脳梗塞による。

F. 研究発表

1. 論文発表

1) Kuroda S, Shiga T, Ishikawa T, et al.: Reduced blood flow and preserved vasoreactivity characterize Oxygen hypometabolism due to incomplete infarction in occlusive carotid artery diseases. J Nucl Med 2004; 45:943-949

2. 学会発表

なし

厚生労働科学研究費補助金（循環器疾患等総合研究事業）
分担研究報告書

内頸動脈閉塞症にともなう血行力学的脳梗塞の発症予防に関する研究

分担研究者　橋本　信夫　京都大学医学研究科脳統御医科学系脳神経外科講座教授

研究要旨　内頸動脈閉塞症に伴う血行力学的脳虚血軽症群の自然経過と高次脳機能に対する影響を追跡調査する

A. 研究目的

血行力学的脳虚血軽症群の自然経過と高次脳機能に対する影響を明らかにしこの群に対するEC/IC bypass術の有効性を判断する基礎資料を得る。

B. 研究方法

内頸動脈系の閉塞性脳血管病変におけるTIAまたはminor strokeを6ヶ月以内に認めた73歳以下の症例でADLが自立し脳循環動態が血行力学的脳虚血軽症群に属すると判断された患者を内科的治療し、6ヶ月、1年目、2年目に定期的にCT, MRI, 脳血流検査、高次脳機能検査を行い経過を追跡する。

（倫理面への配慮）

研究は京都大学医の倫理委員会の承認を得て行い、患者への説明は統一した説明文を用いて行う。患者データは連結可能匿名化して管理しプライバシー保護に配慮する。

C. 研究結果

H16年度に京都大学病院に入院した内頸動脈系の閉塞性脳血管病変を有する患者は34名でありそのうち4名がinclusion criteriaを満たし2名を登録した。

以前より経過追跡していた患者4名を含め6名の追跡調査を行った。性別は6名全員男性、平均年齢60.8歳、本研究で定めた脳血流分類でB群3名、C群1名、D群2名であった。B群の1例が登録6ヶ月後に脳血流および高次脳機能の悪化を来たし、脳血管バイパス術を必要としendpointとなりC群の一例で登録5ヵ月後に急死しendpointとなった。死因は心疾患が疑われている。その他D群の一例で登録1年後に脳血流が中等症にまで悪化したが、高次機能は保たれ神経学的悪化を認めないことから経過観察となった。

D. 考察

軽症群の中にもバイパス手術が必要となる例が存在することが明らかになってきた。

E. 結論

統計学的群間解析を行うためさらなる症例集積および経過観察が必要である。

F. 研究発表

1. 論文発表

なし

2. 学会発表

なし

―登録時チェックリスト―

1. 医療機関名：
2. 代表者名　：　　3．担当医名：
4. 被検者イニシャル：（姓）　　（名）　　5．性別：□男 □女
6. カルテ番号：
7. 生年月日　：　19　　年　　月　　日
8. ＣＢＦ分類：　□Ａ群 □Ｂ群 □Ｃ群 □Ｄ群
9. 登録日　　：　200　　年　　月　　日

Inclusion criteria（以下の項目をチェックして下さい）

1. 臨床的 criteria

□内頸動脈系の閉塞性病変によるTIAまたはminor completed stroke を6ヶ月以内に認める（progressing stroke ないしは crescendo TIA 等の急性期症例は含まない）。
□ADLがほぼ自立している(Modified Rankin disability scale 0,1 or 2)。
□73歳以下である。

2. 放射線学的 criteria

1) CT/MRI 所見：
□一血管支配領域にわたるような広汎な脳梗塞巣を認めない。
□脳梗塞巣はCT上のcontrast enhancementを受けない。

2) 血管造影所見：
□内頸動脈、中大脳動脈本幹の閉塞あるいは高度狭窄を示す（CEAの対象となる症例を除く）。

3) 脳循環動態：
□ 最終発作から３週間以上経過した後にPET, SPECT(^{133}Xe,^{123}IMP),coldXe-CTを用いて軽症のhemodynamic ishcemiaを示す（安静時CBF≧80%または10%≦脳循環予備能＜30%）

Exclusion criteria （該当項目がある時にチェックして下さい）

□神経症候が重篤（Modified Rankin Disability Scale 3以上）
□非動脈硬化性病変によるもの
□悪性腫瘍、心不全、肝不全、腎不全、呼吸不全
□６ヶ月以内の心筋梗塞、および冠動脈不全
□空腹時血糖値が300mg/dl以上、あるいはインスリン治療を要する耐糖能低下
□拡張期血圧　110mmHg以上の高血圧症
□心原性塞栓、Artery to artery embolism

発症から登録までの期間　　□3ヶ月以内 □3ヶ月-6ヶ月

研究事務局 e-mail：bypass@mgt.ncvc.go.jp

Key film 送信先：bypass@mgt.ncvc.go.jp

問い合わせ先：〒565-8565　吹田市藤白台5-7-1　国立循環器病センター脳神経外科
JET-2study 事務局
(TEL: 06-6833-5012, FAX: 06-6836-2876)
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* CTまたはMRI、脳血管撮影、脳血流検査（安静時およびdiamox負荷後）のkey filmを各１枚（Powerpointで作成）メールにて上記アドレスまで送信してください。

* 登録番号をe-mailまたはFAXでご連絡いたしますので連絡先を下記に記入してください。

連絡先e-mailまたはFAX

事務局記載　　登　録　日：200　年　月　日

症例登録番号：＿＿＿＿＿＿＿＿

—登 録 用 紙—

1. 医療機関名：
2. 代表者名　：　　3．担当医名：
4. 被検者イニシャル：（姓）　（名）　5．性別：□男 □女
6. カルテ番号：
7. 生年月日　：　19　年　月　日
8. ＣＢＦ分類：□Ａ群 □Ｂ群 □Ｃ群 □Ｄ群
9. 登録日　：　200　年　月　日　10. 登録番号：

11. 同意取得　：　200　年　月　日
□被検者本人 □代諾者　（続柄　　）

12. 既往疾患　：□高血圧症 □糖尿病 □高脂血症 □虚血性心疾患
□心臓弁膜症 □心房細動 □脳卒中
□その他　（　　）

13. 初回発作　：時期200　年　月　日
神経症状（□右・ □左 ）片麻痺 □失語症
□その他　（　　）
発作型　□TIA □completed stroke

14. 初回発作と最終発作の間の発作：
発作型　□TIA　（回数：　回）
□completed stroke　（回数：　回）

15. 最終発作　：時期　200　年　月　日
神経症状（□右・ □左 ）片麻痺 □失語症
□その他　（　　）
発作型　□TIA □completed stroke

16. 血管撮影所見：責任血管　（□右・ □左 ）ICA （□閉塞・ □狭窄 ）
（□右・ □左 ）MCA （□閉塞・ □狭窄 ）
□合併病変（　　）

17. CBF：　定量法　（□IMP-SPECT・ □Xe-SPECT・ □cold Xe-CT・ □PET ）
安静時CBF 正常値の　　％ 脳循環予備能　（□＋ □－）　　％
□Ａ群 □Ｂ群 □Ｃ群 □Ｄ群
CBF測定時血圧-登録時（収縮期／拡張期）（　　／　　）

18. 大脳高次機能　：

教育年数；＿＿ 年、利き手；□右 □左 □両手　、検査に使用した手；□右 □左

1）WAIS-R：　符号 ＿＿＿＿

2）Verbal fluency test：animal＿＿＿＿ words/min
あ ＿＿＿＿ words/min
ふ ＿＿＿＿ words/min
に ＿＿＿＿ words/min

「あ」、「ふ」、「に」の合計 ＿＿＿＿ words

3）WMS-R：粗点

Information and Orientation ＿＿＿＿ /１４
Mental control（精神統制）＿＿＿＿ /6
Figural memory（図形の記憶）＿＿＿＿ /１０
Logical memory Ⅰ（論理的記憶Ⅰ）＿＿＿＿ /５０
Visual paired Ⅰ（視覚性対連合Ⅰ）＿＿＿＿ /１８
Verbal paired Ⅰ（言語性対連合Ⅰ）＿＿＿＿ /２４
Visual reproduction Ⅰ（視覚性再生Ⅰ）＿＿＿＿ /４１
Digit span（数唱）＿＿＿＿ /２４
Forward（順唱）＿＿＿＿ /１２
Backward（逆唱）＿＿＿＿ /１２
Visual taping span（視覚性記憶範囲）＿＿＿＿ /２６
Forward（同順序）＿＿＿＿ /１４
Backward（逆順序）＿＿＿＿ /１２
Logical memory Ⅱ（論理的記憶Ⅱ）＿＿＿＿ /５０
Visual paired Ⅱ（視覚性対連合Ⅱ）＿＿＿＿ /6
Verbal paired Ⅱ（言語性対連合Ⅱ）＿＿＿＿ /8
Visual reproduction Ⅱ（視覚性再生Ⅱ）＿＿＿＿ /４１

重み付けされた粗点の合計
Verbal Memory（言語性記憶）＿＿＿＿
Visual Memory（視覚性記憶）＿＿＿＿
General Memory（一般性記憶）＿＿＿＿
Attention/Concentration（注意/集中力）＿＿＿＿
Delayed Recall（遅延再生）＿＿＿＿

4）Trail Making Test：A＿＿＿＿ sec
B＿＿＿＿ sec

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JET-2 study 事務局
（TEL：06-6833-5012，FAX：06-6836-2876）
※受付は休日を除く月曜～金曜　10：00～17：00

―登録６ヶ月後の報告―

1. 医療機関名：
2. 代表者名　：　　3．担当医名：
4. 被検者イニシャル：（姓）　（名）　5．性別：□男 □女
6. カルテ番号：
7. 生年月日　：　19　年　月　日
8. ＣＢＦ分類：□Ａ群 □Ｂ群 □Ｃ群 □Ｄ群
9. 登録日　：　200　年　月　日　10．登録番号：

11. 登録後６ヶ月以内の再発作、死亡、新たな手術の施行
□あり　（別紙報告のこと）
□なし

12. 神経学的所見：
登録時に比べ □改善 □不変 □悪化

13. ＡＤＬ：　Modified Rankin Disability Scale　（3以上は別紙報告のこと）
登録時に比べ □改善 □不変 □悪化

14. ＣＴ/ＭＲＩ所見：　新たな梗塞巣 □なし □あり （部位　）
脳萎縮の進行 □なし □あり （部位　）

15. ＣＢＦ：　定量法（□IMP-SPECT・ □Xe-SPECT・ □cold Xe-CT・ □PET）
安静時CBF 正常値の＿＿＿％ 脳循環予備能 （□＋ □－）＿＿＿％
CBF測定時血圧-6ヶ月（収縮期／拡張期）（　／　）

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※受付は休日を除く月曜～金曜　10：00～17：00

― 登録１年後の報告 ―

1. 医療機関名：
2. 代表者名　：　　3．担当医名：
4. 被検者イニシャル：（姓）　　（名）　　5．性別：□男 □女
6. カルテ番号：
7. 生年月日　：　19　　年　月　日
8. ＣＢＦ分類：□Ａ群 □Ｂ群 □Ｃ群 □Ｄ群
9. 登録日　　：　200　　年　月　日　　10. 登録番号：

11. 登録後１年以内の再発作、死亡、新たな手術の施行
□あり　（別紙報告のこと）
□なし

12. 神経学的所見：.....
登録時に比べ □改善 □不変 □悪化

13. ＡＤＬ：　Modified Rankin Disability Scale __　（3以上は別紙報告のこと）
登録時に比べ □改善 □不変 □悪化

14. ＣＴ/ＭＲＩ所見：新たな梗塞巣 □なし □あり （部位　　）
脳萎縮の進行 □なし □あり （部位　　）

15. ＣＢＦ：　定量法（□IMP-SPECT・ □Xe-SPECT・ □cold Xe-CT・ □PET）
安静時CBF 正常値の____％ 脳循環予備能 （□＋ □－）_____％
CBF測定時血圧-1年（収縮期／拡張期）（　　／　　）

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JET-2 study 事務局
（TEL：06-6833-5012, FAX：06-6836-2876）
※受付は休日を除く月曜～金曜　10：00～17：00

― 登録２年後の報告 ―

1. 医療機関名：
2. 代表者名　：　　3．担当医名：
4. 被検者イニシャル：（姓）　（名）　5．性別：□男 □女
6. カルテ番号：
7. 生年月日　：　19　年　月　日
8. ＣＢＦ分類：□Ａ群 □Ｂ群 □Ｃ群 □Ｄ群
9. 登録日　：　200　年　月　日　10．登録番号：

11. 登録後２年以内の再発作、死亡、新たな手術の施行
□あり　（別紙報告のこと）
□なし

12. 神経学的所見：.....
登録時に比べ □改善 □不変 □悪化

13. ＡＤＬ：　Modified Rankin Disability Scale ＿ （3以上は別紙報告のこと）
登録時に比べ □改善 □不変 □悪化

14. ＣＴ/ＭＲＩ所見：新たな梗塞巣 □なし □あり（部位　）
脳萎縮の進行 □なし □あり（部位　）

15. ＣＢＦ：　定量法（□IMP-SPECT・ □Xe-SPECT・ □cold Xe-CT・ □PET ）
安静時CBF 正常値の＿＿＿％ 脳循環予備能 （□＋ □－）＿＿＿％
CBF測定時血圧-2年（収縮期／拡張期）（　／　）

16. 血管撮影(MRA)所見：責任血管　（□右・ □左 ）ICA （□閉塞・ □狭窄）
（□右・ □左 ）MCA （□閉塞・ □狭窄）
（　）
□合併病変

経時的変化（登録時と比較して）
□なし　（　）
□あり

17. 大脳高次機能　：

教育年数；＿＿ 年、利き手；□右 □左 □両手　、検査に使用した手；□右 □左

1）WAIS-R：　符号 ＿＿

2）Verbal fluency test：animal ＿＿ words/min
あ ＿＿ words/min
ふ ＿＿ words/min
に ＿＿ words/min
「あ」、「ふ」、「に」の合計 ＿＿ words

3）WMS-R：粗点

Information and Orientation ＿＿ /14
Mental control（精神統制）＿＿ /6
Figural memory（図形の記憶）＿＿ /10
Logical memory I （論理的記憶 I ）＿＿ /50
Visual paired I （視覚性対連合 I ）＿＿ /18
Verbal paired I （言語性対連合 I ）＿＿ /24
Visual reproduction I （視覚性再生 I ）＿＿ /41
Digit span （数唱）＿＿ /24
Forward（順唱）＿＿ /12
Backward（逆唱）＿＿ /12
Visual taping span（視覚性記憶範囲）＿＿ /26
Forward（同順序）＿＿ /14
Backward（逆順序）＿＿ /12
Logical memory II （論理的記憶 II ）＿＿ /50
Visual paired II （視覚性対連合 II ）＿＿ /6
Verbal paired II （言語性対連合 II ）＿＿ /8
Visual reproduction II （視覚性再生 II ）＿＿ /41

重み付けされた粗点の合計
Verbal Memory（言語性記憶）＿＿
Visual Memory（視覚性記憶）＿＿
General Memory（一般性記憶）＿＿
Attention/Concentration（注意/集中力）＿＿
Delayed Recall（遅延再生）＿＿

4）Trail Making Test：A ＿＿sec
B ＿＿sec

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（TEL：06-6833-5012，FAX：06-6836-2876）
※受付は休日を除く月曜～金曜　10：00～17：00

―脳虚血発作の報告―

1. 医療機関名：
2. 代表者名　：　　3．担当医名：
4. 被検者イニシャル：（姓）　（名）　5．性別：□男 □女
6. カルテ番号：
7. 生年月日　：　19　年　月　日
8. ＣＢＦ分類：□Ａ群 □Ｂ群 □Ｃ群 □Ｄ群
9. 登録日　：　200　年　月　日　10．登録番号：

11. 再発作、死亡の原因疾患、責任血管
□登録時と同じ
□登録時と異なる（　　）

12. 再発作 時期　200　年　月　日

1）発症様式　□TIA
□completed stroke

2）神経症状（□右・□左）片麻痺 □失語症 □意識障害
□その他　（　　）

3）CT/MRI所見：＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

4）血管撮影(MRA)所見：＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

13. 再発作後のADL：Modified Rankin Disability Scale
登録時に比べ　□改善 □不変 □悪化

14. 死亡の場合　死亡年月日　200　年　月　日

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JET-2 study 事務局
（TEL：06-6833-5012，FAX：06-6836-2876）
※受付は休日を除く月曜～金曜　10：00～17：00

—脳虚血発作以外による死亡、disabilityの報告—

1. 医療機関名：
2. 代表者名　：　　3．担当医名：
4. 被検者イニシャル：（姓）　（名）　5．性別：□男 □女
6. カルテ番号：
7. 生年月日　：　19　年　月　日
8. ＣＢＦ分類：□Ａ群 □Ｂ群 □Ｃ群 □Ｄ群
9. 登録日　：　200　年　月　日　10．登録番号：

11. 脳虚血再発作以外による死亡またはdisability(Modified Rankin Disability Scale 3以上)の発生年月日:

200 年　月　日

12. 原因疾患：.....

13. 悪化後のADL：

Modified Rankin Disability Scale ___

14. 死亡年月日：20　年　月　日

研究事務局 Key film送付先 e-mail：bypass@mgt.ncvc.go.jp
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JET-2 study 事務局
（TEL：06-6833-5012，FAX：06-6836-2876）
※受付は休日を除く月曜～金曜　10：00～17：00

― 登録後の新たな手術の施行の報告 ―

1. 医療機関名：
2. 代表者名　：　　3．担当医名：
4. 被検者イニシャル：（姓）　（名）　5．性別：□男 □女
6. カルテ番号：
7. 生年月日　：　19　年　月　日
8. ＣＢＦ分類：□Ａ群 □Ｂ群 □Ｃ群 □Ｄ群
9. 登録日　：　200　年　月　日　10．登録番号：

11. 登録後の新たな手術の施行理由：

□ 1）内科医の判断で外科治療へ移行

□ 2）バイパスの再手術

□ 3）頭蓋内における他の部位の手術

具体的理由

□その他 ；＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

12. 新たな手術の年月日 :200　年　月　日

13. 新たな手術の術式　：＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

14. 術後のADL　：　Modified Rankin Disability Scale

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※受付は休日を除く月曜～金曜　10：00～17：00

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Risk factors for occlusive lesions of intracranial arteries in stroke-free Japanese

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The aim of this study was to identify relevant risk factors for occlusive lesions of the intracranial arteries in stroke-free population. The subjects of this study were 425 patients without a history of stroke or transient ischemic attack and without any abnormality on a neurological examination who consecutively visited a neurology clinic between January 1994 and June 2001 requesting medical evaluation for possible cerebrovascular diseases. Subjects included 245 men and 180 women ranging in age from 33 to 89 years (mean ± SD = 64.0 ± 10.0 years). We performed cervical and intracranial magnetic resonance angiography (MRA) in all subjects. Using a validated rating scheme of MRA for occlusive lesions, we evaluated the degree of stenoses in the extracranial portion of the internal carotid artery (ICA) and the intracranial arteries including the intracranial portion of the ICA, middle cerebral artery (MCA) stem, intracranial portion of the vertebral artery (VA), and basilar artery (BA). More than 25% stenoses were regarded as significant lesions in this study. Multiple logistic regression analyses showed that significant and independent predictors for extracranial ICA lesions were age, hyperlipidemia, and ischemic heart disease (IHD), those for intracranial ICA lesions were age, hypertension, diabetes mellitus, and IHD, those for MCA lesions were age and hypertension, those for intracranial VA lesions were hyperlipidemia and IHD, and those for BA lesions were hypertension and diabetes mellitus. The present study suggested that atherosclerosis of the intracranial VA was related to hyperlipidemia and IHD as was the case for the extracranial carotid artery, whilst atherosclerosis of other sites of intracranial arteries was associated with hypertension and diabetes mellitus in stroke-free Japanese.

Introduction

In a previous study of stroke-free subjects using magnetic resonance angiographies (MRAs) (Uehara *et al.*, 1998), we found that the risk factors for occlusive lesions in the cervical carotid artery and intracranial arteries were different. Age and hyperlipidemia were risk factors for the former, and age and hypertension were risk factors for the latter. In that study we categorized the basilar artery (BA) into a common group of intracranial arteries together with the intracranial internal carotid artery (ICA) and the middle cerebral artery (MCA). However, some investigators (Caplan *et al.*, 1986; Yasaka *et al.*, 1993) have suggested that, in patients with ischemic stroke or transient ischemic attack (TIA), risk factors for BA lesions differ from those for MCA lesions. According to Caplan *et al.* (1986), extracranial ICA and BA lesions belong to a group closely related to hyperlipidemia and coronary heart disease, whilst MCA lesions belong to another group related to hypertension but not to hypercholesterolemia. They also pointed out that the intracranial ICA and the intracranial vertebral artery (VA) did not fall clearly into any of these groups because of a lack of information for these vessel sites (Caplan *et al.*, 1986). Yasaka *et al.* (1993) demonstrated that, in patients with ischemic stroke or TIA, MCA trunk atherosclerosis was related to advanced hypertension, and that atherosclerosis of both the BA and the extracranial ICA was associated with high serum lipid levels, coronary heart disease, and diabetes mellitus. However, until now, no studies have been carried out to examine risk factors for occlusive lesions in each site of the intracranial arteries in stroke-free subjects. We therefore looked for regional differences in the risk factors for occlusive lesions of the intracranial arteries in Japanese without stroke by using MRA.

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Materials and methods

Subjects

Subjects of this study were recruited from outpatients without stroke or TIA who consecutively visited the

clinic of the neurology service in our hospital between January 1994 and June 2001. All the patients without any history of stroke or TIA episode who requested medical evaluation for possible cerebrovascular diseases because of reasons including a simple fear of stroke, positive family history of stroke, vascular risk factors, and non-specific subjective symptoms such as headache or dizziness, and without a contraindication for magnetic resonance imaging (MRI) were invited to the study. Informed consent for the study was obtained from all the patients. Patients were carefully checked for their medical history and given a complete neurological examination, and cranial MRIs were employed. Patients whose examination was indicative of stroke or those whose scans revealed incidental significant lesions (except for asymptomatic lacunar infarcts in white matter, basal ganglia, or thalamus) were excluded (nine patients). Patients with migraine (four patients) and those with vertigo possibly caused by brainstem or cerebellar dysfunction (five patients) were not included in this study. Finally, the subjects of this study were 425 patients, including 245 men and 180 women ranging in age from 33 to 89 years (mean ± SD =64.0 ± 10.0 years). One hundred and fifty-six of these subjects also participated in the previous study (Uehara *et al.*, 1998).

Magnetic resonance angiography examinations

All MRA examinations were performed with a 1.0 tesla MR system (Magnetom Impact; Siemens, Erlangen, Germany). Image acquisition and reconstruction are described elsewhere (Uehara *et al.*, 1994, 1995). The extracranial portion of the ICA was evaluated based on the carotid MRA. The intracranial portion of the ICA, the horizontal portion of the MCA, the intracranial portion of the VA, and the BA were evaluated based on the intracranial MRA. Two investigators (T.U. and M.T.), who were blinded to all clinical information, independently reviewed the MRAs and rated occlusive lesions for each arterial portion into five grades depending on the narrowness of the arteries (Uehara *et al.*, 1994, 1995): <25% reduction of an arterial diameter was graded as normal, 25–49% reduction was graded as mild stenosis, 50–74% reduction was graded as moderate stenosis, 75–99% reduction was graded as severe stenosis, and no opening was graded as occlusion. When the judgment of the two readers was inconsistent, a decision was entrusted to a third investigator (E.M). To measure the percent stenosis of the extracranial portion of the ICA, we compared the diameter of maximal stenosis with that of the normal-appearing proximal ICA beyond the carotid bulb [North American Symptomatic Carotid Endarterectomy Trial (NASCET) Steering Committee, 1991]. Aplasia or hypoplasia of the VA is not uncommon, in which MRA assessment of stenosis is impractical. We regarded as VA aplasia/hypoplasia when fulfilled the followings: (i) the diameter of the VA in the dominant side being not smaller than the diameter of the BA, (ii) a smooth transition from the dominant VA to the BA, and (iii) the VA of the non-dominant side being not visible, constantly narrow through the whole length or terminated into the posterior inferior cerebellar artery.

The accuracy of MRA in detecting occlusive disease of extra- and intra-cranial ICA system was previously shown to be high (Uehara *et al.*, 1994, 1995). An additional validation study was carried out to evaluate the accuracy of MRA for the vertebrobasilar artery system, comparing MRA with conventional angiography. Subjects of this validation study consisted of 58 patients (44 men and 14 women, mean ± SD =60.7 ± 11.3 years old) selected from those who were admitted to our hospital for suspected ischemic cerebrovascular diseases (45 patients with ischemic stroke, 10 patients with TIA, two patients with cervical bruit, and one patient with transient global amnesia) between April 1992 and December 1993 and were given both MRA and conventional angiography studies within 1 month of each other. Seven vessels of the VA, which showed hypoplasia on both MRA and conventional angiography, were excluded because they were unable to estimate the degree of stenosis. The Spearman rank correlation coefficients between the conventional angiography rating and the MRA rating were 0.86 for the VA, 0.89 for the BA, and 0.80 for the posterior cerebral artery (PCA). When considering the normal-abnormal dichotomy, the sensitivity was 100% for the VA, 100% for the BA, and 83.3% for the PCA. The specificity was 93.9% for the VA, 96.0% for the BA, and 83.7% for the PCA. Because PCA lesions were uncommon, this portion was not considered in this study. Moreover, the proxymal portion of the VA was not also taken into consideration in this study, as the origin of the VA, a common site of occlusive lesions, was unable to evaluate on the cervical MRA.

Risk factors

Hypertension, diabetes mellitus, hyperlipidemia, smoking habit, and ischemic heart disease (IHD) were evaluated as risk factors. Hypertension was judged as present when either a systolic pressure of >140 mmHg or a diastolic pressure of >90 mmHg was demonstrated on repeated examinations or when a history of treatment for hypertension was present. Diagnosis of diabetes mellitus was made when the fasting blood glucose level was >126 mg/dl or when a history of treatment for diabetes mellitus was present. Hyperlipidemia was judged as present when laboratory

examination of the serum at presentation showed a high total cholesterol level of >220 mg/dl, a high triglyceride level of >150 mg/dl, a low high-density-lipoprotein cholesterol level of <40 mg/dl, or when a history of treatment was present. Smoking habit included previous history of smoking. IHD was defined as a known history of myocardial infarction or angina pectoris.

Statistical analyses

Multiple logistic regression analyses were used to estimate independent effects of the predictive variables on the cerebral arterial occlusive lesions. The contrast was between those with and without lesion in each site. All statistical analyses were carried out with StatView software (SAS Institute Inc., Cary, NC, USA). The level of significance was set at $P < 0.05$ for all statistical analyses.

Results

Two hundred five subjects (48.2%) were hypertensive, 91 subjects (21.4%) were diabetic, and 113 subjects (26.6%) were hyperlipidemic. One hundred thirty-nine subjects (32.7%) had a smoking habit. IHD was positive in 109 subjects (25.6%).

The results of MRA findings are summarized in Table 1. For estimation of MRA findings, the rate of agreement between two readers (T.U. and M.T.) was 94.6% (kappa = 0.92). Four vessels of the intracranial ICA and five vessels of the MCA were not assessable because of occlusion in their proximal portion. For the VA, 48 vessels were not assessable because of hypoplasia. Bilateral lesions were found in the extracranial ICA in 11 subjects, in the intracranial ICA in three subjects, in the MCA in two subjects, in the intracranial VA in two subjects. Fifteen subjects had both extracranial and intracranial lesions.

Table 1 Magnetic resonance angiography findings

	Extracranial	Intracranial			
Stenosis rating[a]	ICA	ICA	MCA	VA	BA
Normal	384	398	398	409	416
Mild stenosis	26	16	21	9	6
Moderate stenosis	7	7	0	3	1
Severe stenosis	4	3	5	3	2
Occlusion	4	1	1	1	0
Abnormal (%)[b]	9.6	6.4	6.4	3.8	2.1

[a]Based on the rating of more affected side in case of bilateral vessel lesions.

[b]Stenoses of more than 25%.

ICA, internal carotid artery; MCA, middle cerebral artery; VA, vertebral artery; BA, basilar artery.

Multiple logistic regression analyses showed that significant and independent predictors for lesions were age, hyperlipidemia, and IHD for the extracranial ICA, age, hypertension, diabetes mellitus, and IHD for the intracranial ICA, age and hypertension for the MCA, hyperlipidemia and IHD for the intracranial VA, and hypertension and diabetes mellitus for the BA (Table 2).

Discussion

Multiple logistic regression analyses showed that significant and independent predictors of the extracranial ICA lesions were age, hyperlipidemia and IHD, and

Table 2 Predictors for stenoses

Variable	Odds ratio	95% confidence interval	*P*-value
Extracranial ICA			
Age (>65 years)	2.67	1.30–5.48	0.0074
Male sex	1.88	0.93–3.79	0.0782
Hypertension	1.62	0.84–3.11	0.1492
Diabetes mellitus	1.37	0.66–2.86	0.3982
Hyperlipidemia	2.38	1.23–4.60	0.0099
Smoking habit	1.70	0.89–3.27	0.1110
Ischemic heart disease	3.95	2.05–7.64	<0.0001
Intracranial ICA			
Age (>65 years)	5.36	1.82–15.85	0.0024
Male sex	2.08	0.85–5.06	0.1069
Hypertension	5.01	1.85–13.55	0.0015
Diabetes mellitus	4.05	1.81–9.08	0.0007
Hyperlipidemia	2.14	0.95–4.80	0.0664
Smoking habit	1.55	0.69–3.48	0.2847
Ischemic heart disease	2.25	1.00–5.07	0.0496
MCA			
Age (>65 years)	3.36	1.33–8.51	0.0105
Male sex	0.91	0.42–2.00	0.8203
Hypertension	6.96	2.37–20.51	0.0004
Diabetes mellitus	1.90	0.82–4.38	0.1331
Hyperlipidemia	1.69	0.75–3.80	0.2084
Smoking habit	1.23	0.55–2.75	0.6206
Ischemic heart disease	1.78	0.79–4.01	0.1662
Intracranial VA			
Age (>65 years)	2.02	0.69–5.93	0.1984
Male sex	3.31	0.93–11.78	0.0651
Hypertension	2.49	0.85–7.29	0.0967
Diabetes mellitus	2.25	0.80–6.37	0.1256
Hyperlipidemia	13.39	3.74–47.95	<0.0001
Smoking habit	2.12	0.78–5.78	0.1410
Ischemic heart disease	6.98	2.37–20.59	0.0004
BA			
Age (>65 years)	7.41	0.92–59.77	0.0601
Male sex	1.48	0.37–6.00	0.5822
Hypertension	9.07	1.12–73.15	0.0385
Diabetes mellitus	7.67	1.88–31.32	0.0045
Hyperlipidemia	2.25	0.59–8.55	0.2322
Smoking habit	1.03	0.25–4.18	0.9677
Ischemic heart disease	1.46	0.36–5.95	0.5956

that those of the MCA lesions were age and hypertension. These findings were well consistent with the findings of previous studies (Heyden *et al.*, 1970; Crouse *et al.*, 1986, 1987; Salonen *et al.*, 1988; Craven *et al.*, 1990; Handa *et al.*, 1990; Howard *et al.*, 1990; Tanaka *et al.*, 1993; Yasaka *et al.*, 1993; Fabris *et al.*, 1994; Fine-Edelstein *et al.*, 1994; Uehara *et al.*, 1998). Heyden *et al.* (1970), who analyzed a group of patients with angiographically documented non-embolic cerebral artery occlusion, noted that patients with extracranial carotid lesions had a high frequency of associated IHD and hypercholesterolemia. Several ultrasonography studies have shown that extracranial carotid lesion is related to hyperlipidemia (Crouse *et al.*, 1987; Salonen *et al.*, 1988; Handa *et al.*, 1990; Fabris *et al.*, 1994; Fine-Edelstein *et al.*, 1994) and IHD (Crouse *et al.*, 1986, 1987; Craven *et al.*, 1990; Howard *et al.*, 1990; Tanaka *et al.*, 1993).

Although there have been fewer studies of MCA lesions than of extracranial ICA lesions, the results of the present study were consistent with those in the previous studies (Heyden *et al.*, 1970; Yasaka *et al.*, 1993; Uehara *et al.*, 1998; Takahashi *et al.*, 1999). Caplan *et al.* (1986) suggested that very common hypertension and relatively uncommon hypercholesterolemia could explain a predilection for occlusive lesions of the MCA and a low prevalence of occlusive extracranial ICA disease and coronary artery disease in Japanese. Yasaka *et al.* (1993) concluded that advanced hypertension was related to MCA trunk atherosclerosis. Takahashi *et al.* (1999) reported that hypertension and high serum levels of glycosylated hemoglobin A1c were significant and independent predictors of atherosclerotic lesions of the MCA detected by MRA in Japanese.

Like the MCA lesions, the intracranial ICA lesions had age, hypertension, and diabetes mellitus as significant and independent predictors. In addition, we found a weak but significant correlation between intracranial ICA lesions and IHD. Ingall *et al.* (1991) demonstrated that significant and independent predictors of intracranial ICA atherosclerosis found by conventional angiography were duration of cigarette smoking, age, hypertension, and diabetes mellitus. Marzewski *et al.* (1982), who followed up >66 patients with more than 50% stenosis of the intracranial ICA for an average of 3.9 years, concluded that intracranial ICA stenosis was a marker of extensive cerebrovascular and systemic atherosclerotic disease, especially coronary artery disease. Little is known about the risk factors for intracranial ICA occlusive lesions.

In the present study, atherosclerosis of the intracranial VA was related to hyperlipidemia and IHD as was the case for the extracranial carotid artery, whilst atherosclerosis of BA was associated with hypertension and diabetes mellitus. Our results clearly suggested that intracranial VA lesions belong to the same class as extracranial ICA lesions, which are closely related to hyperlipidemia and IHD. Although no studies comparable to the present study have examined the risk factors for intracranial VA occlusive lesions, the New England Medical Center Posterior Circulation Registry (Muller-Kuppers *et al.*, 1997; Shin *et al.*, 1999) reported that the prevalences of hypertension, hyperlipidemia, diabetes mellitus, smoking, and IHD were high in patients with symptomatic intracranial VA occlusive lesions. In addition, the prevalence of coronary artery disease in patients with symptomatic intracranial VA occlusive disease was reportedly quite high, ranging from 20 to 36% (Bogousslavsky *et al.*, 1986; Moufarrij *et al.*, 1986; Muller-Kuppers *et al.*, 1997; Shin *et al.*, 1999), which supports our findings. However, our results failed to verify the previous view. Caplan *et al.* (1986), in a review of occlusive cerebrovascular disease, found that atherosclerosis of the large arteries including extracranial ICA and BA, was closely related to hyperlipidemia and coronary artery disease. Yasaka *et al.* (1993) demonstrated that atherosclerosis of extracranial ICA and BA was strongly associated with high serum lipid levels, coronary heart disease, and diabetes mellitus in patients with ischemic stroke. This discrepancy may be attributable to the different characteristics of the cohorts, a difference between patients with ischemic stroke and stroke-free subjects, or to the small number of subjects with BA stenosis. In the present study, the proxymal segment of the VA was not studied, as it was not accessible on the cervical MRA we used. As the origin of the VA is a critical site, risks for the proxymal VA lesions should be elucidated in future.

Finally, limitations of the present study have to be mentioned. The subjects of this study were patients without a history of stroke or TIA and without any abnormality on a neurological examination who visited a neurology service requesting medical evaluation for possible cerebrovascular diseases. To minimize the selection bias as far as possible, subjects of this study were prospectively recruited from consecutive outpatients. The cohort in the present study is a part of stroke-free general population. However, this kind of study is prone to referral or selection bias. The prevalence derived from such a hospital-based study should be carefully interpreted and applied to general population. Nevertheless, at least the association between risk factors and vascular lesions demonstrated could be generalizable, as the association would be universal. Another weakness is that the individual lesion numbers were all low, which may introduce type II errors. The ideal study method is to conduct a population-based study rather than a hospital-based study,

and larger population-based studies are evidently needed to confirm our findings. Low prevalence also affects the creditability of the MRA rating results. False positives, which may unavoidably occur in MRA, are of concern especially in a low-risk population. The most vulnerable site for MRA is the intracranial ICA, where the false positive rate is considerably high. Signal discontinuity caused by tortuosity of the vessel in this region would be often judged as 'severe' stenosis (Uehara *et al.*, 1994). However, in the present study, as the occasion of 'severe' rating was very few, most of the stenotic ratings should be true.

In conclusion, the present study suggested that atherosclerosis of the intracranial VA was related to hyperlipidemia and IHD as was the case for the extracranial carotid artery, whilst atherosclerosis of other sites of major intracranial arteries was mainly associated with hypertension and diabetes mellitus in stroke-free Japanese. Our results might shed light into the important question why there were ethnic differences in the distribution of atherosclerotic lesion. In the future, a study investigating the correlation between the severity of the occlusive lesions and risk factors is needed to determine the predictors of the development of atherosclerosis.

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研究成果の刊行に関する一覧表

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著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
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