厚生労働科学研究費補助金

難治性疾患等克服研究事業（難治性疾患克服研究事業）

ウイリス動脈輪閉塞症の診断・治療に関する研究

平成23～25年度　総合研究報告書

主任研究者　橋本　信夫

平成26年（2014年）5月

厚生労働科学研究費補助金
難治性疾患克服研究事業

ウイリス動脈輪閉塞症の診断・治療に関する研究

The Research Committee on Spontaneous Occlusion of the Circle of Willis (Moyamoya Disease)

by

Science Research Grants of Ministry of Health, Labour and Welfare, Japan

平成 23-25 年度　総合研究報告書

平成 26 年（2014 年）5 月

主任研究者　橋　本　信　夫 国立
循環器病研究センター　　理事長

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主任研究者

国立循環器病研究センター　理事長
橋本　信夫

2013 年度　総括

まとめ

平成 25 年度は、もやもや病に関する新規研究である無症候性もやもや病の新たな多施設共 同研究(AMORE)が進行している。また、Japan Adult Moyamoya trial (JAM trial)は 2001 年 度から行われてきたがついに最終結果が報告された。そして、昨今社会問題となっている、 高次脳機能障害に対する臨床研究についても Cognitive functional survey of Moyamoya (COSMO) JAPAN study が開始された。また、高齢者のもやもや病に対する MODEST 研究も開 始されている。以上のように、これまで通り、日本のみならず世界において、この研究班が もやもや病の臨床および研究をリードしていくことが期待できる。

平成 25 年度　研究成果

寶金らはこれまでとは別の新たな遺伝マーカーによるもやもや病の病因探索を行うことを計画した。従来の構造解析法で見いだされる染色体構造多型や繰り返し配列多型よりはミクロなゲノム構造多型で、DNA sequencing 法で見いだされる SNP よりはマクロなゲノム多型の遺伝子コピー数多型（Copy Number Variation CNV）が、もやもや病の疾患ゲノムマーカーになりうるか検証する。冨永らは 60 歳以上のもやもや病患者に対する血行再建術の治療成績を検証し、60 歳未満の患者と周術期合併症を含めた治療成績について比較検討した。

宮本らは出血発症もやもや病に対するバイパス手術の再出血予防効果を明らかにすることを目的に、2001 年度から無作為振分け試験（JAM trial）を行っている。平成 20 年 6 月に目標登録症例数 80 例（手術群 42 例、非手術群 38 例）に到達し、新規登録を停止した。平成 25 年 4 月現在、手術群 6 例、非手術群 13 例が primary end point に達した（到達率：手術群 3.2%/年、非手術群 8.2%/年)。多くの登録症例で登録から 5 年（観察期間）を経過し、現在観察期間内で追跡しているのは 1 例（手術群）である。平成 25 年 6 月に全症例観察期間満了し、その結果を報告した。

鈴木らは 2003 年度から 2013 年度までのもやもや病データベースを集計し，解析を行った．2013 年度に新規登録された症例は 77 例であり，2003 年度から 2013 年度までの総計では，計 30 施設より 1348 症例が登録された．また既存登録症例で今年度調査期間内に診

察があり経過観察が行われている症例は，379 例（既存登録症例中 30%）であった.

もやもや病における高次脳機能障害例の画像診断法に関する多施設共同研究 COSMO-JAPAN study では、IMZ SPECT 統計画像に加えて脳血流 SPECT 統計画像の標準化が求められている。中川原らはそこで、脳血流 SPECT 定量画像解析のために開発された QSPECT 画像再構成ソフトを用いて脳血流 SPECT 統計画像解析のための NDB を作成し、平均画像や標準偏差 SD 画像に対して、空間解像度を統一するための画像フィルタ追加の影響や年齢階層別の影響について検討した。その結果、QSPECT 画像再構成により脳血流 SPECT 統計画像解析の標準化が可能と結論した。

小泉らはもやもや病の感受性多型として RNF213 遺伝子の p.R4810K を同定したが、病態に果たす役割は未解明な部分が多い。本年度は、もやもや病疾患 iPS 細胞を血管内皮細胞（iPSEC）に分化して解析を行い、p.R4810K を有するもやもや病患者由来の iPSEC で血管形成能が低下することを明らかにした。さらに、p.R4810K が有糸分裂異常を引き起こし、ゲノム不安定性を誘導することを証明した。

平成 25 年度は、無症候性もやもや病の治療指針を確立すべく計画してきた新たな多施設共同研究（Asymptomatic Moyamoya Registry; AMORE）が本格的に開始された。本研究は無症候性もやもや病の予後を改善するための方策を明らかにすることを目的としている。

以上の様に、平成 24 年度の研究は進展した。今後、引き続いて重要な研究成果がこの研究班より報告されていくことが期待される。

2012 年度　総括

まとめ

平成　24　年度は、もやもや病に関する新規研究である無症候性もやもや病の新たな多施設共同研究(AMORE)が開始された。また、Japan Adult Moyamoya trial (JAM trial)は 2001 年度から行われてきたがついに 2013 年 6 月に結果が出ることとなった。そして、昨今社会問題となっている、高次脳機能障害に対する臨床研究についても Cognitive functional survey of Moyamoya (COSMO) JAPAN study として開始する予定である。また、もやもや病における原因遺伝子であることが示唆されている　RNF213　に関しては、この変異を持つ患者より採取した fibroblast より iPS 細胞を樹立することができた。 以上のように、これまで通り、日本のみならず世界において、この研究班がもやもや病の臨 床および研究をリードしていくことが期待できる。

平成 24 年度　研究成果 寶金らはもやもや病に対する血行再建術の周術期合併症に関して、自験 199 手術例の review と、すでに論文発表された high volume center からの治療成績を Systematic Review する形で、本治療の現状と周術期の問題点を探ることを計画した。自験例からはその発生要因を詳細に分析し、Systematic Review では世界的な治療実施状況と術式別の合併症頻度をメタ解析した。また、もやもや病患者から血行再建術前後に採血し、血管内皮前駆細胞(endothelial progenitor cell, EPC)を測定した。成人、小児とも患者群の術前で EPC の有意な低下が示された。また術前後では EPC の低下がみられた。これらは病変部での EPC 消費亢進を示唆する所見と考えられると報告した。

冨永らは 60 歳以上のもやもや病患者に対する血行再建術の治療成績を検証し、60 歳未満の患者と周術期合併症を含めた治療成績について比較検討した。

宮本らは出血発症もやもや病に対するバイパス手術の再出血予防効果を明らかにすることを目的に、2001 年度から無作為振分け試験（JAM trial）を行っている。平成 20 年 6 月に目標登録症例数 80 例（手術群 42 例、非手術群 38 例）に到達し、新規登録を停止した。平成 25 年 4 月現在、手術群 6 例、非手術群 13 例が primary end point に達した（到達率：手術群 3.2%/年、非手術群 8.2%/年)。多くの登録症例で登録から 5 年（観察期間）を経過し、現在観察期間内で追跡しているのは 1 例（手術群）である。平成 25 年 6 月に全症例観察期間満了の予定であるとしている。

鈴木らは 2003 年度から 2012 年度までのモヤモヤ病データベースを集計し解析を行った。2003 年度～2012 年度までに、総登録施設 30 施設より、総計 1265 症例が登録された。2010 年 10 月 1 日から 2012 年 9 月 30 日までの 1 年間に新規登録された症例は 73 例となり、また同期間中に診察、あるいは画像検査によるフォローが行われた症例は、新規症例を含め 384 例（総症例中 36%）であった。

今年度はデータベースを改訂し従来困難であった経時的なデータ解析を試み、データ移行が不十分な中での解析ではあるが興味深い結果を得ることができたとしている。

もやもや病における高次脳機能障害例の画像診断法に関する多施設共同研究 COSMO-JAPAN study では、IMZ SPECT 統計画像に加えて脳血流 SPECT 統計画像の標準化が求められている。中川原らはそこで、脳血流 SPECT 定量画像解析のために開発された QSPECT 画像再構成ソフトを用いて脳血流 SPECT 統計画像解析のための NDB を作成し、平均画像や標準偏差 SD 画像に対して、空間解像度を統一するための画像フィルタ追加の影響や年齢階層別の影響について検討した。その結果、QSPECT 画像再構成により脳血流 SPECT 統計画像解析の標準化が可能と結論した。

小泉らはもやもや病の感受性遺伝子として RNF213 を同定した。しかし RNF213 の生理的機能および疾患に果たす役割は未解明な部分が多い。本年度は、もやもや病に対する新規の試験管内疾患モデル開発を目的に、もやもや病患者より iPS 細胞の樹立と血管内皮細胞への分化を行った。また RNF213 の機能を明らかにするために、Rnf213 ノックアウトマウスを作成して糖尿病モデルマウスと交配を行い、Rnf213 欠損が糖尿病に与える影響について検討した。

平成 24 年度は、無症候性もやもや病の治療指針を確立すべく計画してきた、新たな多施設共同研究（Asymptomatic Moyamoya Registry; AMORE）が本格的に開始された。本研究は無症候性もやもや病の予後を改善するための方策を明らかにすることを目的としており、これまでの約１年間で 13 例が登録されている。

以上の様に、平成 24 年度の研究は進展した。今後、引き続いて重要な研究成果がこの研究班より報告されていくことが期待される。

2012 年度　総括

まとめ

平成 23 年度は、もやもや病治療ガイドラインの英語版が日本脳神経外科学会の学会誌に採択され、5 月に Neurologia medico-chirurgica 誌に掲載された(Neurologia medico-chirurgica Vol. 52 (2012) No. 5) 、日本発のこのガイドラインが、世界のもやもや病治療のエビデンスに基づいた標準化に役立つことが考えられる。また、当研究班が主催した Asian Neurosurgical Conference on Moyamoya disease が 2011 年 5 月に京都にて開催された。韓国、中国、台湾および日本からもやもや病の専門家が集まり最新の情報交換が行われた。また、新規研究である無症候性もやもや病の新たな多施設共同研究(AMORE)が開始された。 以上のように、これまで通り、日本のみならず世界において、この研究班がもやもや病の臨 床および研究をリードしていくことが期待できる。

平成 23 年度　研究成果

冨永らはもやもや病に対する直接血行再建術における周術期管理指針の確立を目的に、積極的血圧管理（降圧）による症候性過灌流の予防を行ってきたが、降圧時の遠隔部脳虚血の潜在的リスクなどの問題点があることを報告してきた。今回血液脳関門透過性に関与するマトリックス分解酵素 MMP-9 の抑制効果・脳保護効果が知られているミノサイクリンを周術期に併用することにより、より重層的な過灌流予防・合併症回避戦略の構築を試み、報告した。

永田らは全国調査結果を解析し，もやもや病，片側型もやもや病および類もやもや病の患者数を推計し，有病率と発症率を算出した．もやもや病患者は 6670.9 人存在していると推計され，人口 10 万人あたりの有病率はもやもや病 5.22 人，片側型もやもや病 0.66 人，類もやもや病 0.34 人であり，発症率は人口 10 万人に対して 1 年間にもやもや病 1.13 人，片側型もやもや病 0.23 人，類もやもや病 0.11 人と算出し、報告した。

鈴木らは 2003 年度から 2011 年度までのモヤモヤ病データベースを集計し解析を行った。2003 年度～2011 年度までに、総登録施設 30 施設より、総計 1139 症例が登録された。2010 年 10 月 1 日から 2011 年 9 月 30 日までの 1 年間に新規登録された症例は 53 例となり、また同期間中に診察、あるいは画像検査によるフォローが行われた症例は、新規症例を含め 295 例（総症例中 32%）であり、この 295 例の解析からは、STA-MCA バイパス術後に梗塞・出血イベントが、術前に比較し大幅に減少する傾向することが確認された。今後、モヤモヤ病の診断基準の改訂にあわせ、本データベースにおける解析・調査事項の大幅な改訂を検討する予定であるとしている。

野川らはもやもや病の臨床症状としては，虚血性脳卒中あるいは脳出血による運動障害が多いが，「頭痛」(7.4%)あるいは「けいれん」(3.3%)といった本疾患に特異な症状で発症する患者もいるとして、本疾患の「けいれん発作」あるいは「不随意運動」の特徴（種類，

誘因，持続時間）を，PubMed を用いて文献的に検討した．その結果，本疾患の不随意運動には，chorea, choeoathetosis，ballism(us)をはじめ数種類の表現型があり，誘因，持続時間は異なっており、また, 短い持続時間の不随意運動は, TIA の亜型である“ limb shaking ”として捉えられていたと報告した。また今後，その発症機序や影響を及ぼす因子，治療方法に関して検討する必要があるとした。

北川らは甲状腺機能異常や抗甲状腺抗体陽性例の脳血管所見の特徴について検討した。脳血管造影検査または脳MRA検査を施行した患者のうち、頭蓋内脳血管閉塞・狭窄を認めた 60 歳未満の成人で甲状腺機能検査を施行している 19 例(もやもや病を除く)を対象として、脳血管の狭窄部やもやもや血管の有無と甲状腺機能・抗甲状腺抗体の関連を調べたところ、内頸動脈終末部の血管病変を有する例で抗甲状腺抗体陽性率が高かった。甲状腺機能異常と狭窄部位の明らかな関連はみられなかった。内頸動脈終末部病変に免疫学的機序が関与している可能性を報告した。

小泉らは、本年度は、感受性遺伝子の特定を行うとともに、日中韓での感受性遺伝子のキャリアの推定を行い、それに基づき患者の数を推定した。

寶金らはもやもや病患者から血行再建術前、術後における血液中の血管内皮前駆細胞(endothelial progenitor cell, EPC)を測定した。EPC は患者群で低率の傾向がみられ、また血行再建術前後で比較すると、多くの症例で術後に EPC の低下がみられたと報告した。

黒田らは平成 23 年度は、無症候性もやもや病の治療指針を確立すべく、新たな介入型の多施設共同研究（Asymptomatic Moyamoya Registry; AMORE）を開始した。過去の当研究班での研究を前進させて、無症候性もやもや病の予後を改善するための方策を明らかにするとしている。

菊田らはくも膜下出血で発症した、破裂脳動脈瘤合併もやもや病 3 症例の治療経験を報告した。動脈瘤が主幹動脈に存在した 2 例は、瘤内塞栓術により完全閉塞、穿通枝に動脈瘤を認めた他の 1 例は、保存的加療にて発症 1 年後に自然閉塞した。もやもや病に合併する動脈瘤は、その発生部位から、主幹動脈に発生する真性動脈瘤と、もやもや血管や穿通枝に発生する仮性動脈瘤に分かれる。前者では直達手術に比べて低侵襲である血管内治療が安全で効果的と考えられ、後者ではどちらの治療も困難な場合、保存的加療も一つの選択枝となりうると考察している。 宮本らは出血発症もやもや病に対するバイパス手術の再出血予防効果を明らかにすること を目的に、2001 年度から無作為振分け試験（JAM trial）を行っている。平成 20 年 6 月に 目標登録症例数 80 例（手術群 42 例、非手術群 38 例）に到達し、新規登録を停止した。平
成 24 年 4 月現在、手術群 6 例、非手術群 13 例が primary end point に達した（到達率：手術群 3.2%/年、非手術群 8.3%/年)。多くの登録症例で登録から 5 年（観察期間）を経過し、現在観察期間内で追跡しているのは 3 例である。全症例が観察期間を満了するのは平成 25 年 6 月の予定である。

以上の様に、平成 23 年度の研究は進展した。今後、引き続いて重要な研究成果がこの研究

班より報告されていくことが期待される

III. 研究班構成員名簿

①研究者名	②分担する研究項目	③最終卒業校・卒業年次・学位及び専攻科目	④所属研究機関及び現在の専門（研究実施場所）	⑤所属研究機関における職名
橋本信夫	総括	京都大学医学部、昭和48年卒、医学博士、脳神経外科学	国立循環器病研究センター	総長
寶金清博	小児もやもや病に対する急性期治療およびもやもや病に対する再生治療の検討	北海道大学医学部、昭和54年卒、医学博士、脳神経外科学	北海道大学医学研究科脳神経外科	教授
冨永悌二	もやもや病ガイドラインの出版と更新	東北大学医学部、昭和57年卒、医学博士、脳神経外科学	東北大学大学院医学系研究科神経外科学神経科学	教授
宮本享	JAM trialおよびもやもや病の妊娠出産管理	京都大学医学部、昭和57年卒、医学博士、脳神経外科学	京都大学医学研究科脳神経外科	教授
鈴木則宏	もやもや病疫学画像データベース作成と更新	慶応義塾大学医学部、昭和52年卒、医学博士、神経内科	慶応義塾大学医学部神経内科学	教授
中川原譲二	もやもや病における高次脳機能診断とIMZ-SPECT	札幌医科大学、昭和53年卒、脳神経外科	中村記念病院脳神経外科	診療本部長
小泉昭夫	家族性もやもや病の遺伝子解析と原因遺伝子解析	東北大学医学部、昭和53年卒、医学博士、公衆衛生学	京都大学医学研究科社会医学系環境衛生学分野	教授
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Guidelines for diagnosis and treatment of moyamoya disease (spontaneous occlusion of the Circle of Willis)

Health Labour Sciences Research Grant for Research on Measures for Intractable Diseases

Research Committee on the Pathology and Treatment of Spontaneous Occlusion of the Circle of Willis

CHAPTER I. CONCEPTS OF THE DISEASE

1. Concepts of the Disease

The characteristics of moyamoya disease (spontaneous occlusion of the circle of Willis, cerebrovascular "moyamoya" disease) on cerebral angiograph y were reported for the first time in 1957[1], and the concept of moyamoya disease as a separate disease entity was established in the 1960"s[2-6]. Pathologically, moyamoya disease is characterized by chronic progressive stenosis of the terminal portion of the internal carotid arteries bilaterally, which leads to the formation of an abnormal vascular network composed of collateral pathways at the base of the brain (moyamoya vessels at the base of the brain) („moyamoya" is the Japanese term for a "puff of smoke," which has been used to describe the appearance of these collateral vessels on cerebral angiograms[5].). Eventually, with bilateral internal carotid occlusion, the moyamoya vessels at the base of the brain derived from the internal carotid arteries disappear, and the entire brain is perfused by the external carotid system and the vertebral-basilar system[2-7]. This disease is included in the list of diseases for Research on Measures for Intractable Diseases and the Specified Disease Treatment Research Program specified by the Ministry of Health, Labour and Welfare. Currently, the diagnostic criteria for moyamoya disease (spontaneous occlusion of the circle of Willis) laid down by the research committee are as follows[8].

2. Diagnostic Criteria[4]

(1) Cerebral angiography is considered essential for the diagnosis, and must show at least the following findings:
  (i) Stenosis or occlusion of the terminal portion of the intracranial internal carotid artery or proximal portions of the anterior and/or the middle cerebral artery.
  (ii) Abnormal vascular networks in the vicinity of the occlusive or stenotic lesions in the arterial phase.
  (iii) Bilaterality of findings (i) and (ii).

(2) However, when magnetic resonance imaging (MRI) and magnetic resonance angiographic (MRA) findings meet all of the following criteria, cerebral angiography can be omitted. See the "Guidelines for Diagnostic Imaging by MRI and MRA."
  (i) MRA shows stenosis or occlusion of the terminal portion of the intracranial internal carotid artery or proximal portions of the anterior and/or the middle cerebral artery.
  (ii) MRA shows abnormal vascular networks in the basal ganglia.
  Note: When 2 or more visible flow voids are present in the basal ganglia on MRI, at least unilaterally, they can be deemed as representing an abnormal vascular network.
  (iii) Bilaterality of findings (i) and (ii).

(3) Moyamoya disease is an illness of unknown etiology. The differential diagnosis of this disease includes similar cerebrovascular lesions associated with the following underlying diseases , which should, therefore, be excluded: (i) atherosclerosis, (ii) autoimmune disease, (iii) meningitis, (iv) brain tumors, (v) Down"s syndrome, (vi) von Recklinghausen"s disease, (vii) head injury, (viii) cerebrovascular lesions after head irradiation, and (ix) others.

(4) Pathological findings that can be used as references for the diagnosis
  (i) Thickening of the arterial intima, mainly in the terminal portion of the internal carotid arteries , and narrowing or blockage of the lumen caused by this change; usually bilateral. Occasionally, lipid deposits are also present in the thickened intima.
  (ii) Arteries such as the anterior, middle and posterior cerebral arteries composing the circle of Willis occasionally show varying degrees of stenosis or occlusion associated with fibrocellular thickeni ng of the intima, waviness of the internal elastic lamina, and thinning of the media.
  (iii) Numerous small vascular channels (perforat ing and anastomotic branches) can be seen around the circle of Willis.
  (iv) The pia mater may also show reticular conglomerates of small vessels.

3. Diagnostic Assessment

The condition should be classified as mentioned below based on items 2. (1) to (4). When autopsy is performed in the absence of cerebral angiography, the condition should be diagnosed based on the criteria in item (4).

Definitive moyamoya disease: All the criteria listed in (1) or (2) and in (3) should be met. In children, however, the criteria in item (1) or (2) (i) and (ii) on one side, and a visible stenosis around the terminal portion of the internal carotid arteries on the other side are sufficient for a definitive diagnosis.

Probable case: All criteria fulfilled except item (1) (iii) and/or item (2)(iii) among the criteria of (1) or (2) and (3).

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CHAPTER II. EPIDEMIOLOGY

Moyamoya disease (spontaneous occlusio n of the circle of Willis) is a disease that occurs frequently in Asian countries, including Japan, but is rare in Western countries. Epidemiological data reported from Japan are extremely valuable worldwide.

Early epidemiological surveys in Japan include an evaluation in 376 patients performed by Kudo [1] in the early 1970‟s and an evaluation in 518 patients conducted by Mizukawa, et al[2]. Thereafter, a research committee on spontaneous occlusion of the circle of Willis was established in 1977. Since 1983, case registration and follow-up investigation have been carried out each year at medical institutions to which the committee members belong and their related facilities throughout Japan. As of 2006, there were a total of 962 patients, including 785 with a definitive diagnosis of moyamoya disease, 60 with a probable diagnosis, and 62 with quasi-moyamoya disease registered in the database of this research committee on spontaneous occlusion of the circle of Willis[3].

In addition to accumulation of cases in the database at the committee members‟ institutions, three large-scale national epidemiological surveys have been conducted in 1984, 1990 and 1994.

1. Number of Patients/ Male-to-Female Ratio

In a national epidemiological survey conducted by Wakai, et al.[4] in 1994, approximately 3,900 people were estimated to be suffering from moyamoya disease (To be more precise, this was the number of patients that was examined). It affects 3.16 people per 100,000 persons, and occurs at an incidence of 0.35 people per 100,000 population. According to the "number of patients having a certificate for medical care for specified (intractable) disease: Occlusive disease in circle of Willis," the number of patients with moyamoya disease markedly increased from 5,227 patients in 1994 to 10,812 patients in 2005. If a national survey were conducted again now, it is expected that the number of patients would have grown further from that in 1994. This may be attributable to the spreading awareness of and familiarity with the concepts of moyamoya disease, as well as the establishment of the "Guidelines for Diagnostic Imaging by MRI and MRA" in 1995, which enabled the diagnosis of moyamoya disease based on the MRA findings alone.

The male:female ratio reported from various studies is nearly consistent[3,4], 1:1.8 to 1.9. The disease is more common in women. In addition, a positive family history has been reported in about 10.0% of the patients[4].

2. Age of Onset

The 1994 national survey and 2006 database evaluation showed a similar trend in relation to the age at onset of moyamoya disease: a bimodal peak consisting of a major peak in the first decade of life and a moderate peak in the late 20‟s to 30‟s (Figure 1). However, a recent report has indicated a higher age as compared with that mentioned above as the peak age at onset[8].

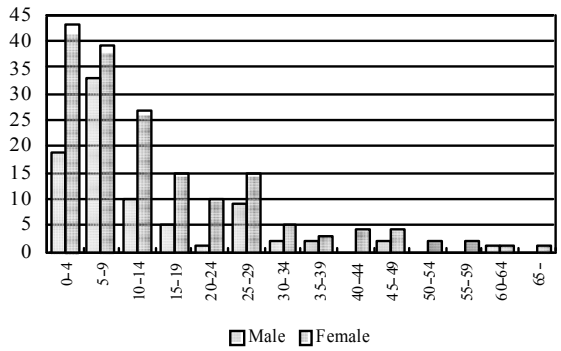

Figure 1. Age of Onset[3]

3. Age of Onset by the Disease Type of the Initial Attack

The various disease types by which the initial attack can manifest are presented in detail in CHAPTER IV "SYMPTOMS." The 2006 database evaluation[3] has reported a unimodal peak age at onset in the late 20‟s for initial attacks of the hemorrhagic type, but a bimodal peak for initial attacks of other disease types (Figure 2). However, according to another report, the peak age range of onset for initial attacks of the hemorrhagic type is the 5th to 6th decade of life (CHAPTER IV, Figure 1).

4. Asymptomatic Moyamoya Disease

In recent years, asymptomatic cases of moyamoya disease and moyamoya disease manifesting with only non-specific symptoms, such as headache, have drawn attention. The increase in the number of such patients could be attributable, at least in part, to the current widespread availability of MRI and the increase in the number of people undergoing medical checkup procedures for the brain.

Ikeda, et al.[5] performed MRI/MRA in 11,402 healthy people (male, n = 7,570; female, n = 3,832) who underwent a medical checkup for the brain and estimated a prevalence rate for moyamoya disease of 50.7 people per 100,000 healthy (asymptomati c) population. In an epidemiological survey conducted by Baba, et al. in Hokkaido[8], the prevalence rate of moyamoya disease was estimated as 10.5 people per 100,000 persons. This prevalence rate is higher than that reported from the previous national survey. While the possibility of

including patients with atherosclerosis cannot be ruled out, it could include a considerable number of patients with latent moyamoya disease (asymptomatic or only minor symptoms).

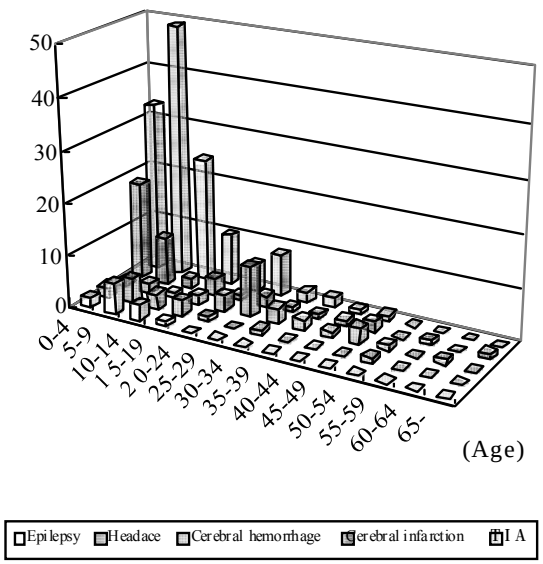

Figure 2. Age of Onset by Disease Type of the Initial Attack [3)]

5. Distribution of Moyamoya Disease in the World

Goto, et al.[6)] accumulated papers published between 1972 to 1989 and reported that 1,063 patients had been notified as being affected by moyamoya disease in the world excluding Japan, and that of these, 625 patients were Asian (Korean: n = 289, Chinese: n = 245), 201 were European and 176 were South or North American subjects. The 1990 national survey reported an estimated 3,000 Japanese patients. Even allowing for a difference in the rate of recognition of the disease, moyamoya disease appears to be a common illness in Asia, with the maximum number of cases from Japan. What is of even greater interest is that many patients of moyamoya disease reported from Europe and South/North America are Asian or African people, with the disease only rarely reported in Caucasians. Ikezaki, et al.[9)] also reported 451 patients from 29 institutions in South Korea in a 1995 survey.

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CHAPTER III. PATHOLOGY/ ETIOLOGY

1. Pathology

The main finding at autopsy is stenosis or occlusion of the terminal portion of the internal carotid arteries. Moyamoya vessels are assumed to represent collateral circulation developed for compensating the cerebral ischemia occurring due to stenosis. In the early stage of the disease (Stage I according to Suzuki"s classification), moyamoya vessels are practically not noted. Degeneration of the smooth muscle cells in the media and the resultant death of the vascular smooth muscle cells cause thinning of the media. The waviness and duplication of the internal elastic lamina, accumulation of necrotic cell components in the interstitium, and proliferation of the vascular smooth muscle cells induce thickening of the intima and narrowing of the intravascular lumen. These are the processes assumed to be involved in the formation of the occlusive lesions[1].

These changes noted in the terminal portion of the internal carotid arteries suggest the possibility of their also occurring in the systemic arteries[2]. Qualitative abnormalities of the vascular smooth muscle cells are considered to be an underlying reason for the internal carotid artery occlusion. Transcription factors such as TGF-□ and growth factors such as bFGF and HGF have also been implicated[3].

Genetic factors are also considered to be closely involved; however, because penetrance is incomplete and depends on the age, accumulation of the effects of genetic factors is believed to induce vascular smooth muscle cell death and proliferation[4].

2. Familial Moyamoya Disease

Both familial moyamoya disease, referring to the accumulation of affected patients among relatives, and sporadic moyamoya disease, where no affected person is identified among relatives, have been reported. Familial moyamoya disease has been reported to account for approximately 10% of all cases of moyamoya disease[5]. Nonetheless, with the recent advances and spread of MRA, a non-invasive test, the number of cases of asymptomatic moyamoya disease among the relatives of patients has been increasing[6].

3. Genetic Factors

For familial moyamoya disease, gene loci have been identified in 3p24-p26[7] and 8q23[8] in a genomewide analysis, and in 6q25 (D6S441)[9] and 17q25[10] in a chromosomal search.

In families with strong genetic factors, in which affected people are identified in 3 or more generations, the disease assumes an autosomal dominant inheritance pattern[5], and a significant linkage to 17q25.3 has been noted in these families[11].

At present, it is thought that the responsible genes are present in multiple gene loci, representing locus heterogeneity.

Cases of unilateral moyamoya disease progressing to bilateral moyamoya disease,[12] and of progression of major artery stenosis on the side contralateral to the initial disease have been reported. Therefore, the possibility that major artery stenosis, unilateral moyamoya disease, and narrow-defined bilateral moyamoya disease are also a series of sequential lesions, established based on the same genetic susceptibility has been suggested for familial moyamoya disease[11]. In addition, familial moyamoya disease is an autosomal dominantly inherited disease with incomplete penetrance, and various stages of the disease are noted in the same family. Consequently, interactions between genetic factors and aging or environmental factors are assumed to be necessary for the development of the disease.

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CHAPTER IV. SYMPTOMS

(1) Disease type manifested at the initial attack

Moyamoya disease may occur at any age from childhood to adulthood. In general, it often manifests with cerebral ischemic symptoms in children and with intracranial hemorrhage symptoms in addition to ischemic symptoms in adults. The distribution of the age of development of the ischemic type and hemorrhagic type of moyamoya disease in 1,127 definitive moyamoya disease patients registered in the national survey conducted by the Research Committee on moyamoya disease until 2000 is illustrated in **Figure 1**[1]. The symptoms and course vary according to the age and the disease type manifested at the initial attack, and varying degrees of severity of symptoms have been noted, such as transient attacks and attacks which are resulted in fixed neurological deficits. With the recent increase in the availability of MRI, many patients who were incidentally identified as having moyamoya disease during the asymptomatic st age[2] or with only the complaint of headache [3] have been reported.

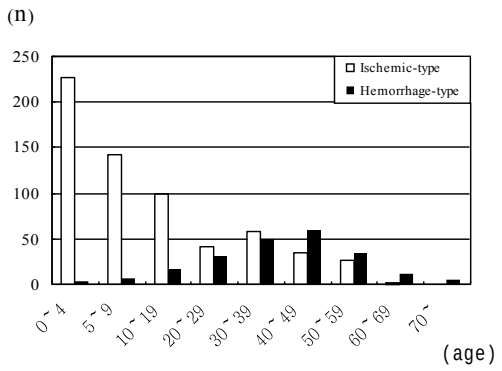

Figure 1. Age of onset of ischemic-type and hemorrhagic-type moyamoya disease (n = 1127)

The Research Committee on Moyamoya Disease classified the initial attacks into 6 types in 1979: “hemorrhagic-type,” “epileptic-type,” “infarction-type,” “transient ischemic attack (TIA)-type,” “frequent TIA-type” (twice or more often per month), and “other.” Subsequently, the “asymptomatic-type” was added, and in 2003 “headache-type” was also added. The proportions of patients with each of the disease types at the initial attack in 962 patients registered from 2003 to 2006 are listed in **Table 1**[4]. The data belong mainly to patients from medical institutions to which the committee members belong ed. In a complete survey in Hokkaido, the frequency of the asymptomatic-type has been reported to have increased further, and the percentage of adult patients has also been suggested to have possibly increased as compared with the figure reported previously[5].

Table 1. Disease type manifested at the initial attack (n = 962)

Disease type manifested at the initial attack	No. of patients
TIA	353 (37%)
Frequent TIA	63 (7%)
Cerebral infarction	165 (17%)
Intracerebral hemorrhage	186 (19%)
Headache	57 (6%)
Epilepsy	29 (3%)
Asymptomatic	32 (3%)
Others	13 (1%)
Details unknown	64 (7%)

Table 2. Initial symptom (n = 1127)

Initial symptom	Hemorrhagic-type	Ischemic-type
Muscle weakness	58.6%	79.8%*
Consciousness disturbance	70.4%*	14.1%
Headache	64.6%*	18.8%
Seizure	8.5%	8.0%
Psychiatric symptom	8.7%	2.5%
Speech disorder	24.5%	20.1%
Sensory disturbance	18.4%	19.3%
Involuntary movement	3.3%	3.0%
Intellectual disturbance	5.3%	6.2%
Visual impairment	2.0%	3.2%
Visual field defect	3.9%	5.0%

* Significantly more frequent as compared with the others ($p < 0.05$).

(2) Frequency of each symptom

The frequency of each initial symptom in the 1 ,127 definitive moyamoya disease patients registered until 2000 is presented in **Table 2** for the patients with the hemorrhagic-type and ischemic-type (infarction-type,

TIA-type and frequent TIA-type) of initial attack. For both types, muscle weakness, consciousness disturbance, headache, speech disorder, and sensory disturbance were the most frequent, however, the incidence of consciousness disturbance and headache was higher and the incidence of muscle weakness lower for patients with the hemorrhagic-type than for the ischemic-type initial attacks ($p < 0.01$)[1].

(3) Characteristics of symptoms according to the age and disease type

Symptoms vary according to the age and disease type. In children, the disease often manifests initially with cerebral ischemic symptoms, particularly after hyperventilation caused by strenuous exercise, crying, harmonica playing, and eating a hot meal. Symptoms such as cataplexy (quadriplegia, hemiplegia and monoplegia), sensory disturbance, consciousness disturbance, seizure and headache occur in a paroxysmal and recurrent manner. The symptoms always appear on the same side in many patients, but occasionally, the affected side interchanges between the right and left sides. In addition, some patients develop involuntary movements such as chorea [6] and limb shaking. Such cerebral ischemia attacks may persist or resolve. In patients with repeated cerebral ischemia attacks, cerebral atrophy occurs, leading to mental dysfunction or diminished intelligence [7], or sequelae of cerebral infarction may remain. In moyamoya disease, the posterior cerebral arteries often remain patent until the advanced stage of the disease [8], however, in some patients, posterior cerebral artery disorder may result in visual impairment or visual field defect[9]. In pediatric patients, particularly those aged less than 5 years old, intracranial bleeding rarely occurs, unlike in adult patients.

In adult patients, especially those aged 25 years or older, moyamoya disease frequently manifests with sudden-onset intracranial hemorrhage (intraventricular, subarachnoid space or intracerebral hemorrhage), causing symptoms such as consciousness disturbance, headache, muscle weakness and speech disorder, according to the site of hemorrhage. Intracranial hemorrhage is often small intraventricular hemorrhage so that the symptoms may abate, however, it may also cause fixed neurological deficits or progress to a more serious condition and lead to death. In addition, the patients are at a high risk of rebleeding, and approximately a half of the patients die as a result of bleeding.

In addition to these symptoms, moyamoya disease may also manifest as cerebral ischemia attacks in adult patients as in pediatric patients. In such patients, age-related vascular changes are also present. This may cause cerebral infarction, resulting in permanent impairment in many cases.

As previously described, with the recent widespread availability of MRI, an increasing number of patients with only headache or even entirely asymptomatic patients are detected to have moyamoya disease. The characteristics of the headache vary, and may be migraine-like throbbing pain or the dull headache noted in tension-type headache. The precise mechanism is not yet fully understood.

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CHAPTER V. SIMILAR CONDITIONS

1. Quasi-moyamoya Disease

1) Definition

Quasi-moyamoya disease refers to the presence of stenosis or occlusion of the terminal portion of the internal carotid artery or proximal portion of the anterior and/or middle cerebral arteries accompanied by an abnormal vascular network detected in association with an underlying disease. Even in cases with unilateral lesions, if an underlying disease is present, the condition is considered as quasi-moyamoya disease.

This condition is also called "rui-moyamoya disease" in Japanese and "quasi-moyamoya disease" in English (synonym of "moyamoya syndrome" or "akin to moyamoya disease"). Unilateral moyamoya disease without underlying disease should be considered as probable moyamoya disease and be differentiated from quasi-moyamoya disease.

2) Supplemental notes

The following illnesses have been reported as underlying diseases: atherosclerosis, autoimmune disease (systemic lupus erythematosus (SLE), antiphospholipid antibody syndrome, periarteritis nodosa, and Sjögren‟s syndrome), meningitis, von Recklinghausen‟s disease, brain tumors, Down‟s syndrome, head injury, irradiation, hyperthyroidism, stenocephaly, Turner‟s syndrome, Alagille‟s syndrome, William‟s syndrome, Noonan‟s syndrome, Marfan‟s syndrome, tuberous sclerosis, Hirschsprung‟s disease, glycogen storage disease type I, Prader-Willi syndrome, Wilms tumor, primary oxalosis, sickle cell disease, Fanconi‟s anemia, spherocytosis, eosinophilic granuloma, type II plasminogen deficiency, leptospirosis, pyruvate kinase deficiency, protein someone deficiency, protein C deficiency, fibromuscular hyperplasia, osteogenesis imperfecta, polycystic kidney, oral contraceptives, and drug poisoning (cocaine, etc.).

3) Evidence

Quasi-moyamoya disease can affect people of all races. Concurrent occurrence with underlying congenital disease is frequent in children, while that with acquired underlying disease is common in adults [1,2]. It may manifest as epilepsy or headache, or be asymptomatic[1,2]. Co-presence of symptoms associated with mental retardation due to underlying disease and those associated with cerebrovascular disorder results in a complicated clinical condition[1].

Cerebral angiographic findings vary widely from those very similar to definitive moyamoya disease to rather different, such as atherosclerotic lesions [1,3]. In a study of quasi-moyamoya disease associated with von Recklinghausen disease, unilateral lesions were noted in 30% of the cases[3]. In quasi-moyamoya disease after irradiation, the affected arteries were enhanced by a contrast agent, whereas no significant contrast enhancement was noted in patients with definitive moyamoya disease[4]. In moyamoya disease associated with irradiation, collateral circulation involving the external carotid arteries is well developed[3]. Pathological findings also vary according to the underlying disease. In quasi-moyamoya disease concurrently associated with von Recklinghausen‟s disease, inflammatory cell infiltration is noted in the lesions[5]. The findings of quasi-moyamoya disease secondary to meningitis were similar to those of definitive moyamoya disease[6].

The treatment of quasi-moyamoya disease is like that of definitive moyamoya disease. For quasi-moyamoya disease associated with hormonal abnormalities, such as hyperthyroidism, or with autoimmune disorder, correction of the hormonal abnormality and immunos uppressive therapy, respectively, are reported to be effective [6,7]. For quasi-moyamoya disease associated with von Recklinghausen‟s disease, Down‟s syndrome or irradiation, revascularization (direct and indirect) has been demonstrated to be effective[8, 9,10]. The effect of revascularization on the prevention of rebleeding in patients with quasi-moyamoya disease has not yet been clarified. In quasi-moyamoya disease, unilateral involvement may progress to bilateral disease[11]. The nature of the underlying diseases influences the prognosis of patients with quasi-moyamoya disease[12].

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