脳梗塞およびTIA全般

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- わが国の脳卒中は、死因の第3位、要介護性疾患の首位を占める。脳梗塞はそのうち6～8割を占める。人口超高齢化の進行に伴い、そのインパクトはますます大きくなるであろう。
- 発症3時間以内の脳梗塞に対するrt-PA（アルテプラーゼ）静注療法の国内承認（2005年10月）により、わが国の超急性期脳梗塞診療は大きく変貌しつつある。海外では、発症3～4.5時間でのrt-PA（アルテプラーゼ）静注療法の有効性が報告され、他の超急性期治療法の開発研究も盛んである。
- 一過性脳虚血発作（TIA）の診断基準が見直されている（持続時間は典型的には1時間以内、かつ画像診断上脳梗塞巣が認められない）。TIAは従来考えられていた以上に短期日の間に完成型脳梗塞を発生するリスクが高いことが明らかにされ、患者・家族・医療従事者への教育・啓発や、診療体制の見直しの必要性が叫ばれている。
- 抗血小板薬クロピドグレルや高リスク頸動脈高度狭窄症に対するステント留置術も国内承認がなされた。再発予防戦略は一層進歩しつつある。
- 脳卒中診療体制には地域差があり、かつこの問題は深刻化しつつある。わが国の脳卒中診療体制の再構築のためには、ガイドライン、インディケータ、データバンクなどの全国的整備、普及が必要である。総合的かつ計画的な脳卒中対策のために、「脳卒中対策基本法（仮称）」の立法化が提唱されている。

わが国における脳梗塞のインパクト

脳卒中（脳血管障害）は、国内死因の第3位（年間約13万人）、要介護性疾患の首位、65歳以上の寝たきり状態の最大の原因である（約4割）。患者数は約270万人（2005年）と膨大であるが、高齢者脳卒中入院患者は今後20年間にわたり増加し続けると予想されている。脳卒中死亡の60％が脳梗塞による。脳梗塞の正確な発症率は不明

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であるが、大まかに10万人対100～200人、40歳以上では10万人対600人前後である。超高齢化が急激に進行するわが国では、脳梗塞の発症・総患者・死亡者・要介護者数のさらなる増加が懸念される。

脳梗塞は、脳内小動脈病変を原因とする「ラクナ梗塞」、頸部～頭蓋内の主幹脳動脈のアテローム硬化性病変が原因の「アテローム血栓性脳梗塞」、心疾患からの塞栓による「心原性脳塞栓症」、および「その他」の4タイプに大別され、わが国の脳梗塞の半数以上をラクナ梗塞が占めるとされてきた。1999～2000年に実施された脳梗塞に関する国内初の全国多施設共同入院患者登録調査Japan Multicenter Stroke Investigators' Collaboration (J-MUSIC)研究では、ラクナ梗塞の減少傾向(39%)、アテローム血栓性脳梗塞の増加(33%)、心原性脳塞栓症(22%)の増加が示唆された[1]。関東や近畿などの大都市圏では、アテローム血栓性脳梗塞の頻度が他のタイプの脳梗塞の頻度より高く、都市部を中心としたライフスタイルの欧米化がその原因と推定された。最近の疫学調査や入院登録調査において、ラクナ梗塞の減少、アテローム血栓性脳梗塞の増加、高齢者層における心原性脳塞栓症の増加傾向は顕著である[2]。

脳梗塞タイプ別の重症度や転帰は、心原性脳塞栓症が最も不良であり、次いでアテローム血栓性脳梗塞、ラクナ梗塞の順である。前述のJ-MUSIC研究では、脳卒中重症度を表すNIH Stroke Scale(NIHSS)スコアの入院時中央値は、ラクナ梗塞4、アテローム血栓性脳梗塞6、心原性脳塞栓症14、その他5であった(点数が高いほど重症)。modified Rankin Scale(mRS)は大まかな転帰を表すスコアであるが、これが退院時に3～5(要介助～寝たきり)であった割合は、それぞれ22.6%、41.4%、44.8%、29.8%で、入院中死亡は1.1%、6.9%、18.6%、10.3%であった[1]。心原性脳塞栓症は最も重症であり、転帰も不良である。アテローム血栓性脳梗塞がこれに続き、ラクナ梗塞は軽症であった。今後の脳梗塞は、ラクナ梗塞のような軽症例が減少し、重症で、要介護度や死亡率の高い心原性脳塞栓症やアテローム血栓性脳梗塞が増加するであろう。大変な事態である。

急性期診療の進歩

1. 虚無主義から積極主義へ

1995年、発症3時間以内の遺伝子組み換え組織型プラスミノゲン・アクティベータ(recombinant tissue-type plasminogen activator；rt-PA)静注療法の有効性が、大規模臨床試験で証明され[3]、脳梗塞診療は「虚無主義から積極主義へ」の歴史的大転換を遂げた。ほぼ同じ頃、MR拡散強調画像(diffusion-weighted image；DWI)やMR angiography(MRA)などの脳卒中画像診断技術が飛躍的に進歩した。頸動脈高度狭窄症に対する頸動脈内膜剥離術(carotid endartectomy；CEA)や、脳卒中ユニット(stroke unit；SU)における急性期診療の有効性も実証された。脳卒中データバンク、診療ガイドライン等々、今日の脳梗塞診療に不可欠のキーワードの多くが、この時代に相次いで誕生した。

わが国でも、2004年に初の脳卒中治療ガイドラインが発表された[4]。しかしながら、本ガイドラインでグレードA(行うように強く勧められる)とされた治療法は少なく、脳梗塞急性期治療に限れば、「血栓溶解療法(静脈内投与)」のrt-PA、「抗血小板療法」の経口アスピリンの2つのみであった。しかし、この当時のrt-PAは未承認であり、経口アスピリンの処方頻度もあまり高くなかった。「脳卒中治療ガイドライン2004」から5年以上が経過し、この間に脳梗塞診療を取り巻く状況は激変した。

2. rt-PA(アルテプラーゼ)静注療法の国内承認のインパクト

脳梗塞に対するrt-PA(アルテプラーゼ)静注療法の国内承認は、米国より9年遅れ、2005年秋であった。筆者は、国内承認の根拠となった第Ⅲ相治験Japan Alteplase Clinical Trial(J-ACT)の試験計画策定、実施、成績発表、その直後に公表された日本脳卒中学会の「rt-PA(アルテプラーゼ)静注療法適正治療指針」作成などに深く関与した[5,6]。

「脳卒中治療ガイドライン2004」では、註で紹介されていた「発症6時間以内の中大脳動脈閉塞に対する局所血栓溶解療法」に関する医師主導型臨床試験MELT-Japanは、アルテプラーゼ静注療法承認で非治療群の設定が不可能となり、中止された。しかしながら、予定の約半分の例数で一定の治療

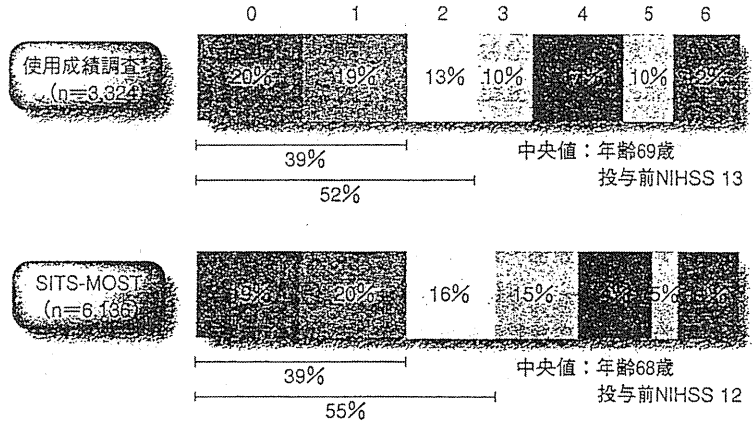

図1　欧州(SIST-MOST)とわが国の市販後使用成績調査の比較：発症3ヵ月後のmRSの比較(文献8、9より引用)

SITS-MOSTの症例選択基準である年齢18～80歳、投与前NIHSS 25未満を満たす症例を選択した場合、国内使用成績調査における発症後3ヵ月後のmRSは、SITS-MOSTのそれとほぼ同じであった。

効果が確認され、その成績は英文専門誌に発表された[7]。

rt-PA(アルテプラーゼ)静注療法承認から4年になる。この間、日本脳卒中学会による「適正使用講習会」が全国各地で約200回以上開催された(受講者約1万人)。本療法は、承認後2年間に約8,300例に実施されたが、これは脳梗塞全体の約2%に過ぎない。

本療法の安全性や有効性に関する市販後使用成績調査(いわゆる全例調査)や、MR画像診断を利用した市販後臨床試験(第Ⅳ相)J-ACTⅡが実施された。全例調査の中間解析では、安全性指標としての「発症36時間以内の症候性頭蓋内出血」、有効性指標としての「発症3ヵ月後のmRS 0～1の転帰良好」のいずれも、J-ACTの結果に比べ低率で、3ヵ月以内の死亡率は約2倍高かった[8]。J-ACTに比べると、75歳以上の高齢者が多く、J-ACTでは対象外であったJCS 100～300の高度意識障害が全体の8%を占め、投与前NIHSSスコア21以上の重症例もより多かった。こうした重症例への投与の偏りが、転帰不良例の増加の主たる原因と推定されている。ちなみに、欧州で実施された同様の市販後登録調査Safe Implementation of Thrombolysis in Stroke-Monitoring Study(SITS-MOST)[9]の基準を満足する約3,000例を選んで分析したところ、SITS-MOSTとほぼ同等の結果であった(図1)[8,9]。J-ACTⅡでも、中大脳動脈閉塞例に対するアルテプラーゼの優れた再開通促進効果、転帰改善効果が確認されている。これらの最終結果は、2009～2010年には英文専門誌に発表される予定で、日本脳卒中学会の脳卒中医療向上・社会保険委員会は、2010年春の「rt-PA(アルテプラーゼ)静注療法適正治療指針」改定を計画している。

3. 新たな展開

欧米各国では、発症後3時間以内のrt-PA(アルテプラーゼ)静注療法の限界打破を目指す新たな治療戦略の開拓、検討が行われている。2008年9月、発症3～4.5時間の脳梗塞患者に対するrt-PA(アルテプラーゼ)静注療法の有効性と安全性とを証明した欧州での大規模臨床試験ECASS 3の結果が発表された(図2)[10]。すでに欧米では、本療法の適応限界を従来の3時間以内から4.5時間以内に延長するガイドラインや勧告が発表され始めている。この問題についての、国内での扱いは今後の課題である。

この他にも、脳保護薬と血栓溶解薬との併用、超音波照射を併用した血栓溶解療法、新しい血栓溶解薬による発症後9時間以内の血栓溶解療法、血栓回収装置(Merci、Penumbra)を用いた血管内治療など、さまざまな試みが

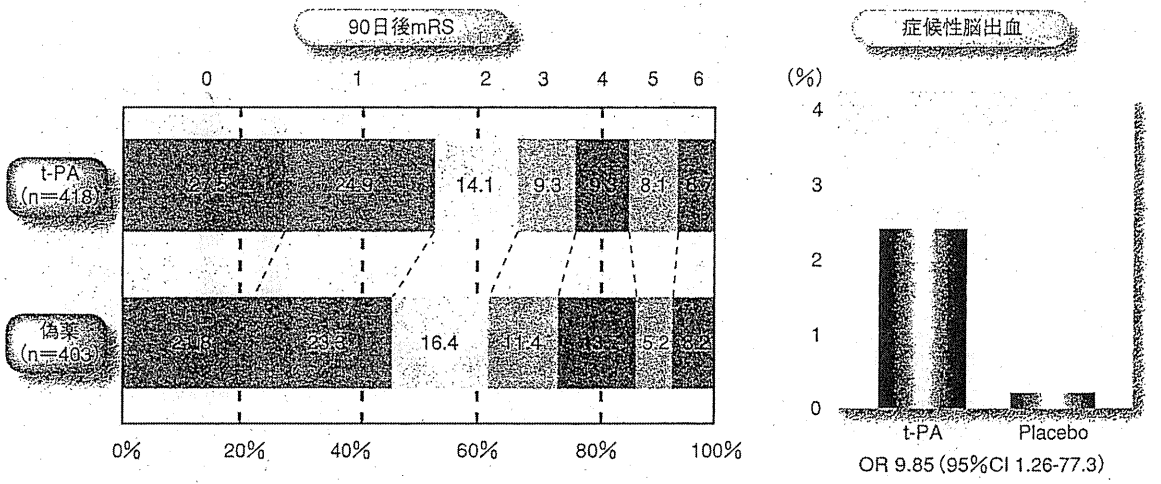

図2　ECASS 3の成績の概要(3～4.5hへの介入)(文献10より引用)

偽薬投与群に比べ、rt-PA投与群の発症90日後の転帰良好例(mRS 0～1)が有意に多かった。ただし、症候性頭蓋内出血もrt-PA投与群で有意に高率であった(OR 9.85)。

なされている。その多くは、いずれわが国でも検討課題となるであろう。

TIAに関するパラダイムシフト

1．診断基準の見直し

近年の画像診断の進歩、特にDWIの応用により、一過性脳虚血発作(transient ischemic attack；TIA)を含めた虚血性脳卒中の診断が大きく進歩した。2002年、米国TIA Working Groupは、従来のTIAの持続時間の定義(24時間以内)を改め、「神経症状がより短時間、典型的には1時間以内に消失し、かつ画像診断上脳梗塞巣が認められないもの」とする新しい定義を提案した[11]。2009年のAHA/ASA報告では、症状持続時間によるTIA診断基準を放棄し、「画像診断上脳梗塞巣が認められない」ことを基準とする立場を示した[12]。

2．TIAの臨床的意義

最近、TIAは従来考えられていた以上に短期日の間に完成型脳梗塞を発生するリスクが高いことが明らかにされている。すなわち、90日以内に15～30%、うち約半数は2日以内に発生するとされ、かなり高率である。TIAや軽症脳卒中に特化した専門クリニックや24時間体制でTIA患者を受け入れるシステムなどの新しい診療体制の構築により、脳卒中発症リスクが劇的に改善した(抑制率80%以上)と報告された[13]。

TIA後の脳梗塞発症の危険因子予測には、ABCDスコア(A＝age、B＝blood pressure、C＝clinical feature、D＝duration of symptoms)やABCD2スコア(ABCDスコア＋D＝diabetes mellitus)、さらにDWI所見を追加したものが有用とされている[14,15]。こうしたスコアの国内での検証も必要である。

3．国内の取り組み

国内では、1990年の循環器病研究委託費平井班による診断基準改定以後、基準の見直しなどは行われず、TIAに関するまとまった臨床研究も乏しい。こうした状況を受け、平成21年度厚生労働科学研究費補助金による「一過性脳虚血発作(TIA)の診断基準の再検討、ならびにわが国の医療環境に則した適切な診断・治療システムの確立に関する研究」班(主任研究者：

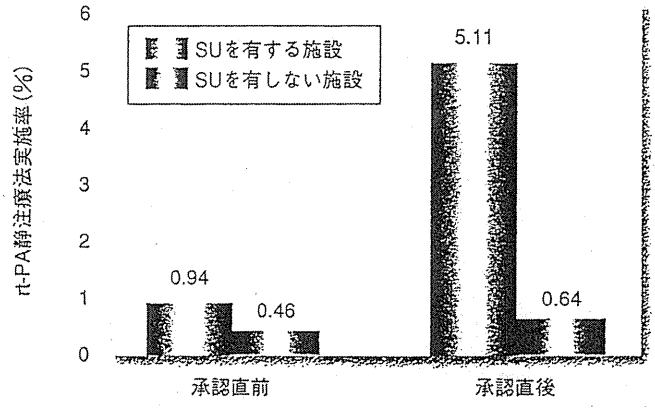

図3　わが国におけるrt-PA承認直前、直後のrt-PA静注療法実施率の変化：The Stroke Unit Multicenter Observational (SUMO) Study（文献16より引用）

SUを有する施設においてのみ、治療実施率が0.94％から5.11％に跳ね上がった。本研究は、脳卒中診療体制による急性期診療実態の全国多施設前向き登録調査として実施された。その調査期間中にrt-PA静注療法の国内承認が行われ、実施検査内容に有意の変化が起こったことが観察されている。

峰松一夫）が結成された。約3年の研究期間のなかで、国内実態調査や診断基準の見直し、診療システムの再構築に関する検討などがなされる予定である。

再発予防対策の新展開

再発予防に関しては、海外で普及していた抗血小板薬クロピドグレルや、頸動脈内膜剥離術との非劣性が確認された高リスク頸動脈高度狭窄症患者に対するステント留置術が国内承認されるなど、海外との格差は徐々に改善しつつある。高コレステロール血症治療薬アトルバスタチンや糖尿病治療薬ピオグリタゾンなどによる脳梗塞再発予防を示唆する海外データも報告された。一方で、非弁膜症性心房細動患者を対象とした経口直接トロンビン阻害薬ximelagatranなど、国際的に注目されながらも、期待通りの成果を上げられなかった大規模臨床試験も少なくない。これらの成績も、ある意味で重要なエビデンスとして、今後の診療の向上に役立つであろう。

わが国における脳梗塞対策の今後

1．国内診療体制の変革

rt-PA（アルテプラーゼ）静注療法の国内承認は、急性期脳梗塞診療に大きな変革をもたらしつつある。発症早期の専門医療機関への受診促進のための市民啓発、救急隊や一般診療医と専門医療機関との連携、SUや脳卒中センター整備など、脳卒中診療体制の再構築を目指した動きが始まっている。本療法は原則としてSUまたはそれに準ずるシステムを保有する施設で実施されるため、SU整備の差がそのまま本療法実施率の地域格差となっている（図3、図4）[16,17]。全国の二次医療圏のうち、rt-PA治療実施適合施設が1つもない医療圏が全体の2割程度を占め、本療法実施状況には極端な地域差が存在する。

すべての国民が等しく、適切にt-PA静注療法を受ける機会を与えられるためには、2時間以内に到達できる範囲に、24時間365日体制で治療実施可能なSUを有する専門病院（脳卒中センター）や病院ネットワークを整備する必要がある。それが困難な離島やへき地に対しても、telemedicine（遠隔医療）整備などが必要である。

2．ガイドライン、インディケータ、データバンク

医療の質を保障し、向上させる仕組みとして「診療ガイドライン」、「インディケータ」、「データバンク」の整備が重視されている。欧米では、特に脳卒中医療分野での取り組みが盛んである。国内に目を向けると、2004年に国内初の「脳卒中治療ガイドライン2004」が発表され[4]、2009年中にはその改訂

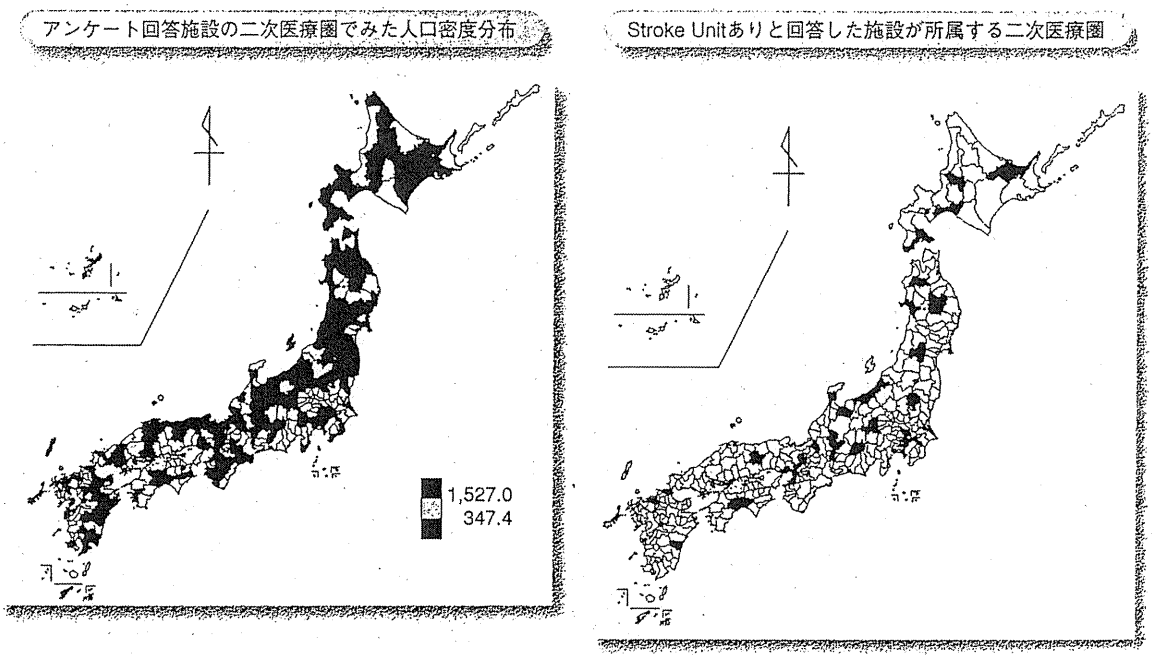

図4　人口密度別にみた全国二次医療圏の脳卒中診療実施医療施設とSUを有する専門的医療施設の分布の差異(文献17より引用)

急性期脳卒中診療の実態を調べるために全国アンケート調査を実施し、回答のあった医療機関の所在する2次医療圏を人口密度(単位:人/km²)によって3分位に分けた(左)。このうち、SUを保有していると回答のあった施設の所在する二次医療圏を右に示した。SUを有する専門的医療施設は比較的少なく、特に低人口密度地域で少ないことが目立つ。

版が発刊される予定である。社団法人日本脳卒中協会にはデータバンク部門が設置され、主要専門医療機関の急性期脳卒中入院患者登録データが蓄積されている。しかしながら、本登録研究への参加は任意であり、悉皆性のある発症登録調査とはなっていない。データ管理やモニタリングなども十分ではなく、回復期以降のデータ収集や長期追跡の仕組みも未完成である。

ガイドラインなどに記載された「エビデンスに基づいた脳卒中診療」の普及のためには、適切な臨床指標(indicator)を用いた監査、公表システムを各医療機関や各医療圏ごとに構築する必要がある。わが国では、改正医療法に基づいた基本的医療機能の公表が始まったばかりで、欧米に比べ著しく遅れている。わが国でも独自のシステム構築を目指すべきと思われる。

3. 脳卒中対策基本法(仮称)の必要性

病院前救護や回復期リハビリテーション、慢性期の介護システム、再発予防のための医療システムなど、効果的な脳卒中地域連携医療の確立も必要である。実際の脳卒中医療・介護システムやその連携状況には、想像を絶する地域間、地域内格差が存在する。問題解決には、国を挙げた取り組みが必要である。

社団法人日本脳卒中協会は、2008年に脳卒中対策検討特別委員会(委員長:峰松一夫)を設置し、総合的かつ計画的な脳卒中対策の検討を開始した。その結果、脳卒中対策立法化の必要性が指摘された。「脳卒中対策基本法要綱案」が検討され、2009年6月にその内容が公表されたところである。そこでは、①予防と発症後の適切な対応について、国民への啓発、教育を行うこと、②全国どこでも、専門的脳卒

中医療を速やかに受けることを可能にすること、③救急搬送、急性期から維持期まで切れ目のない専門的医療が継続されること、④患者と介護を担う家族の生活の質を維持、向上させること、などが基本理念として謳われ、その実現のための方策が提案されている。今後、法制化の実現を目指す取り組みが本格化するであろう。

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ガイドライン 解説

ASA/AHAによる「脳卒中および一過性脳虚血発作患者に対する脳卒中予防に関する推奨事項」改訂版

全2回シリーズ

第1回　非心原性脳梗塞またはTIAの既往のある患者における，脳卒中の予防を目的とした抗血小板薬の使用

原著
Adams RJ, et al. Update to the AHA/ASA Recommendation for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack. *Stroke* 2008; 39: 1647-52.

解説
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最近，非心原性脳梗塞または一過性脳虚血発作(transient ischemic attack, TIA)の既往例における，脳卒中の予防を目的とした抗血小板薬の使用に関して，新たな大規模臨床試験の結果報告が相次いだ．これに伴って，American Heart Association/American Stroke Association (AHA/ASA) Writing Committeeより2006年に発表されたガイドライン[1]が2008年に改定された．本稿では，このAHA/ASAガイドライン改定版の概要につき解説する(表1，2)．

血管イベント発症予防における アスピリンとクロピドグレルの併用について

TIAを含む明らかな心血管疾患もしくは複数の危険因子を有するハイリスク患者15,600例あまりを対象として，低用量アスピリン(75-162mg/日)単独投与群もしくは低用量アスピリンとクロピドグレル75mgとの併用群の二重盲検ランダム化比較試験，Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial[2]が施行された．本試験では，全体の35%が過去5年以内の脳卒中既往例であり，TIAはその1/3の10%，追跡期間の中央値は28ヵ月であった．一次エンドポイントは，致死的・非致死的心血管疾患発症であった．一次エンドポイント発症率は，併用群で6.8%，単独群で7.3%であり，両群間で有意差がなかった．脳出血発症率，致死的もしくは重篤な出血合併症発症率はいずれも両群間で有意差はなかったが，中等度の出血合併症は併用群で多く発生した．併用群では単独群に比べて，二次エンドポイントである入院を要する不安定狭心症，TIA，血行再建術の発生が有意に低かった(12.3% versus 11.1%, p=0.02)．心血管疾患の症候を有する例を対象としたサブ解析では，併用群が単独群に比較して一次エンドポイント発症率がわずかに低かった(7.9 versus 6.9%, p=0.046)．無症候例を対象としたサブ解析では，併用群では単独群に比べて全死亡率(3.8 versus 5.4%, p=0.04)，心血管死亡率(2.2 versus 3.9%, p=0.01)のいずれも高かった．症候例では併用群で心血管死亡が多いという結果が得られなかった．出血性合併症に関しては，症候例が無症候例に比べて，中等度の出血合併症の発生率が高かった(2.1 versus 1.3%, p<0.001)．

3ヵ月以内のTIAまたは脳梗塞例で，他の危険因子を合併したハイリスク例を対象とした，クロピドグレル75mg単独療法とクロピドグレル75mg・アスピリン75mg併用療法との二重盲検ランダム化比較試験Management of Atherothrombosis with Clopidogrel in High-Risk Patients with TIA or Stroke (MATCH) trial[3]では，一次エンドポイント(致死性・非致死性心血管疾患発症，急性虚血性血管イベントによる入院)発生率に両群間で有意差はなく，脳梗塞再発率にも差がなかった．本試験では，クロピドグレルとアスピリンの併

表1　抗血小板療法に関する推奨事項(改訂版)

Class I 推奨事項
1. 非心原性脳梗塞やTIAの患者に対する，脳卒中再発や他の心血管疾患発症防止には，経口抗凝固薬よりもむしろ抗血小板薬が推奨される(Class I, Level A)
2. アスピリン(50-325mg/日)単独療法，アスピリン・徐放性ジピリダモール併用療法，クロピドグレル単独療法はいずれも非心原性脳梗塞およびTIA患者に対する初期治療として妥当な選択肢である．(Class I, Level A)
3. アスピリン・徐放性ジピリダモール併用療法は，アスピリン単独療法よりも推奨される．(Class I, Level B)

Class II 推奨事項
1. 直接比較試験によると，クロピドグレルはアスピリン単独よりも優れている可能性がある．(Class IIb, Level B)
2. アスピリンアレルギーの患者には，クロピドグレルが適切である．(Class IIa, Level B)

Class III 推奨事項
アスピリンとクロピドグレルの併用療法は出血のリスクを増加させる．アスピリン・クロピドグレル併用療法は，本治療の特別な適応(冠動脈ステントや急性冠症候群)を有していない限り，虚血性脳卒中，TIA患者にルーチンには推奨できない．

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表2　ClassとLevelの定義

Class I:　方針や治療の有効性に対して証拠があり，広く受け入れられている．
Class II:　方針や治療の有効性に対して相反する証拠や異なる選択肢がある．
　Class IIa　方針や治療を行ったほうがよいとする証拠がある．
　Class IIb　方針や治療に対する証拠が十分に確立されていない．
Class III:　方針や治療の有効性に関する証拠や一般的な受け入れがない，もしくは，その方針や治療を行うことが適当でない場合がある．

Level A: 複数のランダム化試験のデータに基づいている．
Level B: 1つのランダム化試験もしくは複数の非ランダム化試験のデータに基づいている．
Level C: 専門家の意見もしくは症例研究に基づいている．

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用群では単独群に比べて，生命に関わる重篤な出血性合併症発症のリスクが2倍あった．

以上より，脳梗塞再発防止に対するアスピリンとクロピドグレルとの併用の有効性は示されていない．投与期間限定のアスピリン・クロピドグレル併用療法の適応として，発症後間もない冠動脈疾患例やステント留置例がある．これに関しては，米国心臓学会による最新のガイドラインを参照すること．

アスピリン単独とアスピリン・ジピリダモール併用について

発症6ヵ月以内のTIAもしくは軽症虚血性脳卒中を対象としたアスピリン単独(30-325mg，中央値75mg)とアスピリン・ジピリダモール(400mg，83%が徐放性製剤使用)併用とのランダム化オープンラベル試験the European/Australasian Stroke Prevention in Reversible Ischaemia Trial: ESPRITが施行された．本試験は，血管原性と考えられる虚血性脳卒中例に対する再発防止に，アスピリン単独もしくはアスピリン・ジピリダモール併用のいずれが有効かを明らかにする研究である．塞栓性心疾患，侵襲的治療を要する頸動脈高度狭窄性病変例は除外されている．平均観察期間は3.5年間で，一次エンドポイントは，血管イベントによる死亡，非致死性脳卒中・心筋梗塞，重症出血性合併症の発生である．On-protocol解析では，一次エンドポイント発生率に両群で有意差はなかったが，intention-to-treat解析にて，併用群が単独群に比べて，一次エンドポイント発生率が有意に低かった(ハザード比0.80, 95%CI 0.66-0.98)[4]．各群の生存曲線は，2年目以降に乖離しはじめ，併用療法による絶対リスク低下は年間1%であった．但し，併用群では頭痛を生じやすく，単独群に比べて脱落例が多かった(13% versus 34%)．ジピリダモール服用による心筋梗塞発生リスクの低減効果は見られなかった．

註) 本ガイドライン改定版発表と相前後して，日本を含む35ヵ国，2万例を超える虚血性脳卒中患者を対象として，アスピリン・ジピリダモール併用群とクロピドグレル服用群に分け，さらに降圧薬テルミサルタン服用の有無を掛け合わせて脳卒中再発抑制効果を検討したPrevention Regimen for Effectively Avoiding Second Strokes Trial (PRoFESS)[5]の結果が発表された．それによると，脳卒中再発防止に対して，クロピドグレル服用群に対するアスピリン・ジピリダモール併用群の非劣性は証明されず，テルミサルタン服用の有無で

も脳卒中を含めた血管事故に差がなかったという．本結果は，本ガイドライン改定版には反映されていない．

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Hyoid Bone Compression–Induced Repetitive Occlusion and Recanalization of the Internal Carotid Artery in a Patient With Ipsilateral Brain and Retinal Ischemia

A 61-YEAR-OLD MAN presented with aphasia and right hemiparesis. Severe stenosis of the left internal carotid artery (ICA) was found 2 years previously when he presented with left retinal arterial branch occlusion. Brain magnetic resonance angiography, carotid ultrasonography (US), and cerebral angiography confirmed that the stenosis had progressed to asymptomatic occlusion 1 year before admission (**Figure 1**A). Brain computed tomography revealed an ischemic lesion in the left basal ganglia (**Figure 2**A). However, the left ICA images were confusing; brain magnetic resonance angiography on day 7 indicated left ICA recanalization, whereas carotid US immediately after magnetic resonance angiography showed ICA occlusion with an intraluminal thrombuslike entity (Figure 2B). Cerebral angiography showed recanalization with severe segmental stenosis on day 13 (Figure 1B); the occlusion revealed by magnetic resonance angiography on day 18 was recanalized according to carotid US 1 hour later. Carotid US on day 20 initially detected left ICA flow in the supine position that gradually diminished with an intraluminal thrombuslike entity appearing over a period of 20 minutes. Flow was suddenly visualized again after the patient sat up (video; http://www.archneurol.com). The left greater horn of the hyoid bone seemed to compress the narrowest segment of the ICA from behind (video), confirmed by helical computed tomography (Figure 1C). Because secondary atherosclerosis at the site of compression, suspected before surgery, was not observed, the operative procedure was changed from carotid endarterectomy to adhesiotomy from the circumferential tissues and patch formation of the left ICA. The hyoid bone removal was given up because of the technical difficulty. A pathological examination of the arterial wall tissue showed only fibrotic change. The left ICA remained patent after surgery. Antiplatelet therapy, started before surgery, was continued. The patient recovered without sequelae and was discharged on day 41.

Video available online at www.archneurol.com

COMMENT

This is the first article describing frequent occlusion and recanalization of a nonatherothrombotic ICA caused by the hyoid bone, confirmed by neuroimaging. To our knowledge, 2 articles[1,2] have described stroke and/or transient ischemic attack in the presence of ICA compression by the hyoid bone, but neither identified a direct relationship between the ICA compression and ischemia. Carotid US and helical computed tomography were useful for diagnosis in our patient. Hyoid bone compression should be recognized as a rare cause of ICA stenosis.

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Online-Only Material: The video is available at http://www.archneurol.com.

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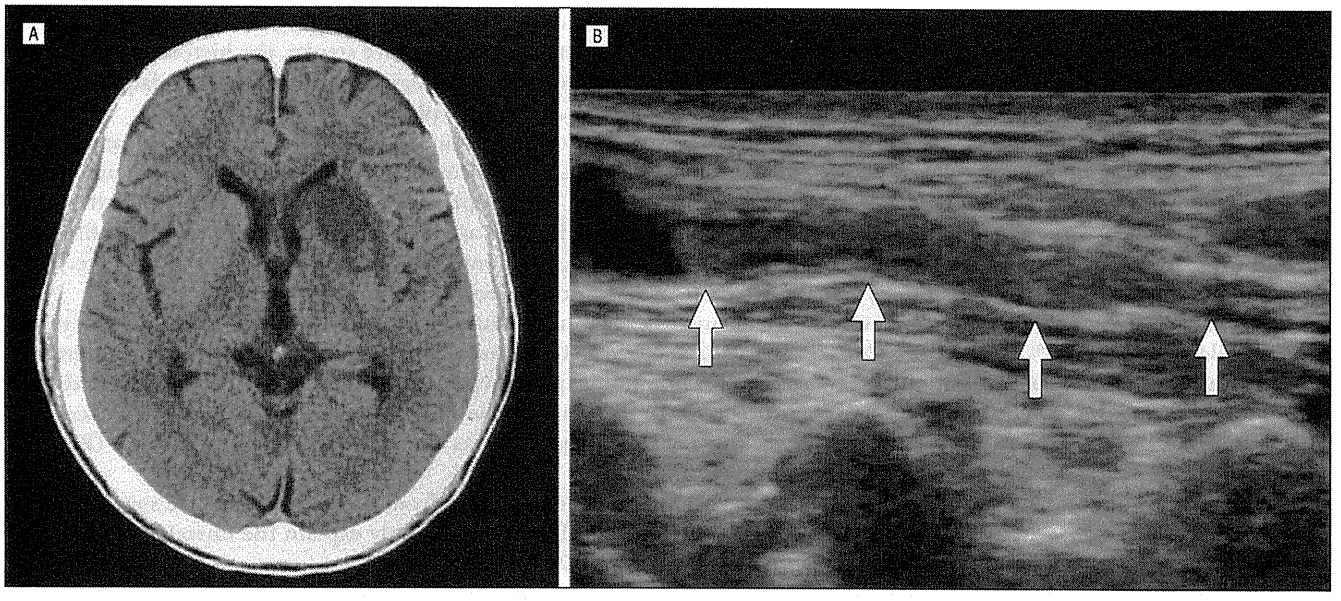

Figure 1. Imaging findings on admission. A, Brain computed tomography shows an ischemic lesion in the left basal ganglia. B, Carotid ultrasound shows a thrombuslike entity in left internal carotid artery.

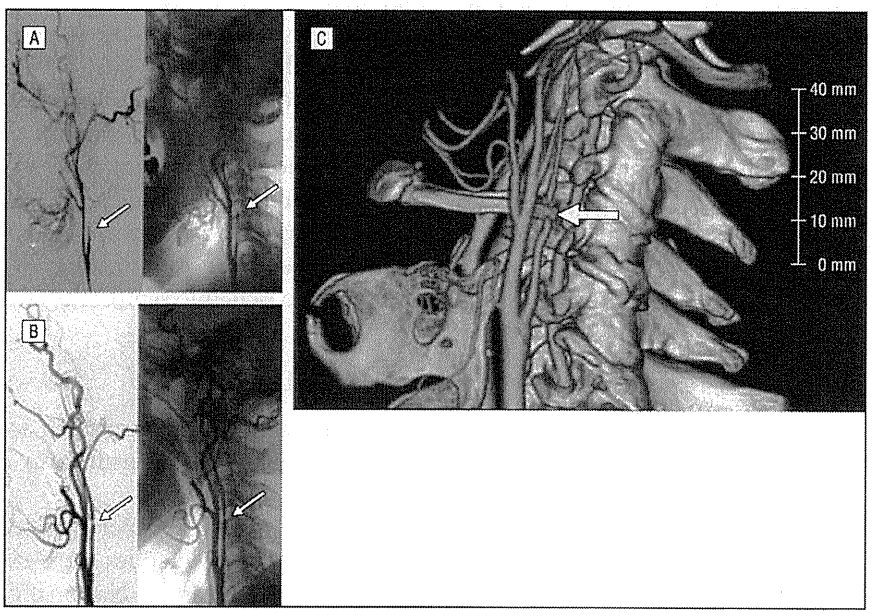

Figure 2. Imaging findings of the left internal carotid artery and hyoid bone. Cerebral angiography showed occlusion of the internal carotid artery 1 year before admission (A), recanalized, with severe segmental stenosis on day 13 (B). C, Helical computed tomography shows the greater horn of hyoid bone compressing the narrowest segment of the left internal carotid artery from behind.

Histologic characterization of mobile and nonmobile carotid plaques detected with ultrasound imaging

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Objectives: Although mobile plaques in the carotid arteries detected by duplex ultrasound imaging are considered to cause unstable neurologic symptoms such as crescendo transient ischemic attack or progressive stroke, the histology of mobile plaques has not been sufficiently documented. This study examined the histopathologic features of mobile plaques of the carotid artery and compared the histopathology between mobile and nonmobile plaques.

Methods: Of 228 carotid plaques assessed by preoperative carotid ultrasound imaging, 21 (9.3%) were diagnosed as mobile symptomatic plaques. Of these, 18 were intact after excision by endarterectomy and enrolled for histologic examination. From the remaining 207 nonmobile plaque specimens, 17 nonmobile but symptomatic plaque specimens were extracted for histologic comparison. An investigator blinded to the ultrasound findings assessed both plaque specimens for fibrous cap thickness, fibrous cap rupture, fibrous cap area, necrotic core size, inflammatory cells, intraplaque hemorrhage, and mural thrombus. Clinical data, including progressive ischemic symptoms after admission, were also examined.

Results: Progressive ischemic symptoms were more frequently seen in patients with mobile plaques than in those with nonmobile plaques (33.3% vs 0%, $P = .02$). The ratio of the cross-sectional area of the necrotic core to that of the entire plaque was significantly larger for mobile plaques than for nonmobile plaques (mean, 0.660 vs 0.417, $P < .0001$). Mural thrombus was more prevalent among mobile plaques (89%) than among nonmobile plaques (59%), but the difference was not significant ($P = .06$). The median minimum thickness of the fibrous cap was extremely small in both groups (80 μm in mobile plaques and 100 μm in nonmobile plaques, $P = .33$).

Conclusions: The histologic characteristics of mobile carotid plaques are different from those of nonmobile symptomatic plaques, especially in the area of the necrotic core. This histologic difference may partly explain the unstable neurologic presentations of patients with mobile carotid plaques. (J Vasc Surg 2011;53:977-83.)

Mobile components in symptomatic carotid plaques, as detected with a duplex ultrasound scan using the recently developed high-resolution real-time B-mode system, are assumed to cause unstable neurologic symptoms such as crescendo transient ischemic attack or progressive stroke. These types of plaque with mobility have been denoted variously in several case reports as "mobile plaques,"[1] "floating plaques,"[2-4] "mobile thrombi,"[5] or "floating thrombi."[6,7] Some authors have emphasized the high potential of the mobile plaque to cause recurrence of ischemic attacks within a short period.[5,8,9] They have also speculated that plaque disruption and mural thrombus resulted in mobile plaques.[5,6]

Previous reports have not, however, sufficiently documented the mechanism of that mobility or the histologic feature of such plaques. We hypothesized that certain histologic differences may exist between mobile and nonmobile symptomatic carotid plaques as long as clinical symptoms caused by mobile plaques are more unstable than those by nonmobile plaques. To confirm this hypothesis, we compared the prevalence of several histologic factors between mobile and nonmobile plaques in symptomatic patients, with the examination of clinical data including progressive ischemic symptoms after admission.

METHODS

This study was performed in accordance with the ethical guidelines of our institution and included patients' informed consent.

Plaque selection. Between April 2003 and March 2008, 228 carotid plaques were excised by carotid endarterectomy (CEA) at the National Cerebral and Cardiovascular Center, Osaka, Japan. All patients had been assessed with preoperative carotid ultrasound imaging, and 21 symptomatic patients (9.3%) had been diagnosed with mobile plaques. The study excluded 3 of 21 mobile plaque specimens after the histologic examination because they

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were damaged during plaque excision. From the remaining 207 nonmobile plaques, 20 symptomatic plaques were randomly extracted for histologic comparison. After the histologic examination, the study excluded 3 of the 20 nonmobile plaque specimens because they were too damaged. The remaining 35 plaque specimens, comprising 18 mobile plaques and 17 nonmobile plaques, were used in this study.

Clinical data. We reviewed clinical data of the 35 patients with excised plaques. Their symptoms at admission were classified into four categories: amaurosis fugax, transient ischemic attack (TIA), transient symptom associated with infarction (TSI), and stroke. Amaurosis fugax was defined as a transient ipsilateral blindness or visual field defect. TIA was defined as a transient neurologic symptom that lasts <24 hours without any evidence of brain infarction confirmed by diffusion-weighted images (DWI) in magnetic resonance imaging. TSI was defined as a transient neurologic symptom that lasts <24 hours with evidence of brain infarction, which is supposed to have higher in-hospital recurrent ischemic rate than TIA.[10] Stroke was confirmed by positive findings in the territory of the ipsilateral carotid artery on DWI. Progressive symptoms were also recorded when the patient experienced a recurrence and worsening of neurologic symptoms after admission, with an increase of ischemic lesions confirmed by DWI.

The degree of carotid stenosis was measured by digital subtraction angiography according to the method used in the North American Carotid Surgery Trial.[11] The other clinical data recorded were age, sex, treatment for hypertension, treatment for diabetes, treatment for hyperlipidemia, smoking within the preceding year, statin administration, and aspirin administration. Median intervals from the last ischemic event to CEA and then from the last ultrasound imaging to CEA were also examined.

Ultrasound imaging. All patients underwent preoperative carotid ultrasound scanning ≤1 month before CEAs using a commercially available, real-time 2-dimensional device equipped with a 7.5-MHz transducer. B-mode scans, B-mode scans with color Doppler imaging, and pulsed-Doppler scans were routinely performed. If a stroke physician suspected the presence of mobile plaques on duplex ultrasound imaging, the images would be recorded as video files. Two skilled stroke physicians, who had no previous knowledge of the patient's clinical information, including a coauthor (K.N.), reviewed video files and made a final diagnosis of mobile plaques. The findings of the mobile plaques were defined and classified as follows:

1. Mobile components that are localized at the surface of the plaque and that rise and fall in a manner inconsistent with or exceeding arterial pulsatile wall motion (jellyfish sign[12]),
2. Mobile components inside the plaque that change slowly and irregularly like viscous liquid (liquefaction sign),
3. Movements localized within an ulcer's inner surface (Fig 1; Video 1, online only), and

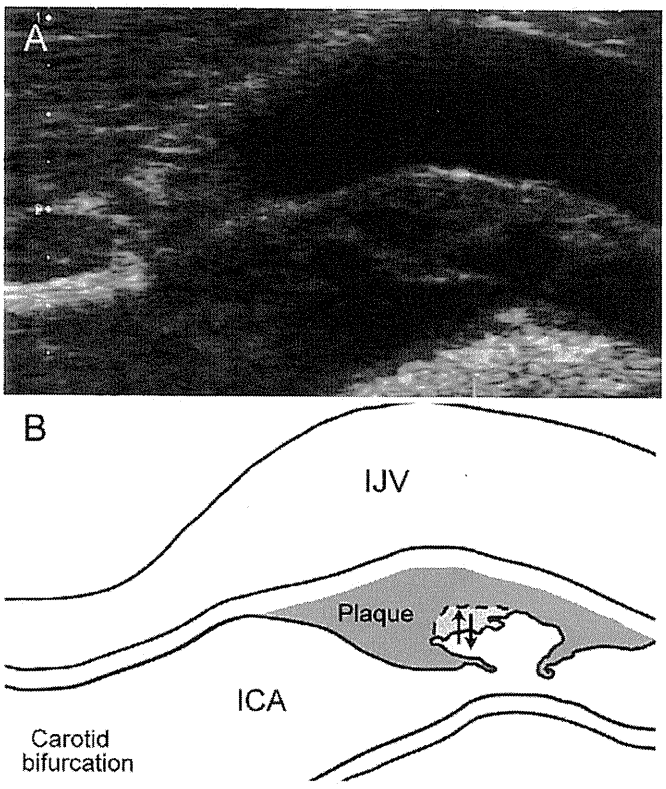

Fig 1. A, A longitudinal duplex ultrasound image of a mobile plaque demonstrates an ulcerated plaque in the extracranial internal carotid artery. **B,** A schema representing the mobile component in the plaque: an ulcer's inner surface rose and fell according to the pulsation, as indicated with *arrows,* which was defined as "movements localized within an ulcer's inner surface" (see also Video 1, online only). *ICA,* Internal carotid artery; *IJV,* internal jugular vein.

4. Movements of protuberances (Fig 2; Video 2, online only).

Plaque excision. General anesthesia was initiated, and CEA was performed using an operating microscope and somatosensory evoked potential monitoring to selectively place the shunt. For some cases with a mobile plaque, each surrounding artery (including the common, external, and internal carotid arteries) was clamped as soon as it was exposed to minimize the risk of distal embolism caused by the manipulation of the internal carotid artery. Upon cross-clamping, the common carotid artery was incised with scalpels to determine the dissection plane, usually made at the level of the internal elastic membrane, under the operating microscope. A microdissector was inserted meticulously, not to disturb the cleavage plane, until the distal end of the plaque and the patent lumen of the distal internal carotid artery were ascertained. The distal and proximal edges of the plaque were cut and finally pulled out from the orifice of the external carotid artery. In this way, most of the carotid plaque could be removed en bloc with minimum surgical trauma. If a cut penetrated the surface of the specimen to the lumen, it could be judged in the histologic examination that the cleavage resulted from surgical trauma, not plaque rupture.

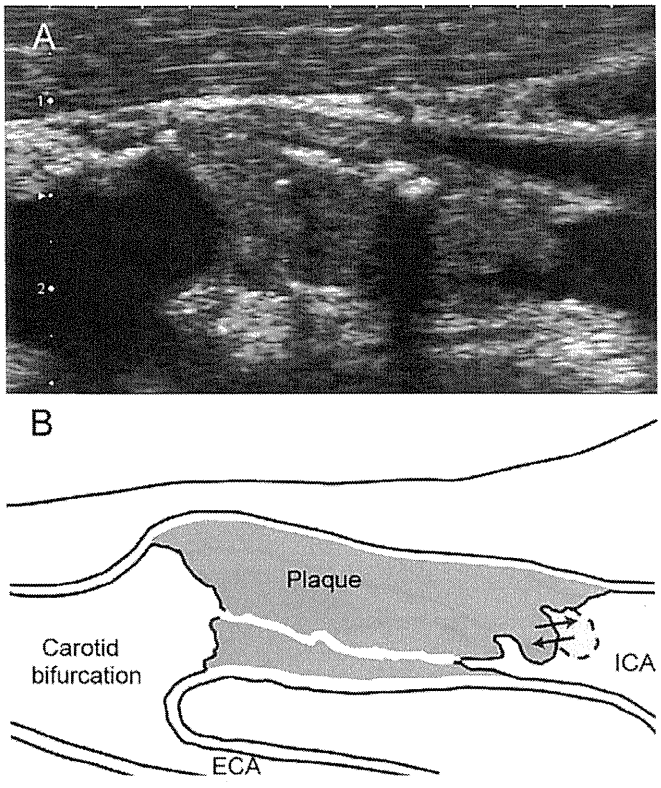

Fig 2. A, A longitudinal duplex ultrasound image demonstrates a massive mobile plaque almost occluding the internal carotid artery (*ICA*) and a protuberance from the distal end of the plaque. **B**, A schema representing the shaking movement of the protuberance (*arrows*): the original video also revealed a mobile component inside the plaque that changed slowly and irregularly like viscous liquid (liquefaction sign, see also Video 2, online only). *ECA*, External carotid artery.

Histopathology. The excised plaques were immediately fixed in Histochoice fixative (Amresco, Cleveland, Ohio) for 48 hours and decalcified by ethylenediaminetetraacetic acid (EDTA). To preserve the immunoreactivity, we used Histochoice for fixation and EDTA for decalcification of specimens before embedding in paraffin blocks.[13] Each plaque was sectioned transversely at the carotid bifurcation, and further sections were taken at 5-mm intervals along the length of internal carotid arteries for embedding in paraffin.[14] Adjacent 5-μm transverse sections were stained with hematoxylin and eosin, elastin van Gieson, Masson trichrome, and von Kossa. When a certain section seemed near the plaque rupture site, additional subserial slices were performed to avoid skipping focal instability. For immunohistochemistry analyses, we performed immunostaining for T cell (CD3, DAKO, Glostrup, Denmark), macrophages (CD68, DAKO). Immunostaining with glycophorin A (CD235a, DAKO) was also performed to detect intraplaque hemorrhage.[15] An experienced cardiovascular pathologist (H.I.) histologically examined all sections without any knowledge of clinical details and findings of carotid ultrasound imaging.

The histologic features of plaques assessed in this study were minimum cap thickness, prevalence of the rupture of fibrous cap and ulceration, necrotic core size, quantity of inflammatory cells (including macrophages and lymphocytes), degree of intraplaque hemorrhage, and prevalence of mural thrombus. Minimum cap thickness was defined as the thinnest part of the fibrous cap in total cross-sections of each plaque measured by a manometer attached to the microscope.[16] Plaque rupture, a break in the fibrous cap, was recorded when there was clear interaction between the lipid core and the lumen, usually at a point of thinning and inflammation and when the break in the cap did not seem to have been created during surgery (Fig 3, *A*). A necrotic core was defined as an amorphous material containing cholesterol crystals (Fig 3, *B*).[17]

To measure the area of necrotic core, we sampled three cross-sections: on the carotid bifurcation, 5 mm distal to the bifurcation, and 10 mm distal to the bifurcation. On each cross-section, the necrotic core and the entire plaque area were measured by WinROOF 5.0 morphometry software (Mitani Co, Kanazawa, Japan), and the ratio of the mean cross-sectional area of the necrotic core to that of the entire plaque area was calculated. We also measured the actual area of the fibrous cap for mobile and nonmobile plaques on the three cross-sections, and the median value of the fibrous cap area in each plaque was calculated.

A "recent" intraplaque hemorrhage was recorded when an area of erythrocytes within the plaque caused disruption of plaque architecture, whereas an "old" intraplaque hemorrhage was recorded when evidence showed organized hemorrhage with the accumulation of hemosiderin-laden macrophages or iron deposits on plaque connective tissue.[18] Old intraplaque hemorrhage was also recorded when the ratio of the glycophorin A-positive area to the whole plaque area was >40%. Plaque inflammation with macrophage and lymphocyte infiltration was recorded according to the number of CD68-negative or CD3-positive cells: infiltration of >20 inflammatory cells in the fibrous cap was defined as positive inflammation to the fibrous cap. Mural thrombus was defined as a fibrin organization of the endothelium or the fibrous cap of plaques (Fig 3, *C*).

Statistical analysis. Patients with mobile plaques and those with nonmobile plaques were compared for baseline characteristics, the prevalence of progressive symptoms, and plaque histologic features using a *t* test, the Wilcoxon rank sum test, or the Fisher exact test, as appropriate. Two-sided values of $P < .05$ were considered significant. Statistical analysis was performed with JMP 7.12 software (SAS Institute, Cary, NC).

RESULTS

Patients displaying mobile plaques and nonmobile plaques exhibited no significant difference in age, sex, diabetes mellitus, hyperlipidemia, smoking, coronary artery disease, administration of statins, administration of aspirin, or degree of stenosis (Table I). All statins were administrated with the usual doses (atorvastatin ≤20 mg, pravastatin ≤20 mg, or pitavastatin ≤2 mg), and no patients received high-dose statin therapy. Hypertension was observed more frequently in patients with nonmobile plaques.

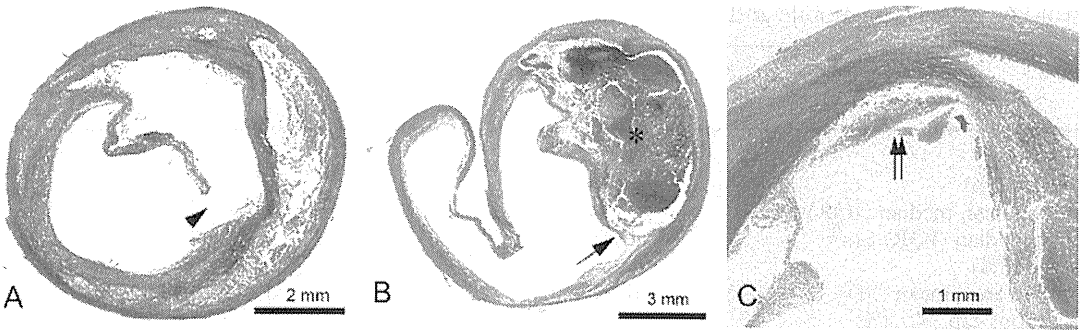

Fig 3. An example of histologic features of a mobile plaque (the same plaque as shown in Fig 1). **A**, A photomicrograph of the carotid bifurcation (Masson's trichrome staining, original magnification ×1) demonstrates complete disruption of the fibrous cap (*arrowhead*). **B**, Another cross-section (Masson's trichrome staining, original magnification ×1) demonstrates a large necrotic core with a fresh intraplaque hemorrhage (*asterisk*), which was covered with thin fibrous cap (*arrow*). **C**, A photomicrograph (Masson's trichrome staining, original magnification ×2) shows intramural fibrin deposit, indicating mural thrombus (*double arrow*).

Table I. Clinical characteristics at the time of carotid endarterectomy of study patients

Characteristics	*Mobile plaques (n = 18)*	*Nonmobile plaques (n = 17)*	P
Age, mean (SD), year	70.8 (11.5)	66.2 (8.7)	.19
Female, No. (%)	3 (16.7)	1 (5.9)	.60
Stenosis, mean (SD), %	73.2 (24.4)	76.5 (15.2)	.63
Risk factors, No. (%)			
Hypertension	11 (61.1)	17 (100)	.01
Diabetes mellitus	4 (22.2)	7 (41.2)	.29
Hyperlipidemia	11 (61.1)	12 (70.6)	.72
Smoking	9 (50.0)	13 (76.5)	.16
Medications, No. (%)			
Statin	7 (38.9)	7 (41.2)	1.00
Aspirin	10 (55.6)	13 (76.5)	.29
Interval to CEA, median (IQR) days			
From last ischemic event	12.5 (7.5-26.75)	33 (13.5-70.5)	.01
From last ultrasound study	3 (1-8.25)	9 (3.5-21.5)	.03
MRI-DWI positive, No. (%)	14 (77.8)	14 (82.4)	1.00

DWI, Diffusion-weighted image; *IQR*, interquartile range; *MRI*, magnetic resonance imaging; *SD*, standard deviation.

The median interval from the last ischemic event to CEA was 12.5 days (maximum, 41 days) in patients with mobile plaques, and the interval between the onset of symptoms and CEA, as well as that between ultrasound imaging and CEA, was significantly longer in patients with nonmobile plaques. No patients in this study had atrial fibrillation or other embolic sources. The incidence of the acute cerebral infarction detected with preoperative DWI did not show significant difference between mobile and nonmobile plaques (77.8% vs 82.4%, $P > .99$).

Clinical symptoms. The first ischemic symptoms among the 18 patients with mobile plaques were cerebral infarct in 11 patients, TSI in 5, TIA in 1, and amaurosis fugax without positive DWI finding in 1. Symptoms among 17 patients with nonmobile plaques included cerebral infarct in 6, TSI in 6, TIA in 3, and amaurosis fugax without positive DWI finding in 2. Progressive symptoms after admission were observed in six patients (33.3%) with mobile plaques, whereas no progression was seen in the patients with nonmobile plaques ($P = .02$).

Histologic features. All histologic features in mobile plaques and nonmobile plaques are summarized in Table II. The ratio of the mean cross-sectional area of the necrotic core to that of the entire plaque area was significantly larger in mobile plaques than in nonmobile plaques (mean, 0.660 vs 0.417, $P < .0001$).

Plaque ruptures were seen in 83% of mobile plaques. The median minimum cap thickness was 80 μm, which is smaller than that considered to be the critical value of minimum cap thickness for cap rupture.[16] There were no significant differences in the prevalence of cap rupture (83% vs 82%) or median minimum cap thickness (80 vs 100 μm) between mobile plaques and nonmobile plaques. The median area of the fibrous cap was, however, significantly smaller in the mobile plaques than in nonmobile plaques (9200 vs 15,900 μm^2; $P = .02$).

Although mural thrombus was more prevalent in mobile plaques (89%) than in nonmobile plaques (59%), the difference was not significant ($P = .060$). There was also no significant difference between mobile and nonmobile

Table II. Histologic features of mobile and nonmobile plaques

Feature	*Mobile plaques (n = 18)*	*Nonmobile plaques (n = 17)*	P
Fibrous cap			
Plaque rupture, No. (%)	15 (83)	14 (82)	>.99
Minimum cap thickness, median (IQR) μm	80 (60-162.5)	100 (60-250)	.33
Fibrous cap area, median (IQR) μm^2	9200 (6300-13,100)	15,900 (9000-21,800)	.02
Mural thrombus, No. (%)	16 (89)	9 (59)	.06
Ratio of necrotic core area, mean (SD)	0.660 (0.098)	0.417 (0.176)	<.0001
Inflammation of fibrous cap, No. (%)			
Macrophages	17 (94)	16 (94)	1.00
Lymphocytes	12 (67)	12 (71)	1.00
Intraplaque hemorrhage, No. (%)			
Fresh	11 (61)	9 (53)	.74
Previous	11 (61)	10 (59)	1.00

IQR, Interquartile range; *SD,* standard deviation.

plaques in the prevalence of cap inflammation or intraplaque hemorrhage.

DISCUSSION

One of our results showed that progressive symptoms occurred more frequently in patients with mobile plaques than those with nonmobile plaques. This result is in line with unstable neurologic presentations depicted in previous case reports of symptomatic mobile plaques.[5,8] A recent study also concluded that the jellyfish sign, which is an ultrasonographic appearance of mobile plaques, was an important predictive factor for repeated ischemic stroke.[12] These findings, along with our results, promoted us to confirm the hypothesis that some histologic differences may exist between mobile and nonmobile plaques, even if both are symptomatic plaques.

There are several reports about mobile plaques in large arteries, including the carotid artery,[2-8,19,20] and some reports have described the histology of mobile plaques. Nakajima et al[5] reported the pathologic findings of a mobile plaque in the brachiocephalic artery that caused fatal recurrent strokes and pointed out that plaque disruption was a cause of the mobility. Arning et al[6] also found a mural thrombus in the histology of a mobile carotid plaque. Our results are compatible with previous pathologic reports about mobile plaques. However, the features of plaque rupture and mural thrombus may not be sufficient to describe the specific histopathology of a mobile plaque, because according to our result, the prevalence of plaque disruption or mural thrombus of mobile plaques is not significantly higher than that of nonmobile plaques. The findings of the present study suggest that the existence of a large, soft, lipid-rich necrotic core is also important for the mechanism of plaque mobility.

This speculation conforms with the results on intravascular ultrasound elastography, a recently developed technique to assess the elasticity of plaque tissue using intravascular ultrasound imaging by measuring the "strain" or small movement of plaque tissue under an applied force.[21,22] The authors of those studies demonstrated that the strain could distinguish lipid-rich components from hard and fibrous components. Mobile structures on carotid plaques may be caused not only by the mural thrombus formed by a fibrous cap rupture but also by a large, lipid-rich necrotic core exposed into the blood lumen.

Several pathologic reviews have reinforced the evidence that a large necrotic core is one of the important features of so-called vulnerable plaque.[23-27] Studies on aortic plaques,[28,29] an in vivo study on magnetic resonance imaging,[30] and histologic studies of carotid plaque[16,31] have also shown that a large necrotic core was strongly associated with thrombosis, fibrous cap rupture, fibrous cap thinning, or neurologic symptoms. Moreover, when the large lipid-rich necrotic core is exposed to blood lumen by plaque rupture, the mural thrombus or debris from the lipid core may become a persistent source of embolism, which may result in an unstable ischemic stroke. On the other hand, Redgrave et al[16] showed that thinning of the fibrous cap covering the necrotic core is another important factor for plaque vulnerability. These authors advocated critical cap thickness (minimum cap thickness <200 μm and a representative cap thickness <500 μm) as a marker for ruptured plaque.

Using these criteria, the fibrous cap of both groups in our study is extremely thin. One possible reason that we did not find a significant difference in minimum fibrous cap thickness in the two plaques is that mobile and nonmobile plaques had an almost equally high prevalence of cap rupture. Given that the actual fibrous cap area was smaller in mobile plaques than in nonmobile plaques (Table II), it is possible that the overall thickness of fibrous caps in mobile plaques is smaller than that in nonmobile plaques.

To our knowledge, only one recent study demonstrated the histologic features of mobile carotid plaques, although it did not include a controlled group in histologic assessment. Kume et al[12] examined histologic features of 15 plaques with ultrasonographic jellyfish sign, and the results showed that the proportional area of the fibrous cap correlated negatively with jellyfish-positive plaque surface movement rate. Our results regarding the fibrous cap area

coincides with their results. They could not, however, document significant correlation between atheromatous lesion area and the plaque motion rate, which is inconsistent with our results. This may be attributed to the differences in a patient population, in definitions of ultrasonographic and histopathologic findings, and in research designs between the two studies. The large necrotic core can still be one of the representative features of mobile plaques because the present results were conducted in a controlled study.

Our study has some limitations. First, the number of the cases we studied was small, and not all of the nonmobile plaques were examined. Larger studies are necessary to confirm higher prevalence of mural thrombus and thinner fibrous cap in mobile plaques.

Second, because nonmobile plaques had a longer duration until CEA, stabilization of the plaque, which can occur within approximately 90 days after the presenting neurologic symptom,[31,32] could have led us to underestimate some of the histologic factors of nonmobile plaques. However, one study showed that the prevalence of a large lipid core and mural thrombus was not influenced by the span of time since the last ischemic events.[31] Spagnoli et al[33] also revealed that a fresh thrombus can present several months after the first cerebrovascular event.

Third, we only studied symptomatic plaques and did not include asymptomatic plaques. Our study, therefore, did not answer the question of whether mobile plaques are more "vulnerable" than nonmobile plaques as long as the word "vulnerable" means the tendency for fibrous cap rupture and the potential of subsequent embolic stroke. That was not, however, the purpose of this study. Further studies including both symptomatic and asymptomatic patients might be essential to determining whether mobile plaques are more "vulnerable" than nonmobile plaques.

A higher prevalence of mobile plaques is shown in this report (9.3% of excised plaque) than in previous study.[1] The most recent study demonstrated an even higher prevalence (19%) of mobile plaques.[12] This high prevalence of mobile plaques may be explained by the evolution of the duplex ultrasound imaging system and sheds light on the clinical importance of mobile plaques.

CONCLUSIONS

In this study, we have clarified the histologic difference between mobile and nonmobile symptomatic carotid plaques. This result may partly explain unstable neurologic presentations of patients with mobile carotid plaques and may add information to the debate regarding the management of mobile plaques. Further studies on the histopathology and natural history of the mobile carotid plaque are needed to establish the most effective acute management for symptomatic mobile plaques.

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AUTHOR CONTRIBUTIONS

Conception and design: TF, KI
Analysis and interpretation: TF, KN, HI
Data collection: TF, KN, TH
Writing the article: TF
Critical revision of the article: KI, SM
Final approval of the article: KI, HI
Statistical analysis: TF
Obtained funding: Not applicable
Overall responsibility: TF

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Correlation of thin fibrous cap possessing adipophilin-positive macrophages and intraplaque hemorrhage with high clinical risk for carotid endarterectomy

Clinical article

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Object. Preoperative clinical risk classification of carotid artery (CA) stenosis anticipates the outcome of CA intervention. A higher incidence of neurological morbidity was noted after CA stenting (CAS) in patients with medical risks than in those without risks. However, little is known about the correlation between clinical risks and plaque composition. The purpose of this study was to characterize the CA plaque histology in 3 groups of patients who were classified based on clinical risks for carotid endarterectomy (CEA). Furthermore, the authors examined whether the plaque with high embolic potential after CA intervention, particularly CAS, could be predicted based on clinical risks for CEA.

Methods. Patients were divided into 4 groups, according to the CEA risk classification system, and 3 groups with more than 10 cases were enrolled in this study as follows: absence of all angiographic, medical, and neurological risks (Grade I, 27 cases); presence of medical risk, but no neurological risk (Grade III, 31 cases); and presence of neurological risk (Grade IV, 17 cases). Histopathological characteristics of CA plaques, including fibrous cap thickness, plaque disruption, thrombus formation, intraplaque hemorrhage (IPH), and adipophilin expression were examined without information regarding clinical status.

Results. Plaques in patients in Grades III and IV demonstrated a thin fibrous cap and enhanced IPH, compared with those in Grade I. Plaques in patients in Grade IV showed more adipophilin-expressing macrophages in the fibrous cap than in those of the other groups.

Conclusions. Plaques in Grades III and IV patients were characterized by thin fibrous cap atheroma with IPH. Adipophilin-positive macrophage infiltration in the fibrous cap might be correlated with instability in neurological status. The plaque morphology in patients with medical and neurological risks needs to be examined carefully with the aid of imaging modalities. In plaques demonstrating a thin fibrous cap and IPH, the CAS procedure should be avoided and CEA should be performed instead. *(DOI: 10.3171/2010.8.JNS10423)*

Key Words • **carotid artery stenosis** • **endarterectomy** • **plaque analysis** • **pathology** • **risk factors**

Atheromatous plaque of the CA is responsible for a substantial number of ischemic strokes.[26] The appearance of ulcerated plaque on CA angiography is a strong risk factor for stroke[12,28] and is a predictor of subsequent acute coronary events.[29] In symptomatic patients, CA plaques exhibit a high incidence of disruption in the connective tissue that is covered over by necrotic debris in the plaque. These plaques are characterized by a large lipid core and dense macrophage infiltrate.[14,27] Intraplaque hemorrhage is common in CA plaques, but it is less frequent in coronary artery lesions. However, the role of IPH as an indicator of subsequent symptoms in patients with CA stenosis is presently under debate.[4,18,22,23]

Carotid endarterectomy and CAS appear to be effective treatments for CA stenosis.[2,3,11,17] However, the incidence of neurological morbidity after treatment for CA stenosis, particularly CAS, is known. Classification of CA stenosis in regard to surgical risk has been determined in large CEA studies, such as the CEA risk classification system outlined by Sundt and colleagues.[30] Four grades were established based on angiographic, medical, and neurological risks. Patients devoid of angiographic, medical, and neurological risks are classified as Grade

Abbreviations used in this paper: CA = carotid artery; CAS = CA stenting; CEA = carotid endarterectomy; IEL = internal elastic lamellae; IPH = intraplaque hemorrhage.