厚生労働科学研究費補助金（難治性疾患克服研究事業）
分担研究報告書

もやもや病における潜在性微小出血の経時変化と放射線学的所見（preliminary report）

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研究要旨

3テスラMRIT2*強調画像を用いてもやもや病患者25名の微小出血巣(MB)追跡研究を行った。初回検査時に11名にMBが検出され、平均12.1ヶ月後の追跡検査で3名において新たなMBが出現した。MBが検出された14名中9名にMRA検査で周囲に微小血管が認められた。経過中MBの個数とサイズが増加し、致死性出血に至った一例ではMB周囲の微小血管が著明に拡大していた。もやもや病における微小出血は経時的に個数の増加およびサイズの拡大する例がある。MBの増加、拡大の機序として周囲微小血管の拡張が関与している可能性がある。

A. 研究目的

脳出血はもやもや病における最大の予後不良因子のひとつであるがその発症機序は明らかではない。近年MRI T2*強調画像により脳内の微小出血巣(MB)が検出可能となり、脳出血との関連が指摘されるようになった[3, 6, 7]。我々はこれまで3テスラMRIを用いた前向き研究によりもやもや病に患者の約40%に潜在性微小出血巣が検出され健常人より有意に高頻度であること[3]、複数のMBがその後の脳出血の独立した危険因子であること[5]、またMBの摘出標本においてMBの周囲には脆弱な微小動脈の集簇が認められること[4]を報告した。本稿においてはMBの経時的変化と周囲の微小血管について放射線学的に検討したpreliminary resultsにつき報告する。

B. 研究方法

＜症例＞2003年11月から開始した京都大学もやもや病3テスラMR前向き研究には2008年1月現在もやもや病確診例77名、類および片側もやもや病患者19名が登録されている。このうち2004年12月までに登録されたもやもや病確診患者25名（男5名、女20名、年齢17-66歳、平均年齢41歳）を対象とした。初回検査後3テスラMR検査を半年後、1年後に行いMBの変化を検討した。追跡期間は5~15ヶ月（中央値12.1ヶ月）であった。

潜在性（無症候性）微小出血の定義はT2*強調画像において直径 10mm 未満の hypointense lesionで、同時に撮像したT1, T2強調画像およびMRAによりvascular flow voidや海綿状血管腫などの出血性疾患を除外したものと定義した。また出血の既往のある患者においては先行出血およびその進展部位と連続のない病変と定義した。

C. 研究結果

潜在性微小出血の経時変化

初回検査時に虚血型もやもや病 18 名中 8 名、出血型もやもや病 7 名中 3 名の合計 11 名に MB が検出された。追跡検査時には虚血型の 2 名と出血型に 1 名において新たに MB が検出され、MB が検出された患者は合計 14 名となった。経過中に虚血型の 2 名において major bleeding(致死性脳内出血 1、シルビウス裂内出血 1)が生じた。

(図 1)

	initial MR study			Follow-up study		
	Ischemic MMD	Hemorrhagic MMD	MMD	Ischemic MMD	Hemorrhagic MMD	MMD
no. of patients	18	7	25	18	7	25
male/female ratio	3:15	2:5	5:20	3:15	2:5	5:20
mean age (yrs)	41.3±14.6	43.7±17.4	42.0±15.2	42.3±14.5	44.7±19.5	42.9±15.5
postoperative patients	13	3	16	17	5	22
preoperative patietns	5	4	9	1	2	3
patients w/ MBs	8	3	11	10	4	14
w/ Major bleeding	5	7	12	7	7	14

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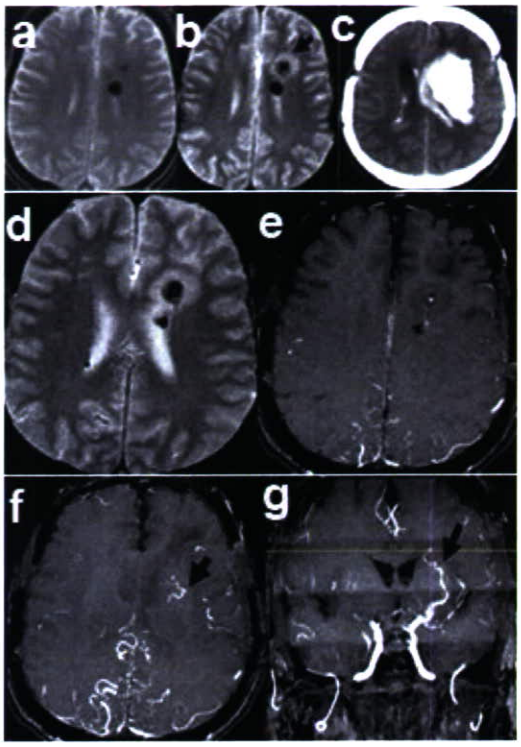
致死性脳内出血発生症例における MR 所見

経過中に致死性出血を認めた 49 歳男性を retrospective に検討した。本患者は脳虚血発作により入院し、もやもや病と確診され、IMP-SPECT 検査で両側前頭葉に著明な脳血流低下と脳血管予備能低下が認められた。入院時の 3 テスラ MRI T2*強調画像で左前頭葉の脳室近傍の深部白質に複数の MB が認められた。両側バイパス術を施行し、その 1 ヶ月後の MR 検査で MB の個数増加とサイズの拡大、および周囲白質浮腫を認めた。血圧管理を行ったがその 3 ヵ月後に致死性の左脳内出血を生じた。

術後 1 ヶ月後の MRA 元画像を検討すると、拡大した MB 内に拡張した血管と血流増加が認められ、coronal 像では IC top から MB に還流するもやもや血管のが拡張が認められた。

(図 2)



a 術前 MR T2*画像。左前頭葉深部白質に複数の MB が認められる。

b 両側バイパス術後 1 ヶ月の MR T2*画像。MB の個数増加とサイズの拡大、および周囲白質浮腫を認める (矢印)。

c 両側バイパス術後 4 ヶ月後 CT。致死性左脳内出血発生

d 両側バイパス術後 1 ヶ月の MR T2*画像。MB の個数増加とサイズの拡大。

e 両側バイパス術後 1 ヶ月の MRA の MB と同一スライス画像。 MB 内に血流を認める。

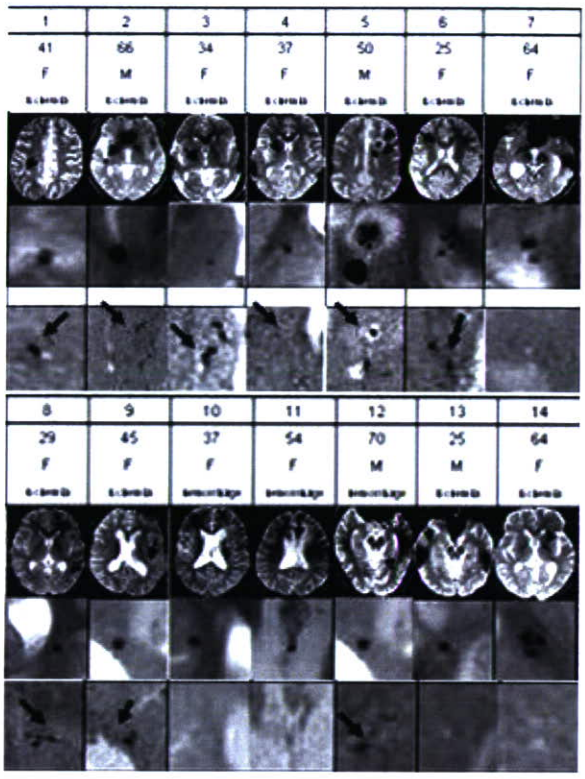
f MB 周囲に血管拡張を認める (矢印)。

g 両側バイパス術後 1 ヶ月の MRA。IC top から MB に環流するもやもや血管の拡張が認められる (矢印)。

微小出血周囲の血管構築

追跡 MR 検査時に MB が認められた 14 名について、MB 周囲に血管拡張がないか同一スライスの MRA 元画像を用いて検討した。14 名中 9 名 (63%)において MB 周囲に微小血管拡張が認められた。

(図 3)



もやもや病確診患者25名中14名に確認されたMBとその周囲の微小血管拡張。14名中9名(63%)にMB周囲の微小血管拡張（矢印）が認められた。

D. 考察

Imaizumi らはラクナ梗塞および一次性脳内出血といった Small vessel disease (SVD)の前向き追跡研究において5個以上の MB および脳出血の既往が SVD 再発に相関することを報告し[1]、さらに経過中に MB が増加する MB の dynamics についても報告した[2]。今回の検討はもやもや病の MB においても虚血型、出血型の両者において MB が dynamics を示すことを示唆するものである。我々はもやもや病患者の約40%に微小出血巣(MB)が潜在し、さらに複数の MB はその後の脳出血の危険因子であることを指摘したが[3,5]、MB がどのように出血に関与するかはいまだ不明である。MB の摘出標本において MB の周囲に一部内弾性板断裂を伴う微小血管の集簇が認めらることから、これら周囲微小血管の破綻がもやもや病患者における MB の形成と進展に関与する可能性が示唆される[4]。

今回の検討では経過中に脳内出血を生じた症例において、出血前に MB の個数増加とサイズの拡大が認められていた。さらにその MB には IC top から拡張したもやもや血管が還流していた。このことは MB 周囲の微小血管の拡張と血流増加により、脆弱な微小血管が破綻をきたし、MB の増加拡大およびひいては症候性出血を来たす可能性を示唆し、臨床上重要な知見と考えられる。

実際にMBが検出されたもやもや病患者14名において同様に MRA を用いて周囲微小血管を検討した結果、その 63%において画像上 MB 周囲の微小血管集簇が確認された。

本結果はわずか25名の解析結果であり、もやもや病における MB の dynamics、および出血転化と周囲血管の変化についてより多数例で検討する必要があろう。

いまだ推論の域を出ないが、MB とその周囲血管の拡張変化が出血の原因であるとすれば、その検出は出血を事前に知る指標となり、MB 周囲血管に対する intervention はもやもや病の出血に対する根本治療となる可能性がある。今後の一層の研究が必要と考えられる。

E. 結論

もやもや病における微小出血は経時的に個数の増加およびサイズの拡大する例がある。増加、拡大の機序として周囲微小血管の拡張が関与している可能性がある。

F. 文献

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G. 知的財産権の出願・登録状況

なし

研究成果の刊行に関する一覧表

橋本信夫（主任）

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