| | 療法群[N=53] | 対照群[N=52] | |
|---|---|---|---|
| 男：女 | 34：19 | 33：19 | n.s. |
| 年齢[歳] | 66.6±9.5 | 67.0±8.8 | n.s. |
| 割付時間[分] | 196±59 | 207±56 | n.s. |
| NIHSS | 14.8±5.1 | 13.9±4.2 | n.s. |
| 心原性塞栓 | 87% | 75% | n.s. |
| 入院時血圧[mmHg] | 154/89 | 144/81 | n.s. |
| 血圧違反 | 13 | 6 | n.s. |

表3　背景因子の中間解析結果

| | 療法群 | 対照群 | |
|---|---|---|---|
| 閉塞血管 | | | |
| M1近位 | 14 | 16 | |
| M1遠位 | 23 | 22 | |
| M2 | 16 | 14 | n.s. |
| 側副血行 | | | |
| 不良 | 18 | 9 | |
| 軽度 | 23 | 27 | |
| 良好 | 10 | 16 | |
| 未報告 | 2 | 0 | n.s. |
| CT早期虚血性変化 | 24 | 23 | n.s. |

表4　神経放射線学的因子の中間解析結果

ドワイヤーの細かい規定はないが、バルーンカテーテルやステントなどマイクロカテーテル以外の使用は禁じられている。マイクロカテーテルを血栓より遠位に誘導し、ウロキナーゼ60万単位を生理食塩水50mLに溶解したものをシリンジポンプを用いて12万単位/10mLを5分間で注入する。ガイドワイヤーやマイクロカテーテルによる塞栓破砕は行ってもよい。ウロキナーゼの注入は60万単位に達するか、注入開始1時間まで続ける。

2005年10月に登録開始3.5年目の中間報告がなされた(表3～6、図1、2)。すでに予定登録期間の7割を経過しているが、200例の目標登録症例数に対して、まだ半数強の116例が登録されているのみである。3ヵ月の追跡期間を終了した105例において一時エンドポイントであるmRS0～2は、対照群で20/52であるのに対し、療法群では26/53であるが有意差ではない。二次エンドポイントのmRS0～1は、対照群で11/52であるのに対し、療法群では21/53であるがこれも有意差には至っていない。

## Japan alteplase clinical trial (J-ACT)

1995年に発表されたNINDS studyにより[5]、米国では発症3時間以内の脳梗塞に関しては、静注療法が標準的治療となった。NINDS studyで使用されたalteplaseは、わが国においても米国においても急性心筋梗塞に対して臨床使用が認められているが、その適応量はわが国においては0.5～0.75mg/kgとされ、米国においては100mgとされている。米国成人の標準的な体重を67～100kgと考えると、米国での投与量は1.0～1.5mg/kgとなるので、日本では米国の半量が適応量とされていることになる。このようなことがあるので、NINDS studyの投与量をそのままわが国に移行すると過剰投与になると判断され、日本人に適した投与量でのtrialが必要とされた。これがJ-ACTで、国内の23施設が参加して2002年4月より2003年9月にかけて行われた。種々の検討の結果alteplaseの投与量は0.6mg/kgに設定され、その他の点はNINDSに準じているが、対照群を

おかないopen trialとして行われた。103例が登録され、心原性塞栓症が80％を占めた。治療前のNIHSSはNINDSと同等で、発症から投与開始までの所要時間は約2.5時間であった。発症後3ヵ月の予後良好例（mRS 0～1）は37％で、死亡症例は10％、症候性頭蓋内出血は5.8％であった。これらの結果はNINDSのそれと同等であった（NINDSでは順に39％、17％、6.4％）。この結果を受けて、わが国でもついに2005年10月にt-PA静注療法が保険適応となった。

| | | |
|---|---|---|
| ウロキナーゼ投与量 | 0 | 1例 |
| | ＜60万単位 | 15例 |
| | 60万単位 | 37例 |
| 機械的破砕施行 | 37例（70％） | |
| 再開通 | なし | 15例 |
| | 50％未満 | 11例 |
| | 50％以上 | 24例 |
| | 完全 | 3例 |

表5　療法群における治療結果

| | 療法群 | 対照群 | |
|---|---|---|---|
| Primary end point (mRS≦2) | 20/53 (49.1％) | 20/52 (38.5％) | n.s. |
| Secondary end point (mRS≦1) | 21/53 (39.6％) | 11/52 (21.2％) | n.s. (0.056) |
| 死亡 | 3/53 (5.7％) | 2/52 (3.8％) | n.s. |
| 脳内出血 | 5/53 (9.4％) | 1/52 (1.9％) | n.s. |
| 脳浮腫 | 2/53 (3.8％) | 2/52 (3.8％) | n.s. |

表6　有効性、安全性の中間解析結果

## IV-t-PA認可後のMELT Japan

実は前述した2005年10月のMELT Japan中間報告会では、重大な決議がなされた。脳梗塞に対するt-PAの静注療法が、報告会の時点では未承認であったが、承認されるのが確実視されていたのを受け、IV-t-PA時代以降のMELT Japanについて討議された。

J-ACTやMELT Japanを行うにあたっての倫理的な正当性は、保存療法と静注療法、局所線溶療法の3者の間でどれが有効であるのかはわかっていない、ということであった。J-ACTの結果自体は局所線溶療法を否定するものではないが、J-ACTによって静注療法が保存療法よりも有効であることが確認されたので、MELT Japanのコントロールとして保存療法を行うことは倫理的に大きな問題がある。そこで、t-PA静注療法の保険認可後は、安全監視委員会の勧告により少なくともそれまでと同じプロトコルでのMELT Japanは継続しないことが決定された。このことは、発症3時間以内の脳梗塞に対しては、わが国でもt-PA静注療法がスタンダードとなったことを意味している。

## 局所線溶療法の今後

MELT Japanについては、上述したように当初のプロトコルに従った臨床研究の登録は終了した。これまでの登録症例の3ヵ月後のフォロー

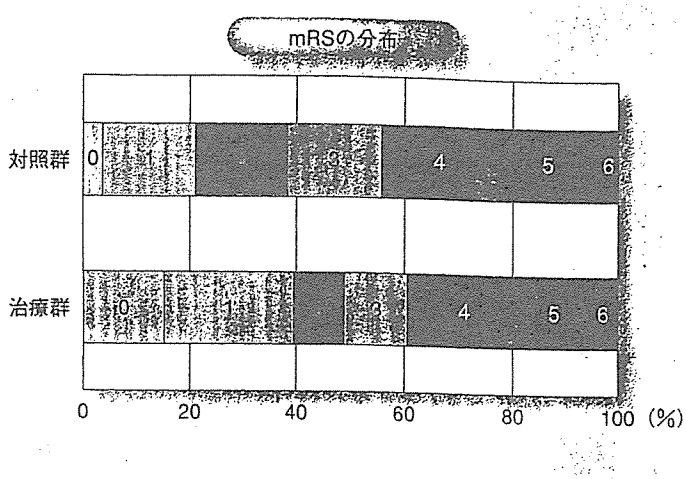


図1　3ヵ月後のmodified Rankin Scale

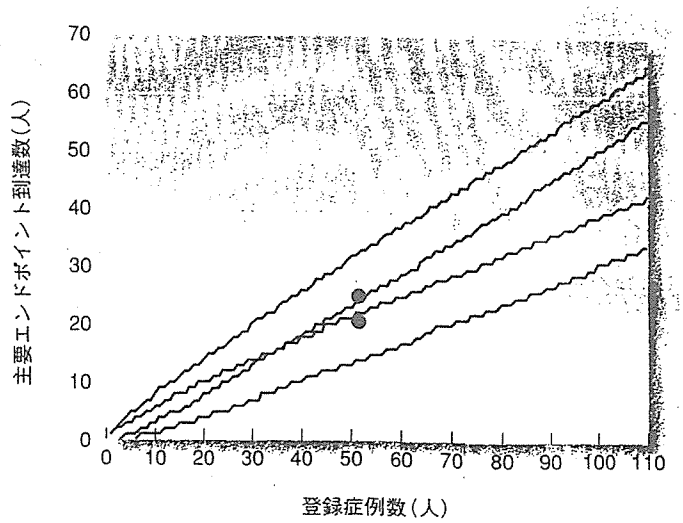


図2　登録症例数と主要エンドポイント到達症例数

(●：療法群、●：保存群)2本の帯は両群の予測範囲を示す。

アップが終了後中断時点での最終報告がなされる予定である。

そもそも欧米のstudyも含めて、静注療法と局所線溶療法を比較しようという試みは、まだ行われていないのであるが、ともに保存療法を対照としたMELT JapanもPROACT Ⅱも結果はほぼ同様で、局所線溶療法は有効ではあるものの静注療法をはるかに凌駕するほどではない、ということである。

そうすると局所線溶療法の対象として考えつくのは、静注療法の適応外である発症3時間以上の症例をターゲットにすることである。しかし、発症3～5時間を対象としたATLANTIS studyは無効という結果に終わっており[6]、静注療法と局所線溶療法の違いはあるものの、発症3時間を超えると血栓溶解療法が有効な症例は少なくなってくるものと思われる。また最初から意図して静注療法と組み合わせて行うか[7]、静注療法が無効だった症例の追加療法とする[8]など、静注療法と組み合わせて行うことも考えられる。

また、局所線溶療法におけるこれまでの多くのstudyは、中大脳動脈塞栓症を標的病変としているか、結果的に中大脳動脈塞栓症が主な対象疾患となっているが、脳底動脈塞栓症に代表される後方循環系の塞栓症では、中大脳動脈塞栓症と異なり生命予後に直接関わる疾患であること、患者数が少なく大規模臨床試験が困難であるなどの理由から、局所線溶療法を第一に考慮していいのではないかと思われる[9]。

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今月の主題　ブレインアタック2006—t-PA時代の診断と治療

t-PAで変わるブレインアタック治療

# t-PA静注療法か局所線溶療法か

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t-PAで変わるブレインアタック治療

# t-PA静注療法か局所線溶療法か

江面 正幸・松本 康史・高橋 明

**ポイント**

- 2005年10月に脳梗塞急性期(発症3時間以内)に対するt-PAの静注療法が保険適用となったため，脳塞栓症を否定できない発症3時間以内の脳梗塞に対しては，t-PAの静注療法が第一選択である．
- 発症3時間以上を経過した症例，特に脳底動脈塞栓症に対しては，局所線溶療法を検討する必要がある．

## 2005年10月まで

本号の特集は「t-PA時代の診断と治療」であるが，t-PA時代の到来に伴って最も大きな影響を受けるのが筆者の担当する「t-PA静注療法か局所線溶療法か」である．出島から覗きみるだけだった欧米の実情が黒船に乗って直接やってきたくらいのインパクトがある．

iv-t-PAが認可される前には，欧米はともかく本邦では脳梗塞急性期症例に対して静注療法と局所線溶療法に保存療法を加えた3者でどの治療が優れているのか結論が出ていなかった．このため1990年代には各施設で独自の治療が行われており，標準的治療が確立されていなかった．このような状況が憂慮され，2000年代前半に保存療法を対照としたいくつかの臨床試験が企画された．

## MCA embolism local fibrinolytic intervention trial (MELT) Japan

本邦で実施された局所線溶療法の無作為割付け試験である．2001年に開始され，2002年より症例登録が始まった[1]．対象疾患は中大脳動脈塞栓症のみで，20～75歳，発症時間が特定可能で発症から6時間以内に局所線溶療法を開始できる，症候上はNational Institutes of Health Stroke Score(NIHSS)5～22などの条件がある．神経放射線学的評価項目はCT scanのみであり，CTで全く変化を認めないか軽微な初期虚血変化のみを認める場合はenrollされる．近年MRI拡散強調画像(diffusion weighted image：DWI)の有用性が報告されており[2]，DWIを必須検査とするか否かについては最も議論がなされたところであるが，DWIを時間の制約なく施行できる施設がまだ限られていたこと，DWIの高輝度領域が不可逆的脳損傷を示すということは，現時点では臨床的印象に基づくものであり，科学的に証明されたものではないという2つの理由により不採用となった．CTに続いて脳血管撮影を行い，中大脳動脈(middle cerebral artery：MCA)の塞栓性閉塞症が確認されれば症例の割付けに進み，局所線溶療法が割付けられればそれを行う．

このstudyでは手技の標準化委員会が組織され，MCAの局所線溶療法に対する標準的な方法が提示された．マイクロカテーテルやガイドワイヤーの細かい規定はないが，バルーンカテーテルやステントなどマイクロカテーテル以外の使用は禁じられている．マイクロカテーテルを血栓より遠位に誘導し，ウロキナーゼ60万単位を生理食塩水50 m*l*に溶解したものをシリンジポンプを用いて12万単位/10 m*l*を5分間で注入する．ガイドワイヤーやマイクロカテーテルによる塞栓破砕は行ってもよい．ウロキナーゼの注入は60万

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単位に達するか，注入開始1時間まで続ける．

2005年10月に登録開始3.5年目の中間報告がなされた[3]．すでに予定登録期間の7割を経過しているが，200例の目標登録症例数に対して，まだ半数強の116例が登録されているのみである．3カ月の追跡期間を終了した105例において一時エンドポイントであるmodified Rankin Scale (mRS) 0～2は，対照群で20/52であるのに対し，療法群では26/53であるが有意差ではない．二次エンドポイントのmRS 0～1は，対照群で11/52であるのに対し，療法群では21/53であるがこれも有意差には至っていない．

## Japan alteplase clinical trial (J-ACT)

1995年に発表されたNINDS studyにより[4]，米国では発症3時間以内の脳梗塞に関しては静注療法が標準的治療となった．NINDS studyで使用されたアルテプラーゼは，本邦においても米国においても急性心筋梗塞に対して臨床使用が認められているが，その適応量は本邦においては0.5～0.75 mg/kgとされ，米国においては100 mgとされている．米国成人の標準的な体重を67～100 kgと考えると米国での投与量は1.0～1.5 mg/kgとなるので，日本では米国の半量が適応量とされていることになる．このようなことがあるので，NINDS studyの投与量をそのまま本邦に移行すると過剰投与になると判断され，日本人に適した投与量でのtrialが必要とされた．これがJ-ACTで，国内の23施設が参加して2002年4月より2003年9月にかけて行われた．種々の検討の結果アルテプラーゼの投与量は0.6 mg/kgに設定され，その他の点はNINDSに準じているが，対照群をおかないopen trialとして行われた．103例が登録され，心原性塞栓症が80%を占めた．治療前のNIHSSはNINDSと同等で，発症から投与開始までの所要時間は約2.5時間であった．発症後3カ月の予後良好例(mRS 0～1)は37%で死亡症例は10%，症候性頭蓋内出血は5.8%であった．これらの結果はNINDSのそれと同等であった(NINDSでは順に39%，17%，6.4%)．この結果を受けて，本邦でも遂に2005年10月にt-PA静注療法が保険適用となった．

## 2005年10月以降

t-PA静注療法が保険認可をされたことは，MELT Japanにとっても重大な意味をもつ．J-ACTやMELT Japanを行うにあたっての倫理的な正当性は，保存療法と静注療法，局所線溶療法の3者の間で，どれが有効であるのかはわかっていない，ということであった．J-ACT自体は局所線溶療法を否定するものではないが，J-ACTによって静注療法が保存療法よりも有効であることが確認されたので，MELT Japanのコントロールとして保存療法を行うことは倫理的に大きな問題がある．そこで，t-PA静注療法の保険認可後は，安全監視委員会の勧告により少なくともそれまでと同じプロトコールでのMELT Japanは継続しないことが決定された．このことは，発症3時間以内の脳梗塞に対しては本邦でもt-PA静注療法がスタンダードとなったことを意味している．

## 局所線溶療法の今後

静注療法の有効性が確認された現在，局所線溶療法は新たな展開を余儀なくされている．そもそも欧米のstudyも含めて，静注療法と局所線溶療法を比較しようという試みはまだ行われていない．ただ共に北米で行われたNINDSとPROACT IIの結果によれば，局所線溶療法は有効ではあるものの静注療法を遥かに凌駕するほどではない，ということである．そうすると局所線溶療法の位置づけは，静注療法の適応外である発症3時間以上の症例をターゲットにするとか，すでに静注療法を実施された症例のadjuvant療法とするなどがある[5]．また，局所線溶療法におけるこれまでの多くのstudyは，中大脳動脈塞栓症を標的病変としているか，結果的に中大脳動脈塞栓症が主な対象疾患となっているが，脳底動脈塞栓症に代表される後方循環系の塞栓症では，中大

脳動脈塞栓症と異なり生命予後に直接かかわる疾患であること，患者数が少なく大規模臨床試験が困難であるなどの理由から，局所線溶療法を第一に考慮していいのではないかと思われる．


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書評

## 富野康日己 編集
## 内科医のための薬の禁忌100


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最も薬剤を使用する機会の多い内科領域において，薬剤に関する医療ミスが増加している．これらのなかではdo処方により必要な変更がなされていないことや，似た名前の薬剤を誤って書いてしまうミス，さらには薬局段階で誤投薬がされるなど，不注意によるミスが多い．当然，処方箋記載後も薬局，院外薬局とダブルチェック機能もあり，大きな問題にならないことが多いが，注意が必要であることは言うまでもない．一方で，病態によっては投与できない処方があり，また併用においても行ってはいけないものもある．これらは，処方箋を作成するうえでのミスとは異なり，むしろ薬剤に関する知識が不十分であることによっておきるもので，それだけ事は重大となる．

今回，順天堂大学の富野康日己教授によって編集された『内科医のための薬の禁忌100』は，そのような意味でも薬剤による医療ミスを予防するうえで大きな意義を有する書籍である．

多くの医師は，自分の専門領域の薬剤については，使用禁忌，慎重投与，副作用，併用禁忌についてはよく知っているものである．本書はまずは，それらの確認を手早くできるのがありがたい．時には専門領域でも知らない項目があったり，機序・病態の内容で再確認される項目もあり勉強になる．一方，専門分化が進む今日の医学では他領域の薬剤の開発，新薬への切り替えも多く，専門外の領域においては，必ずしも十分な薬剤知識を有することは容易ではない．本書の特徴と有用性は，循環器内科領域から膠原病・アレルギー領域まで内科全体をカバーして薬の禁忌を紹介している点にある．広い内科領域について，重要な項目を絞って紹介されているため読者にとっての意義がさらに大きくなっている．

本書の特徴としては，病態と薬剤を明確にした見出しがコンパクトで分かりやすい点も挙げられる．さらに，その病態や同様の使用機序で起き得る禁忌，そして対策や代替療法など現実的に必要な知識が分かりやすく説明されている．見事な構成でついつい目を奪われ，一気に読んでしまう内容となっている．

また，書籍は，一度読んでも何かの折に，また確認や読み直しをするものである．本書のコンパクトサイズの判型は，座右の書としていつでもとり出して見ることのできるサイズであり，この点も本書の特徴である．富野教授の読者に対する気遣いが随所に表れている名著である．


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# A Case-Control Analysis of Intra-Arterial Urokinase Thrombolysis in Acute Cardioembolic Stroke

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**Key Words**
Intra-arterial urokinase thrombolysis · Cardioembolic stroke · Acute ischemic stroke · National Institute of Health Stroke Scale score · Modified Rankin scale score

**Abstract**
***Background:*** Intra-arterial urokinase (IA-UK) thrombolysis is frequently given in Japan to selected patients with acute cerebral artery occlusion. However, it is not clear whether or not IA-UK thrombolysis has an efficacy for acute stroke patients. The purpose of this study was to assess the effects of IA-UK thrombolysis in acute cardioembolic stroke patients, by performing a case-control analysis using data from Japan's Multicenter Stroke Investigator's Collaboration (J-MUSIC). ***Methods:*** 16,922 acute ischemic stroke patients were enrolled into J-MUSIC. From these patients, we selected 91 patients (UK group) who met the following criteria: treatment with IA-UK; 20–75 years of age; cardioembolic stroke; presenting with a carotid stroke; admission within 4.5 h of symptom onset, and a National Institutes of Health Stroke Scale (NIHSS) score of 5–22 points on admission. A control group of 182 patients without IA-UK treatment and matched to the NIHSS score, gender, and age was chosen. We compared the modified Rankin scale (mRS) score at discharge and the mortality between the 2 groups. ***Results:*** In both groups, the mean age was 65 ± 8 years, and the median NIHSS score was 14. The mean interval between symptom onset and UK administration was 3.4 ± 1.3 h, and the IA-UK dose was 392,000 ± 200,000 units. The mRS score at discharge was lower in the UK group than in the control group (mean, SD, median; 2.8, 2.9, 2 in UK group vs. 3.3, 1.8, 4, in the control, respectively p = 0.031). A favorable outcome (mRS of 0–2) was more frequently observed in the UK group (50.5%) than in the control group (34.1%, p = 0.0124). No difference in the mortality rate was seen between the UK group (11.0%) and the control group (13.3%). As well, there was no difference in the length of hospital stay between the UK group (46 ± 41 days, mean ± SD) and the control group (42 ± 42 days, mean ± SD). ***Conclusions:*** IA-UK thrombolytic therapy may improve the outcome in hyperacute cardioembolic stroke patients.



Intravenous (IV) thrombolytic therapy using recombinant tissue plasminogen activator (rt-PA) has been shown to be an effective treatment for ischemic stroke if used within 3 h of stroke onset [1, 2]. Recently, prolyse in acute cerebral thromboembolism (PROACT) I and II reported that local and intra-arterial (IA) thrombolytic therapy with pro-urokinase (proUK) could improve the outcome

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for ischemic stroke patients if used within 6 h of symptom onset [3, 4]. In Japan, the use of rt-PA for acute ischemic stroke has not been approved by the government. Therefore, IA thrombolytic therapy with urokinase (IA-UK) is mainly performed as a replacement of IV-rt-PA thrombolysis for acute cerebral artery occlusion, and in particular, for embolic occlusion of the middle cerebral artery. Several investigators have reported that IA-UK therapy was safe and effective for acute ischemic stroke [5–15]. However, their sample sizes were small, and not all their studies were randomized controlled trials.. Therefore, it remains unclear whether IA-UK therapy is effective for acute stroke patients. The aim of this study was to assess the efficacy of IA-UK thrombolysis for acute stroke patients by a case-control analysis using data from J-MUSIC [16, 17].

## Subjects and Methods

We conducted a multicenter, prospective, hospital-based registration study (J-MUSIC) from May 1999 to April 2000 in which 156 hospitals from all over Japan participated [16, 17]. A total of 16,922 consecutive patients with acute ischemic stroke and transient ischemic attack within 7 days of onset were registered in this study.

The following data were assessed in all the patients, using common data-sheets prepared by the protocol committee: (1) age and gender; (2) time from onset to hospital arrival; (3) a history of stroke; (4) National Institutes of Health Stroke Scale (NIHSS) score on admission; (5) site of acute lesions on CT or MRI; (6) stroke subtype (clinical category); (7) thrombolytic therapy (IV and IA rt-PA, IA UK) within 12 h of onset; and (8) outcome at discharge.

Clinical categories were defined by using clinical and radiographic diagnosis rubrics according to the classification of cerebrovascular diseases III developed by National Institute of Neurological Disorders and Stroke [18]. The main subtypes included: lacunar, atherothrombotic, cardioembolic, and other stroke. The modified Rankin Scale (mRS) [19] score and mortality were used to assess clinical outcome at hospital discharge.

We selected patients treated with IA-UK (UK group) and patients who had been treated without thrombolytic therapy (control group) from 16,922 patients. The UK group was identified as the patients treated with IA-UK who met the following criteria: aged 20–75 years; presence of a cardioembolic stroke or a carotid stroke; admission within 4.5 h of symptom onset, and an NIHSS score of 5–22 points on admission. We randomly selected control patients who had no thrombolytic therapy, such as IA-UK, IA-rt-PA, and IV-rt-PA and were matched to the UK group patients with respect to age, gender, and NIHSS score. The number of control group patients was set to be twice the number of the UK group patients.

*Statistical Analysis*

Analyses were made with a commercially available software package (Stat-View, version 4.5; ASA Institute, Cary, N.C.). We compared the mRS score, mortality, and length of hospital stay between the two groups. The statistical significance for differences between the two groups was assessed by the Wilcoxon signed-rank test for the mRS score, the $\chi^2$ test for favorable outcome (mRS score 0–2) and mortality, and the paired t-test for length of hospital stay. A p value $<0.05$ was considered statistically significant.

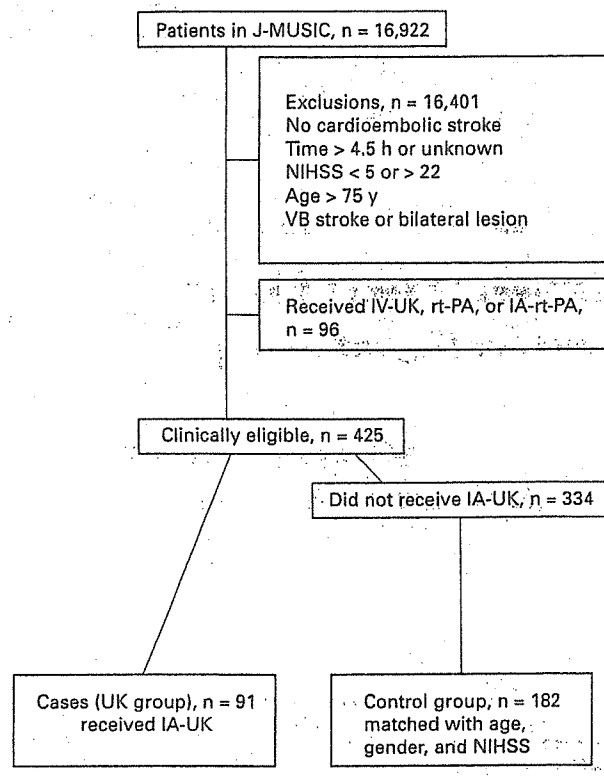


**Fig. 1.** Flow chart showing process of patient selection.

## Results

Ninety-one patients met the criteria for inclusion into the UK group and 182 patients were selected for the control group (fig. 1). Table 1 shows the baseline characteristics of the two groups. In each group, the average age was 65 ± 8 years. The median NIHSS score for the two groups was 14. In the UK group, the mean interval between the onset of symptoms and UK administration was 3.4 ± 1.3 h, and the IA-UK dose was 392,000 ± 200,000 units. The mRS score at discharge was lower in the UK group than in the control group (mean, SD, median; 2.8, 2.9, 2 vs. 3.3, 1.8, 4, respectively; p = 0.031). Patients with

**Table 1.** Characteristics of the two groups

| | UK group | Control group | p |
|---|---|---|---|
| Patients | 91 | 182 | |
| Gender, F/M | 24/67 | 48/134 | |
| Age, years (mean ± SD) | 65 ± 8 | 65 ± 8 | |
| NIHSS score on admission | 14 | 14 | |
| Interval time from stroke onset to hospital, h (mean ± SD) | 1.1 ± 0.2 | 1.1 ± 0.3 | |
| Interval time from stroke onset to treatment, h (mean ± SD) | 3.4 ± 1.3 | – | |
| Range | 1–6 | | |
| Mega units of UK administered (mean ± SD) | 0.39 ± 0.20 | – | |
| Mean, SD, median of mRS score at discharge | 2.8, 2.9, 2 | 3.3, 1.8, 4 | 0.031 |
| mRS ≤2, % | 50.5 | 34.1 | 0.012 |
| Mortality, % | 11.0 | 13.2 | 0.745 |
| Length of hospital stay, days (mean ± SD) | 46 ± 41 | 42 ± 42 | 0.347 |

favorable outcome were more frequently found in the UK group than in the control group (50.5 vs. 34.1%, p = 0.0124). However, no difference between the two groups was observed in the mortality rate (11.0 vs. 13.2%) or the length of hospital stay (46 ± 41 vs. 42 ± 42 days, mean ± SD).

We analyzed the relationship between time interval from stroke onset to IA-UK thrombolytic therapy and patients' outcome. The percentage of favorable outcome was higher in patients treated within 2 h of stroke onset than in those between 2–4 h and over 4 h [63% (17/27), 45% (21/47), and 47% (8/17)]. However, no significant differences among them were observed (p = 0.30).

## Discussion

This case-control study based on the data from J-MUSIC demonstrates the effectiveness of IA-UK thrombolysis in acute stroke patients. Patients with IA-UK thrombolysis had an increased frequency of good outcomes, approximately 1.5 times greater than patients without IA-UK thrombolysis. However, no difference in mortality rate was observed between patients with and without IA-UK thrombolysis.

The PROACT II study [4] demonstrated a significant benefit from treatment with IA proUK in patients with a middle cerebral artery occlusion treated within 6 h of stroke onset. Their proUK group had a higher recanalization rate (66 vs. 18%) with a greater number of patients with good outcomes (mRS score 0–2) after 3 months of stroke onset (40 vs. 25%). However, the incidence of symptomatic intracranial hemorrhage was 10% in the proUK group, but only 2% in the placebo group.

In 1988, del Zoppo et al. [5] studied 20 patients and showed that local IA fibrinolytic therapy using UK or streptokinase might lead to cerebral arterial recanalization in patients with an acute carotid territory thrombotic stroke. Mori et al. [6] also assessed 22 patients and reported on the safety and efficacy of UK thrombolytic therapy for acute thromboembolic occlusion of the middle cerebral artery. Recently, Gonner et al. [8] performed IA-UK thrombolytic therapy in 43 ischemic stroke patients within 6 h of symptom onset, and reported that therapy was effective except in patients with a carotid artery occlusion. Arnold et al. [20] analyzed the clinical and radiological findings, and assessed the functional outcome 3 months after IA-UK thrombolysis for 100 consecutive patients. They concluded that IA-UK thrombolytic therapy was safe and could be efficacious. The results of the present study also lead us to conclude that local IA thrombolytic therapy using UK could be effective for acute ischemic stroke.

The therapeutic time window of IV thrombolytic therapy with rt-PA is within 3 h [1, 2]. However, in the PROACT II study proUK could be administered within 6 h of stroke onset [4]. Therefore, IA thrombolytic therapy may allow the extension of the therapeutic time window for treating acute stroke from 3 to 6 h. In the future, thrombolysis using proUK as well as UK may provide an alternative to IV thrombolysis with rt-PA in selected patients with acute ischemic stroke.

Our study has some limitations. Firstly, the aim of the J-MUSIC [15] study was to determine the present state of stroke managements in Japan, and not to investigate the effectiveness of thrombolytic therapy. Secondly, we did not require to describe the presence and frequency of symptomatic cerebral hemorrhage after thrombolytic therapy in J-MUSIC. There was a higher rate of symptomatic intracranial hemorrhage with IA proUK in PROACT II (10.2%) [4] compared to IV-rt-PA in NINDS (6.4%) [2]. However, there is no evidence that the rate of symptomatic brain hemorrhage is lower with IV thrombolysis than with IA thrombolysis. Thirdly, this was not a randomized study. Therefore, there may be some selection bias against choosing stroke patients with complications, such as heart diseases and infection. Patients with

such complications were not likely to be treated with thrombolytic therapy, and outcomes of such patients were not as good as those in patients without such complications. Furthermore, control patients did not always undergo angiography. The catheter placement itself might be benefit for destruction of the clot. Moreover, physicians who assessed patients' outcome were not blinded to treatment. Therefore, it is possible that efficacy of IA-UK thrombolysis is overestimated.

In conclusion, IA thrombolysis using UK could potentially be effective for acute ischemic stroke patients, and would allow the possible extension of the 3-h therapeutic window. This would lead to an increased number of patients being eligible for thrombolytic therapy.

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# 4. EBM and Current State in Japan of Thrombolytic Therapy for Acute Ischemic Stroke

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# 4. EBM and Current State in Japan of Thrombolytic Therapy for Acute Ischemic Stroke

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*Key words:* acute ischemic stroke, penumbra, intracranial hemorrhage, tissue plasminogen activator

### *Introduction*

The new era has began for acute stroke management since intravenous thrombolytic therapy using tissue plasminogen activator (t-PA) was reported to be effective in increasing a complete or near-complete recovery in 3 months, if administered within the initial 3 hours after stroke onset (1). The treatment is now approved for use in ischemic stroke patients in USA, Canada, and European countries. Stroke becomes a medical emergency and is called "Brain Attack". Most guidelines of stroke therapy in these countries strongly recommend the use of t-PA for patients with acute ischemic stroke (2, 3).

Favorable outcome induced by hyperacute t-PA therapy were first suggested by randomized controlled trials (RCT) carried out in Japan (4, 5). The first Japanese guideline of stroke management published in 2004 recommends the use of intravenous t-PA therapy (Grade A) and local prourokinase (proUK) therapy (Grade B) (6), although both therapies have not yet been approved in Japan.

### *Theory and history*

The strategy of thrombolytic therapy is based on the concept that early reperfusion rescues reversibly damaged brain tissues in the ischemic penumbra (7, 8). Therefore, it is a reasonable speculation that thrombolytic therapy can promote early reperfusion, resulting in good clinical outcome.

Clinical trials with the first generation thrombolytic agents, streptokinase (SK) and urokinase (UK) failed to show favorable results but caused increases in symptomatic intracranial hemorrhage and in the death rate. In the 1980's, it was demonstrated with RCTs that the 2nd generation thrombolytic agents such as alteplase could improve outcome in patients with acute coronary thrombosis. The agents, then, began to be tested in acute ischemic stroke patients.

The results of several phase 3 RCTs with intravenous t-PA for the urgent treatment of patients with stroke have been reported (1, 5, 9, 10). Among them, only the NINDS trials could demonstrate a significant increase in patients with very favorable outcome at 3-months (1). Cost-effectiveness and long-lasting efficacy were also demonstrated in subanalysis of the study (11, 12). Other trials with a 6-hour time window, however, could not demonstrate the effectiveness and safety of t-PA therapy (9, 10).

The Prolysis in Acute Cerebral Thromboembolism II (PROACT II) trial was the first RCT in which intraarterial thrombolysis was shown to have a benefit in patients who have had a stroke caused by occlusion of the middle cerebral artery (MCA) and were treated within 6 hours after clinical onset (13). However, the therapy has not been approved in the United States.

In Table 1, the results of major RCTs with thrombolytic therapy for acute ischemic stroke patients reported in the English language literature are summarized.

### *Guidelines*

In most guidelines of acute stroke management in the North America and Europe, intravenous t-PA (0.9 mg/kg, maximum dose 90 mg) is strongly recommended for carefully selected patients who can be treated within 3 hours of onset of ischemic stroke (Grade A) (2, 3). The decision for treatment with t-PA should be based on several clinical features, mostly based on the protocol of the NINDS study. A recent case series indicated that implementation of intravenous t-PA therapy may not always be easy and safe, but in other series the safety and efficacy of this treatment were similar to those in the NINDS trial (14, 15). Violation of the NINDS protocol, particularly in the case of delayed treatment after 3 hours of stroke onset, may cause an increase in patients with symptomatic intracranial hemorrhage and result in a poor outcome (16).

As mentioned earlier, the first Japanese guideline of stroke management published in 2004 strongly recommends the use of intravenous t-PA therapy (Grade A) and local prourokinase (proUK) therapy (6). The recommendation, however, duplicates the statement of the American guideline. No studies demonstrating high-level evidence, nor guidelines specific to Japanese patients have been available.

### *Current status of thrombolytic therapy in Japan*

There were no studies to clarify the state of stroke management in Japan. To respond to this question, the Japan

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**Table 1. Summary of Major Randomized Clinical Trials with Thrombolytic Therapy**

| Trials | No. of patients | Time of therapy | Dose | Results | Intracranial hemorrhage |
|---|---|---|---|---|---|
| 1. t-PA intravenous therapy* | | | | | |
| JTSG (Japan) | 98 | <6 hs | 20 MU | Effective? | unchanged |
| NINDS (USA) | 624 | <3 hs | 0.9 mg/kg | Effective | increase |
| ECASS-I (Europe) | 620 | <6 hs | 1.1 mg/kg | Not effective** | increase |
| ECASS-II (Europe) | 800 | <6 hs | 0.9 mg/kg | Not effective*** | increase |
| ATLANTIS (USA) | 579 | 3～5 hs | 0.9 mg/kg | Not effective | ? |
| 2. SK intravenous therapy | | | | | |
| ASK (Australia) | 340 | <4 hs | 1.5 MU | Harmful | increase |
| MAST-I (Italy) | 622 | <6 hs | 1.5 MU | Harmful | increase |
| MAST-E (Europe) | 270 | <6 hs | 1.5 MU | Harmful | increase |
| 3. proUK intraarterial (local) | | | | | |
| PROACT-II (USA) | 180 | <6 hs | 9 mg | Effective | increase |

*JTSG (Japan Thrombolysis Study Group) used duteplase, and other trials used alteplase. **Effective if exclude 109 cases with protocol violation. ***Partly effective in some outcome measures.

Multicenter Stroke Investigators Collaboration, so-called J-MUSIC, conducted a multicenter study on stroke management from May 1999 to April 2000 (Chief Investigator: Yamaguchi T) (17). In 156 hospitals all around Japan, 16,922 acute ischemic patients admitted within the initial 7 days were consecutively registered. In the data of J-MUSIC, t-PA was administered intravenously to only 0.3%. In contrast, intraarterial t-PA (0.5%) or UK (1.6%) therapy was given to 2.5% of the patients.

In the database of J-MUSIC, we had 91 patients with acute ischemic stroke who were 20 to 75 years of age, admitted within the initial 4.5 hours, had a NIHSS score greater than 4 but less than 23 on admission, and treated with intraarterial UK therapy. We also selected from the J-MUSIC database 182 control patients who had similar clinical backgrounds but were not treated with thrombolytic agents, then compared the clinical outcome between the cases and controls. Patients who had a good outcome at discharge were significantly more frequent in the patients treated with intraarterial UK than in the controls (data submitted to an English journal).

### *Clinical studies in Japan*

The suggestion by the case-control study of the J-MUSIC is now tested with a RCT, so-called MELT-Japan (MCA-Embolism Local Fibrinolytic Intervention Trial Japan), chaired by Professor Ogawa. The detailed information of the study is opened to the public in the MELT-Japan homepage [http://melt.umin.ac.jp (Feb 8, 2005)]. The study is designed to consist of a total of 200 patients and is now on going.

A phase III trial using open-labeled, single-dose alteplase has just been finished in Japan (Japan Alteplase Clinical Trial, J-ACT). The study was designed to confirm the results of the t-PA group in the NINDS study. The study protocol was almost compatible to that of the NINDS study, except for several modifications. They included lower dose administration of alteplase (0.6 mg/kg) in the J-ACT than that (0.9 mg/kg) in the NINDS study. The results of the J-ACT were briefly presented in the joint symposium of the 29th annual meeting of the Japan Stroke Society and the 33rd annual meeting of the Japanese Society of Cerebral Stroke (Nagoya, March 19, 2004). The clinical background of the patients was similar to those in the NINDS study. Frequencies of very favorable outcome at 3-months and symptomatic intracranial hemorrhage were comparable between the studies. Mortality at 3-months, however, was less frequent in the J-ACT.

The J-ACT results mentioned above are very promising. The MELT-Japan will hopefully provide the class I evidence for local UK therapy within 6 hours after stroke onset in the near future. A great amount of investigative work will be needed to validate the potential of thrombolytic therapy for acute stroke patients in Japan. We are now entering an exciting new era for stroke management.

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# 5. Future Aspects of Gene Therapy in Acute Ischemic Stroke

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*Key words:* gene therapy, brain ischemia, macrophage, neurogenesis

Neural stem/progenitor cells remain in the adult mammalian brain, including the human brain. Neurogenesis continues throughout life in the two restricted zones, the hippocampal subgranular zone (SGZ) and the rostral migratory stream, where newly generated immature neurons migrate from the anterior subventricular zone (SVZ) into the olfactory bulb. Brain injury including ischemia stimulates neurogenesis in the SGZ and SVZ (1, 2). Therefore, therapeutic strategy for enhancing neurogenesis after ischemia may be of value for promoting functional recovery in stroke patients with neurological deficits. Intracerebral or intraventricular injections of neurotrophic factors could stimulate neurogenesis in the ischemic hippocampus and caudoputamen (3, 4). However, dependence on invasive surgical procedures for delivery could limit clinical application (Fig. 1A, B). Therefore, noninvasive, safe, and inexpensive strategies would be required for clinical application for enhancing neurogenesis in stroke patients. Several previous studies including our own have demonstrated that circulating monocytes or macrophages begin to infiltrate ischemic tissue after infarction develops (5). Peripheral blood mononuclear cells and macrophages have drawn much attention as novel cellular vehicles for gene therapies in which these cells are genetically modified *ex vivo* and then reintroduced into the body (6). Furthermore, cationic liposome/DNA complexes have been shown to be capable of transfecting monocytes/macrophages *in vivo* in blood, liver, and spleen (7). These observations suggest that after systemic intravenous injection of a cationic liposome/DNA complex, circulating monocytes/macrophages could take up the introduced gene and infiltrate infarcted tissue. Therefore we tried to develop the systemic gene therapy using infiltrating macrophages as cell vehicles. We used an enhanced green fluorescent protein (EGFP) expression vector complexed with cationic liposomes for systemic gene therapy. After systemic administration of pIRES-EGFP plasmid vector with Lipofectin into normal rats, no EGFP-positive cells or macrophages were observed in intact brain. However, macrophages markedly accumulated in the brain tissue once infarct developed (Fig. 1C), and large numbers of EGFP-positive cells were detected in the marginal zone of the infarct. Expression of the exogenous EGFP gene was

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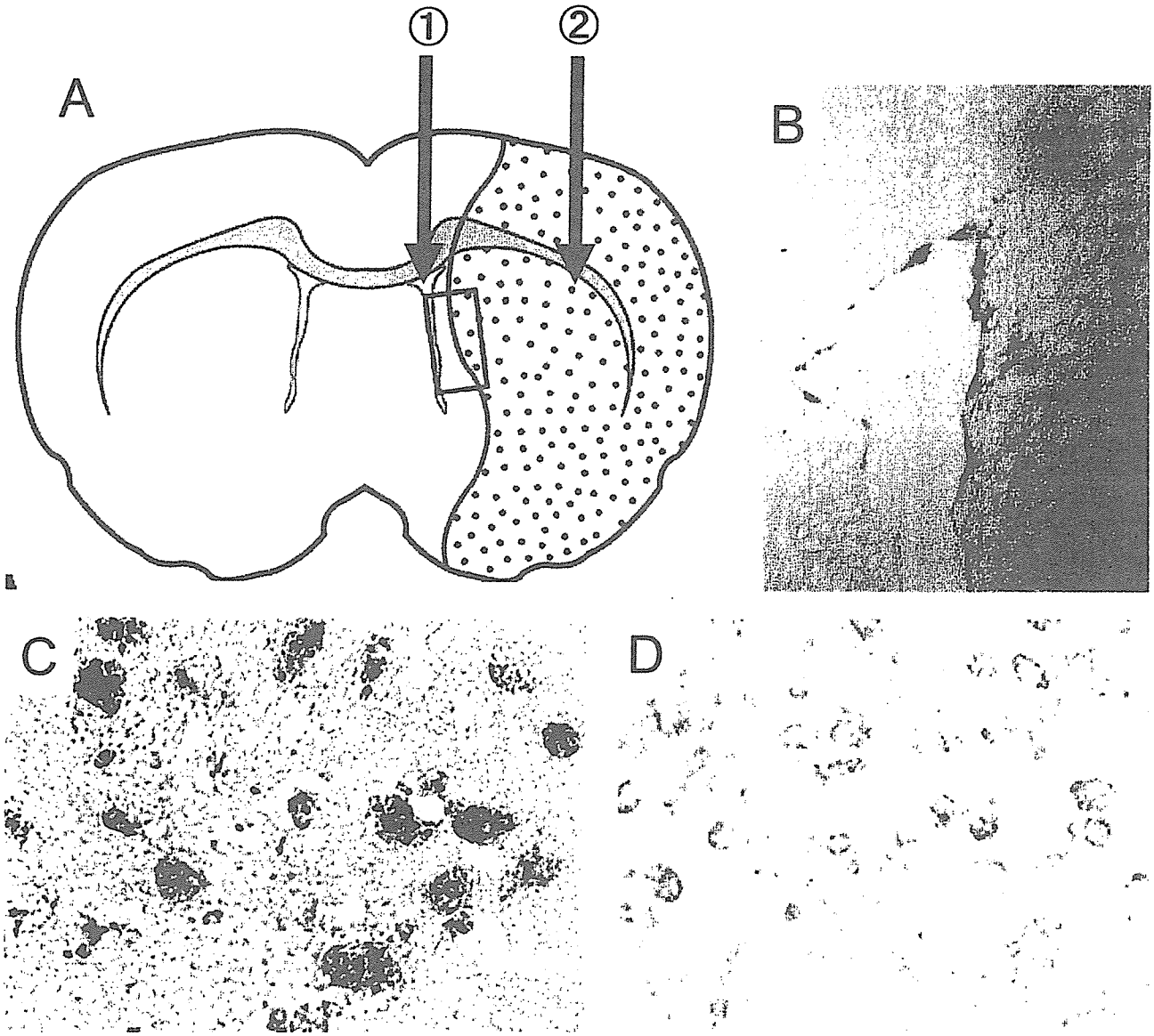


**Figure 1. The diagram depicts sections of the rat brain after middle cerebral artery (MCA) occlusion with the infarct shown as stippled (A). The border area is indicated by the rectangular box in the striatum. Intraventricular (1) or intracerebral (2) injection is widely used for gene transfer into the brain. Intraventricular administration of adenoviral reporter gene resulted in expression of exogenous gene on the wall of the lateral ventricule (B). Macrophages accumulating along the margin of the evolving infarct are shown with anti-Mac2 antibody in (C). Immunohistochemistry with anti-EGFP antibody was used to confirm EGFP protein expression in the ischemic caudoputamen after intravenous injection of pIRES-EGFP plasmid vector (D).**

confirmed immunohistochemically using an anti-EGFP antibody (Fig. 1D). Most EGFP-positive cells expressed monocyte/macrophage specific antigens. To deliver exogenous FGF-2 gene to the infarct, we injected pIRES-FGF2-EGFP plasmid. Marked expression of both FGF-2 and EGFP was observed in the infarct (Fig. 2A–C). Administration of pIRES-FGF2-EGFP plasmid increased the number of neural progenitor cells (Fig. 2D, 2E) in the lateral wall of the SVZ after MCA occlusion (Fig. 2F).

Gene therapy for stroke holds promise because of its ability to induce expression of desired molecules by cells for a long period. Gene transfer for neurotrophic factors (8), anti-apoptotic protein (9), and heat shock protein (10) can ameliorate ischemic brain damage when administered before or even after induction of ischemia. Post ischemic treatment could be given to stroke patients provided that efficacy and safety were proven. However, the viral vectors such as herpes simplex virus and adenovirus used in experimental stud-

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## 3D Rotational Angiographic Demonstration of Dissection of the Anterior Cerebral Artery

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*Introduction*

Dissection of intracranial arteries presents with a much less specific angiographic appearance than that of the extracranial portion of the cervicocephalic artery, rendering a correct diagnosis using common diagnostic tools difficult. We describe the usefulness of three-dimensional rotational angiography (3D-RA) for visualizing the double lumen sign, which is the pathognomonic finding of arterial dissection.

*Case Report*

A 59-year-old man developed sudden onset of weakness in the left lower limb and neck pain after karaoke singing. He was admit-

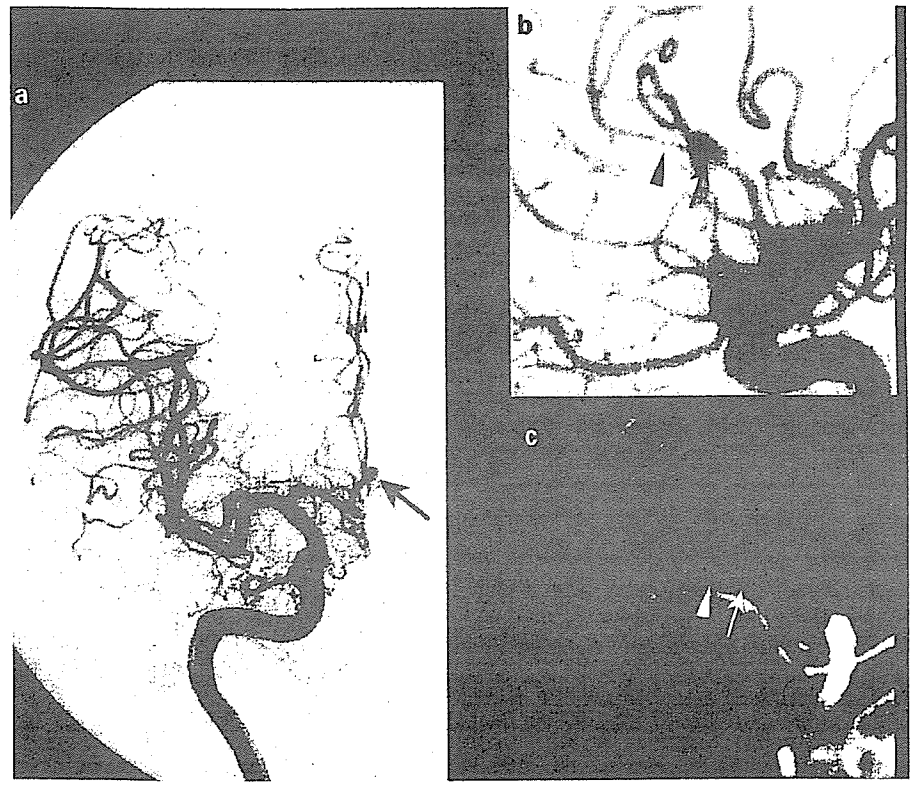


**Fig. 1.** Conventional cerebral angiography and MRA. Right carotid conventional angiography 30 days post-ictus, anteroposterior view (**a**) and lateral view (**b**), revealing aneurysmal dilatation of the right proximal A2 portion (arrow), followed by segmental arterial stenosis (arrowhead). MRA (**c**) shows aneurysmal dilatation of the right proximal A2 portion (arrow) with segmental arterial stenosis (arrowhead).

ted to our stroke care unit the following day. Blood pressure was 160/90 mm Hg. General physical examination revealed no abnormalities.

Upon neurological examination, the patient was alert and fully oriented. He spoke clearly and fluently. Cranial nerve functions were normal. Muscle strength testing revealed left-sided hemiparesis with crural predominance. Coordination and sensation to light touch and pinprick were normal. Deep tendon reflexes were exaggerated on the left side. Plantar responses were extensor on the left. No signs of callosal disconnection syndrome were observed.

Magnetic resonance (MR) images of the brain, performed 2 days post-ictus, demonstrated fresh brain infarction in regions supplied by the right ACA. Conventional cerebral angiography, performed 2 days after onset, revealed slightly dilatation of the right proximal A2 portion, followed by segmental narrowing. We suspected the residual stenosis by brain embolism or dissection of the ACA. To confirm the findings, angiography was performed 30 days after onset which revealed aneurysmal dilatation of the right proximal A2 portion, followed by segmental narrowing (fig. 1a, b). Both MRI and magnetic resonance angiography (MRA) (fig. 1c) failed to detect the double lumen sign. Examination using 3D-RA with a standard Integris BV5000 biplane system (Philips Medical System, Best, The Netherlands) demonstrated the same abnormalities mentioned above (fig. 2a, b), and clearly identified an intimal flap (fig. 2c), leading to a diagnosis of dissecting aneurysm.

*Discussion*

Cerebral arterial dissections are being detected with increasing frequency, which is partially attributable to increasing interest in the clinical and radiological features of this disorder, and also to the increasing availability of non-invasive neuroimaging techniques, which are steadily improving in quality. However, dissection involving small-caliber vessels, such as the intracranial arteries, displays a non-specific angiographic appearance, and the diagnostic roles of MRI and MRA remain limited in such cases. Many patients with dissection involving these vessels might have been overlooked [1]. Chaves et al. [2] recently reported on 10 patients with spontaneous dissection of the intracranial portion of the internal carotid artery (ICA). They emphasized that ICA dissection should be considered as a differential diagnosis for intracranial ICA stenosis or occlusion.

The 'string sign' [3], 'rosette sign' [4] and 'pearl reaction' [5] have been reported as angiographic characteristics of arterial dissections. However, these findings are not considered particularly specific, as they are also seen in atherosclerotic vascular diseases [6]. Although the double lumen sign, which is visible flow in both the true and false lumen [6], has been suggested to be a pathognomonic, it is rarely seen in intracranial arteries [1]. To the best of our knowledge, only 4 cases of the double lumen sign in the ACA have been reported in the English literature [7–9]. Kazui et al. [10] reported 17 patients with solitary infarction in the territory of the ACA, including 4 of undetermined etiology. One patient had an A2