^{31}P-MRS[2]

組織内の化学物質の構成によって磁気共鳴スペクトルの周波数が変動すること（化学シフト）を利用するもので，MRI装置にスペクトル計測用の表面コイルを装備して計測する。使用する核種（^{1}H, ^{31}P, ^{19}F, ^{13}Cほか）によって異なる化学シフトが観察される。心臓で用いられる^{31}P-MRS法では，クレアチンリン酸（CP），ATPの3つの分離したピーク，無機リン酸（Pi），糖リン酸などのピークからなるスペクトルが観察される。このピークの高さ（面積）の違いは，それぞれの物質濃度の相対比を反映する。臨床計測では絶対量の計測が困難であるため，心筋エネルギー状態の評価には，CP＋ ADP→ATP＋Crの関係に基づいて，一般にCP/ATP比が使用されている。

2．^{123}I-BMIPP SPECT[3]，^{18}F-FTHA PET[4]

ともに長鎖脂肪酸の細胞内停留型トレーサーである。^{123}I-BMIPPは，長鎖脂肪酸のカルボキシル基のβ位にメチル基を導入した側鎖型脂肪酸のヨード標識SPECT製剤で，天然の遊離脂肪酸と同様に細胞内に摂取されるが，ミトコンドリアでのβ酸化を受けずに主として脂質プールにトラップされる性質をもつ。その細胞内への停留性に基づいて，心筋の脂肪酸利用の状態が評価できる。特に虚血心筋部での局所的な集積低下像は，冠動脈疾患の診断情報として有用性が認められている。^{18}F-FTHAもほぼ同様の原理に基づくPET製剤であるが，現在のところ本邦では臨床応用されていない。

3．^{11}C-palmitate PET[5]

長鎖脂肪酸の代謝型トレーサーである。その心筋クリアランス速度に基づいて脂肪酸β酸化の代謝速度が評価できる。静脈投与直後からのダイナミックスキャン（1 min/frame）によって，心筋のトレーサー摂取ならびにクリアランスの動態解析を行う。心筋集積は投与後約5分でピークに達した後にクリアランスされる（biexponential）。初期の急速クリアランス相は^{11}C-palmitateのβ酸化と$^{11}CO_2$としての洗い出しの代謝プロセスを反映すると考えられ，そのクリアランス速度に基づいて評価を行う。

4．^{18}F-FDG PET[6]

グルコースの2位の炭素に結合する水酸基を^{18}F

で置換したもので，細胞内輸送とヘキソキナーゼによる代謝の段階まではグルコースと共通の経路をたどり，^{18}F-FDG-6-リン酸となるが，それ以後は代謝を受けない。また，脱リン酸化も非常に緩徐であるため，摂取された^{18}F-FDGは細胞内に捕捉された状態となる（metabolic trap）。したがって，細胞のグルコース利用の状態を^{18}F-FDG集積の程度から評価が可能である。また，ダイナミックスキャンと代謝のコンパートメントモデル解析に基づいて心筋グルコース代謝速度の計測が可能である。

5．^{11}C-acetate PET[7]

TCAサイクルの基質であるアセテートを^{11}C標識したもので，好気的な心筋エネルギー代謝の状態を，エネルギー基質（脂肪酸，糖）の血中濃度に影響されずに評価できる。^{11}C-acetateは，アセテートの代謝プロセスに沿って，^{11}C-acetyl-CoAとなり，TCAサイクルに入り，^{11}C-CO$_2$になって心筋から放出される。したがって，ダイナミックスキャンで計測された心筋のクリアランス曲線から，このアセテートの代謝速度，ひいてはTCAサイクルの代謝回転を評価することが可能である。同曲線の指数関数近似から求めたクリアランス速度定数（Kmono）が，心筋酸素消費量に相関することが示されている。また，心臓の酸素効率を示す指標として，Kmonoと心仕事量の計測に基づいて，work-metabolic index（WMI＝心拍数×1回拍出量×平均血圧/Kmono×体表面積）が計算され，臨床応用されている。

Ⅲ．代謝イメージングの臨床応用

心筋エネルギー代謝は，胎児からの成長とともに，グルコース依存から脂肪酸依存へと代謝の変換が進み，成人では基本的には脂肪酸代謝が優位となる。それでも両代謝系の相補的な調節が存在し（glucose-fatty acid cycle），生理的には，グルコース代謝へのシフトが，高炭水化物食の摂取後（血糖値の上昇とインスリン分泌の亢進）や運動時（心仕事量の増大に伴う細胞内Ca^{2+}濃度の増加を刺激としてグルコーストランスポーターが動員される）に出現する。一方，このグルコースへの代謝シフトは，種々の病態においてエネルギー欠乏を補うべく作動することが知られている。現在の代謝イメージング技術は，この非生理的な代謝シフトを観察するところに臨床的意義が認められる[8]。以下に，その臨床知見を基礎研究の成果と併せて紹介する。

1．加齢

加齢に伴う代謝系の変化として，ミトコンドリアにおける脂質異常，酸素ラジカルによる障害，carnitine palmitoyltransferase 1（CPT-1）活性の低下，長鎖脂肪酸摂取の律速酵素の活性低下，PPARαによる転写活性の低下などが報告され，脂肪酸代謝障害の進行が指摘されている。健康人を対象としたPETによる検討では，加齢に伴い脂肪酸代謝の低下と相補的なグルコース代謝の亢進があり，上記の基礎研究の成績に合致した所見が観察されている[9]。また一方，高齢者は若年者に比べてドブタミンによる交感神経刺激に対してグルコース利用を増加させる能力が低下しているとの報告もあり，代謝系全体の加齢効果について，さらなる研究が必要とされている。

2．心筋虚血・再灌流

心筋虚血によって好気的代謝が抑制されるなかで，嫌気的解糖系が作動しグルコース代謝が亢進する。また，再灌流により虚血が回避された後にも，虚血によって発現したグルコーストランスポーター（GLUT-1，GLUT-4）の増加が持続し，グルコース代謝優位の状態が遷延すると報告されている。このような虚血・再灌流に伴う代謝シフト現象は，急性心筋梗塞再灌流療法後の患者で，^{123}I-BMIPP SPECTと^{18}F-FDG PETによって臨床的に観察されてきた（図❷）[10]。この虚血心筋のグルコース代謝亢進は，冠動脈疾患の心筋バイアビリティ評価における^{18}F-FDG PETの有用性の基盤である。

3．心筋肥大

脂肪酸代謝系の酵素に遺伝的な欠損をもつ子供は心筋肥大を起こすことが知られている。また実験動物でも，脂肪酸のβ酸化を抑制した場合に心筋肥大が出現することが報告されている。また最近では，^{123}I-BMIPP SPECTで心筋無集積像を呈するI型CD36欠損症（長鎖脂肪酸の細胞膜輸送タンパクであるCD36の欠損）と心筋肥大の関係が示唆さ

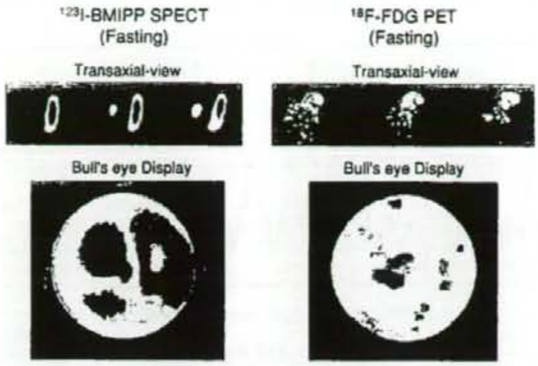
第2章 生物学的応用編

れている（図❸）[11]。逆に，圧負荷が持続的に加えられた心臓では，脂肪酸代謝の酵素発現が減少し，脂肪酸代謝の低下とグルコース代謝の亢進が起こることが多くの実験動物モデルで報告されている。臨床例でのPETによる検討でも同様の代謝シフトが報告されている[12]。肥大型心筋症では，最近になって脂肪酸代謝の調節因子の1つであるadenosine-monophosphate-activated protein kinase（AMPK）の遺伝子の突然変異が発見されているが，代謝イメージングでは ^{123}I-BMIPPの集積低下と ^{18}F-FDGの集積亢進が以前から観察されてきた[13]。

4．拡張型心筋症/心不全

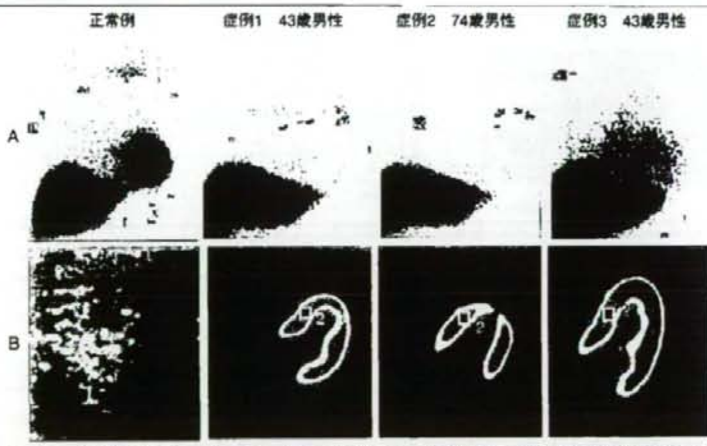
心不全の実験動物モデルでの検討で，心肥大から左室不全への移行に伴い，脂肪酸 β 酸化酵素の遺伝子発現が減少し，その結果，胎児心臓のようなグルコース代謝優位の状態になることが示されている（胎児化現象）[14]。この現象は，グルコース代謝の酸素節約効果を介して不全心の酸素需要が減少するけれども，相対

図❷　急性心筋虚血における代謝シフト



急性心筋梗塞で再灌流療法が実施された症例。発症後1週間目の検査で，虚血・再灌流の前壁中隔部に ^{123}I-BMIPP欠損と鏡像的な ^{18}F-FDG集積亢進が観察された。脂肪酸利用の低下に対しグルコース利用の亢進が持続していることが示唆される。　（グラビア頁参照）

図❸　I型CD36欠損症における代謝シフト

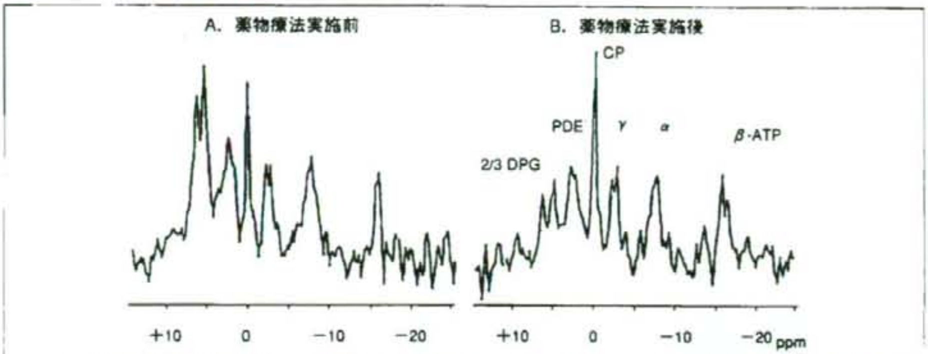


CD36欠損症のうち血小板と単球の両者で欠損のあるI型では，心筋細胞で長鎖脂肪酸輸送を担うタンパクとしてのCD36欠損があるため，心筋には ^{123}I-BMIPPが摂取されない（症例1～3）。そして，脂肪酸利用の低下に対してグルコース利用が亢進することを反映して，高度な ^{18}F-FDGの心筋集積が認められる。

A．^{123}I-BMIPP (anterior planar image)

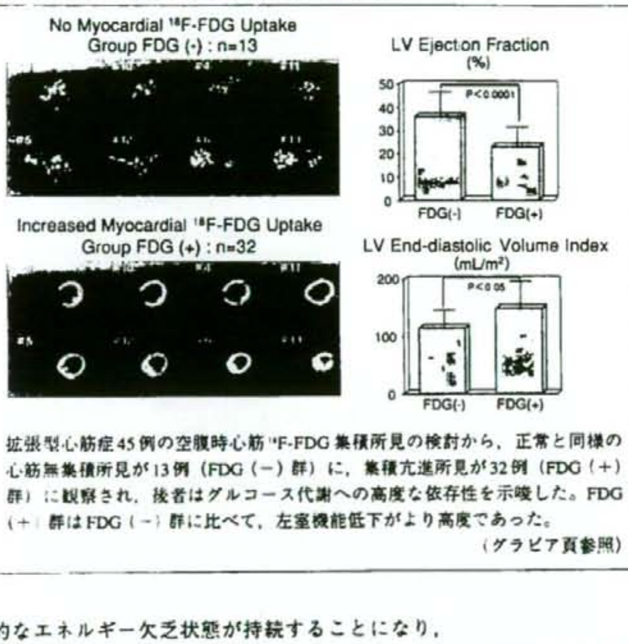
B．^{18}F-FDG (transaxial image)　（グラビア頁参照）

図❹　拡張型心筋症患者の ^{31}P-MRS（文献2より）



Aは心不全薬物療法（ジギタリス，利尿剤，ACE阻害薬，β-ブロッカー）の実施前，Bは同実施後18週目の所見である。心機能改善とともに，CP/ATP比の改善が認められ，心筋エネルギー状態の改善が示唆される。

図❺　拡張型心筋症における代謝シフト（文献17より）



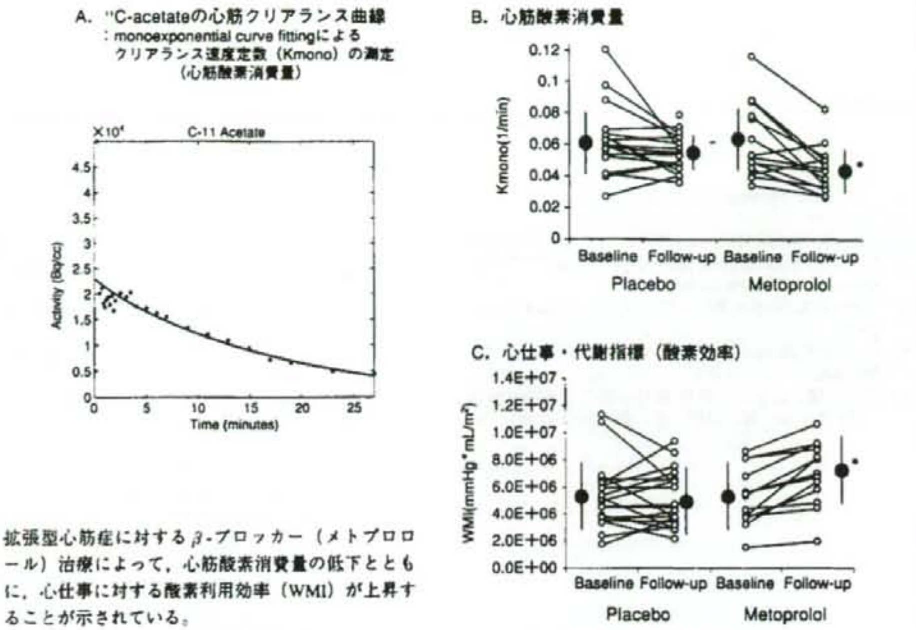
拡張型心筋症45例の空腹時心筋 ^{18}F-FDG集積所見の検討から，正常と同様の心筋無集積所見が13例（FDG（−）群）に，集積亢進所見が32例（FDG（+）群）に観察され，後者はグルコース代謝への高度な依存性を示唆した。FDG（+）群はFDG（−）群に比べて，左室機能低下がより高度であった。

（グラビア頁参照）

的なエネルギー欠乏状態が持続することになり，収縮機能を低下させる原因となる。このような代謝シフトの現象は，最近では新しい心不全治療のターゲットとして注目されている。例えば，心不全にインスリン抵抗性の病態が加わった場合，心筋は心不全によってグルコースを基質として利用する状態にあるために，ATP産生の低下・エネルギー欠乏を助長する結果になると想定される。これを背景に，最近では心不全治療におけるインスリン抵抗性の改善薬の効果が検討されている[11]。

この分野では，代謝イメージングを利用した多くの臨床報告がある。^{31}P-MRSによる検討では，心不全患者でCP/ATPの減少が観察され（図❹），臨床的な心不全重症度や機能指標の変化に相関することが示されている[2]。SPECT/PETによる検討では，^{123}I-BMIPPの心筋集積の低下が，拡張型心筋症の患者で報告されている[16]。また，^{11}C-palmitateの初期急速相のクリアランスの低下が心不全重症度に相関することが示されてきた[5]。著者らは，拡張型心筋症の患者で，空腹条件下で心筋への ^{18}F-FDGの陽性集積が観察される患者は，非集積の患者に比べて左室機能不全が高度であることを示した（図❺）[17]。

図❻ ^{11}C-acetate PETによる心筋酸素消費量の計測に基づく心仕事の酸素効率WMIの評価（文献19より）



拡張型心筋症に対するβ-ブロッカー（メトプロロール）治療によって，心筋酸素消費量の低下とともに，心仕事に対する酸素利用効率（WMI）が上昇することが示されている。

最近のDavila-Roman ら報告によると，非虚血性の拡張型心筋症の患者では，年齢をマッチさせた健常人と比較したとき，心筋脂肪酸摂取ならびにβ酸化が明らかに低下し，その逆に心筋グルコース代謝は亢進を示すことが示されている[16]。この中で^{18}F-FTHA PETを用いた報告だけが心不全患者での心筋脂肪酸摂取の増加を示し，他との食い違いをみせているが[17]，この原因はよくわかっていない。また一方，心不全治療の効果判定にも，代謝イメージングは有用性が認められる。^{31}P-MRSによる検討では，拡張型心筋症でβ-ブロッカー治療によってPCr/ATPが有意に増加することが観察されている[18]。また，^{11}C-acetate PETと心仕事量の計測に基づく心筋酸素効率の検討では，心不全患者に対する運動療法，β-ブロッカー治療，CRT治療で顕著な改善が認められている（図❻）[19]。

以上，これまでに報告されてきた代謝イメージングの主な臨床知見を紹介したが，現在のところ提供される情報は極めてグローバルな代謝変動に関するものであると言わざるを得ない。すなわち，エネルギー欠乏状態の把握，代謝の脂肪酸依存性あるいはグルコース依存性の評価，心筋酸素効率の推定などに限られている[20]。したがって，例えば観察された代謝変動が，生体にとって代償的な反応なのか，あるいは非代償的な異常を示すのかという極めて重要な疑問には十分に応えられていないのが現状である。代謝を制御する個別因子をターゲットとするイメージング技術のさらなる進歩が必要であろう。

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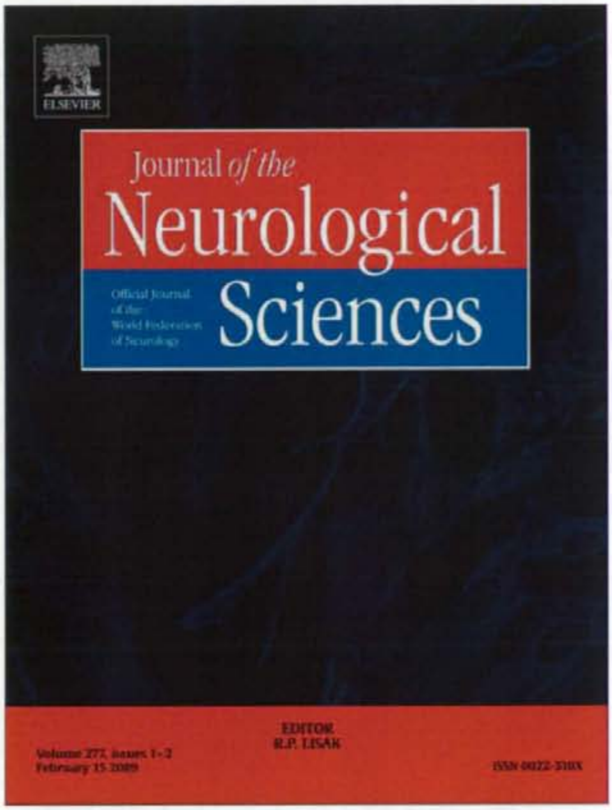
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Journal of the
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EDITOR
R.P. LISAK

Journal of the Neurological Sciences 277 (2009) 50–53

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

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

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ARTICLE INFO

Article history:
Received 2 July 2008
Received in revised form 6 October 2008
Accepted 8 October 2008
Available online 7 November 2008

Keywords:
Albuminuria
Metabolic syndrome
Stroke recurrence
Predictor
Japan

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

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doi:10.1016/j.jns.2008.10.002

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 χ^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.

Acknowledgments

This study was supported in part by a grant from the Takeda Medical Research Foundation, by Grants-in Aid from the Ministry of Health, Labor and Welfare of Japan (18C-2, 19C-3) and by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science.

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Letter to the Editor

European Neurology

Eur Neurol 2008;59:192–194
DOI: 10.1159/000114043

Received: April 4, 2007
Accepted: May 11, 2007
Published online: January 29, 2008

Isolated Hemifacial Sensory Impairment with Onion Skin Distribution Caused by Small Pontine Hemorrhage

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Dear Sir,

Isolated trigeminal sensory neuropathy due to pontine hemorrhage has only been found in a few previous cases [1–4]. In these, the hemorrhage affected either the principal sensory nucleus [1, 2] or the trigeminal nerve roots [3, 4] and produced facial sensory impairments along the ophthalmic (V1), maxillary (V2) and/or mandibular (V3) nerve dermatome. We report a patient with a small pontine hemorrhage that affected the upper part of the spinal trigeminal nuclei, mainly the nucleus oralis and interpolaris. She developed isolated facial tactile sensory impairment with 'onion skin' distribution in the absence of other neurological deficits. Onion skin type facial sensory impairment caused by these upper spinal trigeminal nuclei due to stroke has never been previously reported.

Case Report

A 61-year-old woman suddenly felt numbness around the right side of her lips while talking on the telephone. She experienced neither headache nor vomiting. She had a history of hypertension and hyperlipidemia but received no medical treatment. She was admitted to our hospital 1 h after onset. At the time of admission, her blood pressure was 200/114 mm Hg, while the heart beats were 108 per minute and regular. Neurological examinations revealed an alert and well-oriented woman with isolated tactile sensory impairment over the right trigeminal distribution including the oral cavity. Pain and temperature sensations were not impaired. The hypesthesia showed so-called onion skin distribution and was least intense in the perioral and perinasal areas and most prominent in the most peripheral parts of the face, such as the forehead and chin. Corneal sensation and corneal reflex were well preserved. No weakness of the masseteric muscle or jaw deviation was observed. Taste sensation was normal. There was no abnormality in cranial nerves, coordination or body sensation, except for the face.

Brain CT performed on admission and 1.5 h after onset demonstrated a small, high-density area at the right pontine tegmentum (fig. 1). The diameter of the hematoma was less than 1 cm and did not enlarge on a second CT performed 6 h after onset. T_1-weighted MRI on the seventh day showed a column-shaped hematoma in areas extending from the middle part to the lower portion of the pons and accompanied by a smaller sublesion (fig. 2A–C). The hematoma did not reach the medulla oblongata, as confirmed by coronal MRI. MR angiography on the seventh day disclosed no abnormality suggestive of arteriovenous malformation, aneurysm or cavernous angioma. The diagnosis of hypertensive pontine hemorrhage was established on the basis of such imaging studies. She was discharged on day 11, at which time her facial hypesthesia was mild in degree. Three months thereafter, her facial hypesthesia was confined to the areas around the right side of the lips.

Discussion

Pontine hemorrhage presenting a trigeminal neuropathy is usually associated with other cranial nerve deficiencies. Even in cases of small hematoma localized in the tegmentum, neurological examination usually reveals a variety of symptoms depending on the magnitude of basilar involvement, such as oculomotor abnormalities, ataxia, action tremor, ipsilateral miosis, hemiparesis or facial numbness [5]. Isolated trigeminal sensory neuropathy is seldom observed in cases of pontine hemorrhage. To the best of our knowledge, only 4 such cases have been reported previously [1–4] (table 1). In these 4 cases, the lesions affected the principal sensory nucleus or the trigeminal nerve roots, and all of the facial sensory impairments were observed along the V1, V2 or V3 dermatomes.

The trigeminal nerve contains both sensory and motor components. The ma-

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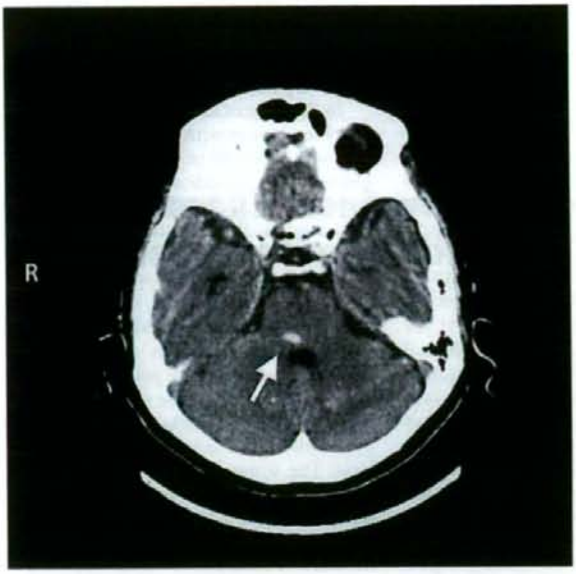

Fig. 1. Brain CT, obtained 1.5 h after onset of symptoms, discloses a small, high-density area (arrow) in the medial portion of the right pontine tegmentum.

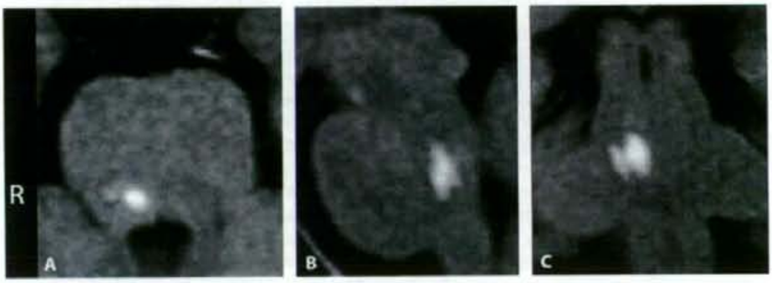

Fig. 2. T_1-weighted MR images obtained on the seventh day. **A** Transaxial image discloses hematoma at the pontine tegmentum, the diameter of which is smaller than 1 cm. **B, C** The sagittal and coronal images demonstrate that the hematoma is column-shaped, extending from the middle pons to the lower pons and accompanied by a smaller sublesion.

Table 1. Reported cases of pontine hemorrhage with isolated trigeminal sensory neuropathy

Authors and year	Age years	Sex	Distribution	Location of the lesion
Holtzman et al. [1], 1987	45	M	V2, V3	trigeminal principal sensory nucleus
Kim et al. [2], 1994	31	M	V1 < V2, V3	trigeminal nerve root and trigeminal principal sensory nucleus
Komiyama et al. [3], 1993	49	M	V1	trigeminal nerve root
Almeida et al. [4], 1999	62	M	V1	trigeminal nerve root
The present case	61	F	V1~V3 'onion skin' pattern	nucleus oralis or interpolaris of trigeminal spinal nucleus

jority of trigeminal sensory fibers conveying tactile sensation does not descend but enters the principal sensory nucleus. Other trigeminal sensory fibers carrying pain and temperature sensations descend in the trigeminal tract and enter the spinal trigeminal nucleus. The spinal trigeminal nucleus consists of 3 components – the nucleus oralis, nucleus interpolaris and nucleus caudalis – which are located along the longitudinal axis of the brain stem [6–8]. Among these nuclei, the fibers carrying pain and temperature sensations enter the nucleus caudalis, which is located at the most caudal part of the spinal trigeminal nucleus. The somatotopic representation of the face within the nucleus caudalis is in a segmental distribution similar to onion skin: the perioral areas of the face are represented by the rostral portion of the nucleus, and more outer areas of the face are represented by the caudal portion of the nucleus. Therefore, lesions affecting the nucleus caudalis at the medulla oblongata may cause onion skin type sensory impairment, as occasionally observed in cases of syringobulbia. On the other hand, the functions of the other 2 nuclei – the nucleus oralis and interpolaris – still remain unclear. Fibers carrying tactile sensation mainly enter the principal sensory nucleus and partly so the upper part of the spinal trigeminal nucleus – the nucleus oralis and interpolaris [9]. The tactile representation of the face within the nucleus oralis and interpolaris remains unclear.

In the present case, isolated tactile sensory impairment with onion skin distribution was observed in the hemifacial area ipisilateral to the side of the small pontine hemorrhage. According to the CT and MRI studies, the hematoma was located more medially to the principal sensory nucleus and affected the upper part of the spinal trigeminal nucleus, such as the nucleus oralis and interporalis. The onion skin type hypesthesia is unlikely to be caused by lesions of the principal sensory nucleus. The present case suggests that the onion skin type hypesthesia may be caused by lesions in the nucleus oralis or interpolaris. The somatotopic representation of the face in the nucleus oralis and interpolaris may be in a segmental, onion-skin-like distribution pattern similar to that in the nucleus caudalis.

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Original Paper

Cerebrovascular Diseases

Cerebrovasc Dis 2008;25:241–246
DOI: 10.1159/000113862

Received: February 5, 2007
Accepted: September 21, 2007
Published online: January 24, 2008

Extremely Early Computed Tomography Signs in Hyperacute Ischemic Stroke as a Predictor of Parenchymal Hematoma

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Key Words

Acute stroke diagnosis · Computed tomography · Hemorrhagic transformation · Intracerebral hemorrhage · Ischemic stroke

Abstract

Background: In acute ischemic stroke, thrombolysis with intravenous recombinant tissue plasminogen activator is more effective when given within 90 min of onset compared to that given later than 90 min. However, the significance of early CT signs (ECTs) during such early periods has not yet been fully clarified. We investigated the usefulness of ECTs within 90 min for predicting parenchymal hematoma (PH) in patients without thrombolysis. ***Methods:*** We evaluated 212 consecutive patients with initial ischemic stroke in the anterior cerebral circulation who underwent the first CT within 6 h of onset. The patients were divided into 3 groups according to the interval from onset to CT: within 90 min (group A, n = 90), 91–180 min (group B, n = 76) and 181–360 min (group C, n = 46). Patients who had received thrombolytic therapy were excluded. ECTs were evaluated according to the Alberta Stroke Program Early CT Score (ASPECTS). The relationships between ECTs and the subsequent development of PH were compared among the groups. ***Results:*** In patients with ASPECTS values between 0 and 7, PH was developed more frequently in group A (35%) than in groups B (14%) or C (15%) (group A vs. B: p = 0.036, group A vs. C: p = 0.094). In group A, atrial fibrillation, elevated pretreatment blood pressure and ASPECTS ≤7 were independent predictors of PH. ***Conclusions:*** The manifestation of ECTs as represented by ASPECTS ≤7 within 90 min after stroke appears to indicate a high risk of PH.

Introduction

In hyperacute ischemic stroke, thrombolysis with intravenous recombinant tissue plasminogen activator (rt-PA) was found to improve the 90-day functional outcome when given within 3 h of symptom onset in the National Institute of Neurological Disorders and Stroke (NINDS) trial [1]. On the other hand, the frequency of intracranial hemorrhage (ICH) was shown to increase significantly in stroke patients treated with thrombolysis [1–3]. Thus, the pretreatment predictors of ICH are currently one of the most important issues in clinical practice. At present, computed tomography (CT) is the most widely available and convenient technique for evaluating stroke, and the prediction of ICH using CT would be exceedingly valuable. The European Cooperative Acute Sroke Study (ECASS) investigators suggested that baseline early CT signs (ECTs), according to the so-called one third rule, could be predictive of ICH [2]. However, there was no reference to ECTs in the NINDS trial [1]. The subanalysis of NINDS data could not confirm the relationship between ECTs and ICH either, although they found such a ten-

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dency that symptomatic hemorrhages develop more commonly in patients whose ECTs extend over more than one third of the middle cerebral artery territory [4]. In addition, a recent meta-analysis of 6 major intravenous thrombolytic therapy trials suggests that the benefit of rt-PA is greater if started within 90 min compared to that later than 90 min [5]. However, the significance of ECTs in such very early periods has not yet been fully clarified.

Recently, a new scoring system was developed to better locate and semiquantify the early ischemic changes on CT: the Alberta Stroke Program Early CT Score (ASPECTS) [3]. This semiquantitative scoring method improved the interobserver agreement ratio [6] and facilitated the detection of earlier and more subtle changes [7]. We hypothesized that the time from onset to the appearance of ECTs would correlate with the severity of cerebral ischemia and the frequency of subsequent parenchymal hematoma (PH). We investigated the usefulness of ECT evaluation using ASPECTS within 90 min for predicting the risk of spontaneous PH in the following acute or subacute phase in patients without thrombolysis.

Patients and Methods

Patients

Among 1,679 patients with ischemic stroke admitted to the stroke care unit of the National Cardiovascular Center, Japan, between January 1998 and June 2005, we retrospectively evaluated 655 consecutive patients who underwent the first CT within 6 h after onset. We excluded patients with a history of symptomatic stroke or intracranial surgery. We also excluded patients with unclear onset including stroke at awakening and those with infarction limited to the posterior circulation alone. Thirty-five patients who had received thrombolysis (intravenous or intra-arterial) were also excluded. In Japan, the use of intravenous rt-PA for acute ischemic stroke was approved in October 2005, by which time the present study had been completed. Therefore, during the study period, thrombolytic therapy was performed only in patients who were enrolled in other clinical trials. Consequently, 212 consecutive patients with initial ischemic stroke in the anterior cerebral circulation were enrolled in this study. The 212 patients were divided into 3 groups according to the interval from onset to the first CT: within 90 min (group A, n = 90), 91–180 min (group B, n = 76) and 181–360 min (group C, n = 46). Anticoagulants and/or antiplatelet agents were administered to the patients in case the attending physicians considered these therapies were sufficiently safe and valuable.

CT Studies

All patients underwent noncontrast CT scans using an X-Vigor (Toshiba, Tokyo) on arrival. The scanning parameters were nonhelical, 120 kV, 170 mA, 10-mm collimation, matrix size of 512 × 512 and 2- or 3-second scan time. Routine photography was performed at window level and a width of 30 and 70–80 Hounsfield units (HU), respectively. Follow-up CTs were performed at 24 h and 7–14 days after stroke, as well as at the discretion of treating neurologists and reviewed in this study when performed within 14 days. All baseline CTs and follow-up CTs were retrospectively evaluated by 2 expert neurologists (S.O. and H.M.) with knowledge of the side of the affected hemisphere but blinded to treatment assignment, stroke severity or other clinical details. ECTs were scored according to ASPECTS [3, 6]. ASPECTS was assessed by scoring 10 regions (caudate nucleus, internal capsule, lentiform nucleus, insula and 6 cortical regions) systematically on the CT scan. A score of 1 was assigned for normal and 0 for a region showing ECTs. A normal CT scan has ASPECTS values of 10 points. Score 0 indicates diffuse ischemia throughout the territory of the middle cerebral artery. The ASPECTS study group suggested that baseline ASPECTS values in 2 categories (≤7 and >7) discriminated poor and good functional outcome, or high and low risk of ICH [3]. Therefore, we compared the incidence of ICH between a group with ASPECTS ≤7 and one with ASPECTS >7 in each period.

ECTs were defined as X-ray hypoattenuation, loss of the gray-white boundary or effacement of cortical sulci [3, 6]. ICH was classified as hemorrhagic infarction and PH; hemorrhagic infarction was defined as petechial infarction without space-occupying effect, and PH was defined as hemorrhage with mass effect. PH was subdivided into PH1, as blood clots in ≤30% of the infarcted area with some slight space-occupying effect, and PH2, as blood clots in >30% of the infarcted area with a substantial space-occupying effect, corresponding to ECASS II criteria [2]. In cases of disagreement in the findings, these 2 observers reviewed the CTs together and discussed the findings until a consensus was established.

Clinical Evaluation

Risk factors for ischemic stroke (i.e. age, sex, hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation and smoking) were evaluated in all patients. According to the exclusion criteria of NINDS [1], we defined 'elevated pretreatment blood pressure' as systolic blood pressure >185 mm Hg or diastolic blood pressure >110 mm Hg. Because the second analysis of NINDS showed that patients >75 years of age or with National Institutes of Health Stroke Scale (NIHSS) scores >20 were associated with poor outcome and high risk of ICH [9], we decided on the cutoff points of age >75 years and NIHSS score >20 on univariate analysis. The trial of ORG10172 in Acute Stroke Treatment criteria [10] were used to classify stroke subtypes.

Data Analysis

We determined the predictive value of ASPECTS referring to the findings of follow-up CT obtained at 24 h as a standard. ECTs were judged 'true positive' if a definite infarct was correctly located on the follow-up CT. If it was absent on the second CT, the reading was 'false positive'. The readings were judged 'true negative' if both baseline and follow-up CT did not reveal any infarcted changes. The readings were defined as 'false negative' if ECTs were not detected on the baseline CT and a definite infarct was visible on the follow-up CT. On the basis of these definitions, we assessed the predictive value in each of the 10 regions in each patient, then summed the results all together and calculated the sensitivity and specificity.

Table 1. Baseline characteristics of the 3 groups classified by time from stroke onset to initial CT

Variables	Group A (0–90 min)	Group B (91–180 min)	Group C (181–360 min)	p value
Patients	90	76	46	
Age, years	71 ± 11	70 ± 11	70 ± 12	0.783
Male	61 (68)	56 (74)	31 (67)	0.655
Hypertension	64 (71)	54 (71)	31 (67)	0.889
Diabetes mellitus	21 (23)	22 (29)	15 (33)	0.480
Hyperlipidemia	27 (30)	26 (34)	17 (37)	0.690
Atrial fibrillation	45 (50)	37 (49)	22 (48)	0.968
Smoking	25 (28)	23 (30)	12 (26)	0.588
Pretreatment, mm Hg				
Systolic blood pressure	162 ± 26	160 ± 26	171 ± 25	0.072
Diastolic blood pressure	87 ± 15	87 ± 13	90 ± 14	0.377
Elevated pretreatment blood pressure	20 (22)	12 (16)	9 (20)	0.578
NIHSS scores, median	12	9	6	0.097
1–5	20 (22)	24 (32)	21 (46)	
6–10	22 (24)	18 (24)	10 (22)	
11–15	14 (16)	7 (9)	5 (11)	
16–20	20 (22)	19 (25)	6 (13)	
>20	14 (16)	8 (11)	4 (9)	
ASPECTS, median	9	8	8	0.111
≤7	34 (37)	35 (46)	20 (44)	

Categorical values are expressed as numbers with percentages in parentheses, continuous variables as means ± SD. The χ^2 test was conducted for categorical variables, ANOVA for continuous variables and the Kruskal-Wallis test for scoring variables.

Statistical Analysis

Continuous data are expressed as means ± SD. For analysis of baseline characteristics, categorical variables were compared by χ^2 test, continuous variables by 1-way ANOVA and scoring variables by Kruskal-Wallis test. For univariate analysis of the predictors of PH, categorical variables were compared by χ^2 test, continuous variables by unpaired t test and scoring variables by Mann-Whitney U test. Multivariable analysis was undertaken using a logistic regression model. The results were considered significant at $p < 0.05$. Dr. SPSS II for Windows 11.0.1J was used for all calculations.

Results

Two hundred and twelve patients (148 men, 64 women) with ages ranging from 41 to 101 years (70 ± 11) were enrolled into this study. The stroke subtype was cardiogenic embolism in 118 patients, large-artery atherosclerosis in 29, small-vessel disease in 16 and other or unknown etiology in 49. As shown in table 1, the baseline characteristics were not significantly different between groups A, B and C.

ECTs were positive in 142 (67%) of the 212 patients. The predictive value for any ECTs with ASPECTS in each group was as follows: sensitivity 60% and specificity 95% in group A, sensitivity 79% and specificity 91% in group B, and sensitivity 75% and specificity 90% in group C. PH was observed in 25 (12%) of the 212 patients. PH1 occurred in 14 patients and PH2 in 11. There were no differences in baseline CT findings and clinical characteristics between PH1 and PH2. Antithrombotic agents were used in 188 patients (89%) within 2 weeks from onset; 143 patients (68%) were treated with intravenous heparin and 79 patients (37%) with antiplatelet agents. Among the 188 patients with antithrombotic therapy, only 15 (8%) developed PH. On the other hand, 10 (42%) of the 24 patients without antithrombotic therapy developed PH. Figure 1 shows the proportion of PH by ASPECTS category in each group. When the ASPECTS values were between 0 and 7, PH was developed in 12 (35%) of the 33 patients in group A, showing a significantly higher frequency as compared with group B (14%) or group C (15%) (group A vs. group B: $p = 0.036$, group A vs. group C: $p = 0.094$).

Table 2 details the univariate analysis of predictors of PH within 90 min. Atrial fibrillation, elevated pretreatment blood pressure, NIHSS score and ASPECTS ≤7

Table 2. Univariate analysis of PH predictors in cases of CT examination within 90 min

Variables	PH (16 patients)	no PH (74 patients)	p value	Odds ratio
Age	73 ± 11	70 ± 11	0.33	
>75 years	7 (44)	24 (32)	0.40	1.62 [0.54, 4.87]
Male	12 (75)	49 (66)	0.57	1.53 [0.45, 5.24]
Hypertension	14 (88)	50 (68)	0.14	3.36 [0.71, 15.98]
Diabetes mellitus	6 (38)	15 (20)	0.19	2.36 [0.74, 7.53]
Hyperlipidemia	5 (31)	22 (30)	1.00	1.07 [0.33, 2.65]
Smoking	8 (50)	39 (53)	1.00	0.90 [0.30, 2.65]
Atrial fibrillation	13 (81)	32 (43)	0.011	5.69 [1.49, 21.66]
Elevated pretreatment blood pressure	7 (44)	13 (18)	0.042	3.65 [1.15, 11.58]
NIHSS scores, median	16.5	10	0.006	
>20	4 (25)	10 (14)	0.26	2.13 [0.57, 7.93]
ASPECTS, median	5	9	<0.001	
≤7	12 (75)	21 (28)	0.001	7.36 [2.14, 25.33]

Categorical values are expressed as numbers with percentages in parentheses, continuous variables as means ± SD. Figures in square brackets are 95% confidence limits. Elevated pretreatment blood pressure is defined as systolic blood pressure >185 mm Hg or diastolic blood pressure >110 mm Hg. Antiplatelet therapy includes aspirin, cilostazol, ticlopidine, argatroban and sodium ozagrel. Anticoagulant therapy includes heparin and warfarin.

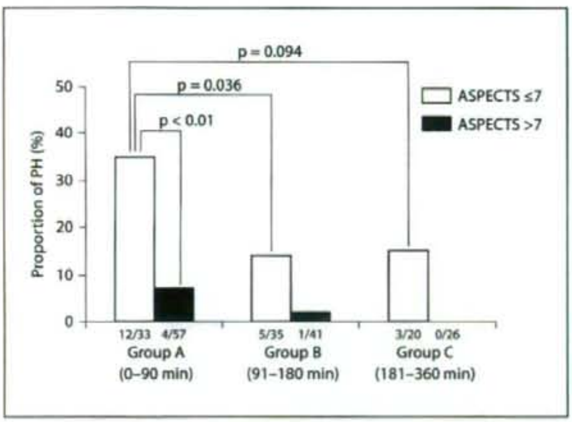

Fig. 1. Incidence of PH after ischemic stroke by categories of time from stroke onset to CT, comparing ASPECTS ≤7 with ASPECTS >7. Values are numbers of patients with PH divided by the total patients in each group (n/n).

Table 3. Predictors of PH in cases of CT examination within 90 min: multivariable logistic regression analysis

	p value	OR	95% CI
NIHSS (per 1 score increase)	0.308	1.05	0.95–1.17
ASPECTS ≤7	0.013	6.14	1.47–25.66
Elevated pretreatment blood pressure	0.022	5.45	1.28–23.25
Atrial fibrillation	0.045	5.02	1.03–24.37

Elevated pretreatment blood pressure is defined as systolic blood pressure >185 mm Hg or diastolic blood pressure >110 mm Hg. OR = Odds ratio; CI = confidence interval.

were associated with PH. Multivariate logistic regression analysis for prediction of PH is presented in table 3. ASPECTS ≤7, elevated pretreatment blood pressure and atrial fibrillation were independent predictors of PH within 90 min of onset.

Discussion

We conducted the present study to evaluate the clinical significance of ECTs in the hyperacute phase of ischemic stroke and found that the manifestation of ECTs within 90 min after stroke indicates a high risk of subsequent PH. We evaluated PH as a type of ICH which may be more closely related with symptomatic deterioration than hemorrhagic infarction [11]. In our study, PH was observed in 12% of the patients. The frequency of PH was higher than that in ECASS II (3.1%) [2]. Okada et al. [12] reported that PH was found in 10% of 160 Japanese patients with acute cerebral embolism. Because our study enrolled more patients with cardiogenic embolism than the ECASS II trial, the frequency of PH may become higher. Another explanation for the dissociation of PH frequency between our study and ECASS II is the racial difference in blood coagulation-fibrinolysis factors, such as fibrinogen and factor XII, between Japanese and Caucasians [13].

Several factors related to ECTs were reported to be important. CT density decreases linearly over time, describing the course of water uptake after ischemia [14]. The severity of perfusion impairment also correlates with the degree of CT density reduction [15]. In a recent study using single-photon emission CT, the time from onset to CT and residual cerebral blood flow were independent factors that contributed to the presence of ECTs [16]. Another study using positron emission tomography also shows that ECTs reflect the coupling of the severity of ischemia [17]. These findings suggest that the earlier the manifestation of ECTs, the severer the depth of brain ischemia. ECTs in the extremely early stage likely indicate severe ischemic brain damage associated with poor collaterals, leading to damage to the integrity of the blood-brain barrier [18]. Disruption of the blood-brain barrier contributes to the risk of ICH [19]. Our study showed that the sensitivity of ECTs was relatively low during the initial 90 min, however, the specificity was sufficiently high in each period. These findings were remarkably similar to the results of the study which assessed the significance of X-ray hypoattenuation at CT using the ECASS II population [20]. Careful detection of these subtle findings in the very early periods of ischemic stroke may facilitate the prediction of ICH.

The dichotomized score of ASPECTS 0–7 versus 8–10 was previously validated and shown to have prognostic value among patients treated with intravenous rt-PA for acute ischemic stroke within 3 h of onset [3, 6]. Recently, Dzialowski et al. [21] examined 800 patients within 6 h of stroke onset in the subanalysis of ECASS II and reported that ASPECTS ≤7 was a substantially increased risk of thrombolysis-related PH. These results are compatible with our study showing that in patients without thrombolysis, ASPECTS ≤7 was an independent predictor of PH, a sign of poor prognosis.

Several previous studies of intravenous rt-PA therapy suggested that ECTs were not associated with increased risk of ICH [4, 22]. These studies did not describe the interval between onset and CT, and the relationship between the ECT manifestation and the subsequent hemorrhagic transformation was not clarified. However, Demchuk et al. [22] concluded on the basis of such results that there was no evidence of treatment effect modification from the baseline ASPECTS value by thrombolysis. Data from animal models and human clinical trials have demonstrated that earlier stroke treatment is associated with better outcome [5, 23, 24]. There is a possibility that thrombolysis in the very early stage of ischemic stroke may diminish the disruption of the blood-brain barrier and reduce the risk of ICH.

The present study has several limitations. First, it was designed prior to the government approval of intravenous rt-PA in Japan. Therefore, we could not compare the neuroradiological and functional outcome between patients with thrombolysis and those without in spite of the fact that such a comparison may allow us to definitively define a subgroup of patients receiving benefit from thrombolysis. Second, we defined the ECTs according to ASPECTS criteria which include parenchymal hypoattenuation and brain swelling. There is increasing evidence that brain swelling without parenchymal hypoattenuation may be reversible [25]. On the other hand, brain swelling theoretically can represent early stages in a process that manifests finally as PH [26]. The actual relationship between brain swelling and PH remains unclear.

In conclusion, the manifestation of ECTs as represented by ASPECTS ≤7 within 90 min after stroke appears to indicate a high risk of parenchymal hemorrhage even when thrombolysis was not performed. Whether or not thrombolysis is indicated for such cases should be clarified in the future by a large-scale study.

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