

# **4<sup>th</sup> International Moyamoya Meeting Berlin, July 2-4, 2015 Germany**

## **Programme**

- **Epidemiology and Natural History**
- **Diagnosis and Classification**
- **MMD Genetics and Vascular Pathobiology**
- **Pediatric Moyamoya**
- **Surgical Treatment Strategies**
- **Moyamoya Syndrome / Quasi-Moyamoya**
- **New Experimental Approaches to Diagnosis and Treatment**
- **Free Topics**

**[www.moyamoya2015.com](http://www.moyamoya2015.com)**



The moment you expand the surgical boundaries  
beyond what seems possible.  
**This is the moment we work for.**



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## Welcome Address

Dear Colleagues and Friends,



Moyamoya Disease is a rare disease of children and adults characterized by multiple steno-occlusive changes around the circle of Willis, leading to a significantly increased stroke risk. Although the first patients were identified among the Asian population recent epidemiological studies have shown that Moyamoya Disease also contributes markedly to rare causes of stroke among European patients. In part, this is due to an increased awareness among physicians dealing with these patients.

The aim of this meeting is to further foster international training and education in this rare disease, and to improve our understanding of the underlying disease as well as current and future therapeutic options. The theme of this 4<sup>th</sup> International Moyamoya Meeting is to strengthen the interdisciplinary approach, bringing together neurosurgeons, neurologists, paediatricians, neurointensivists, and stroke epidemiologists. Furthermore, we aim at unravelling the complex vascular biology underlying the disease. Therefore, we will highlight the basic science biology of neurovascular development and angiogenesis, vascular plasticity and remodelling, neurovascular signalling, as well as neurovascular genetics.

Berlin is a highly attractive venue, especially in summer. The charm and character of Berlin provides an unforgettable experience. The variety of new and historic places and buildings, museums, cultural events and just life in the streets is unbeatable. You also can enjoy the spirit of the “Berliner” people with their open and direct mind by visiting the 4<sup>th</sup> International Moyamoya Meeting in Berlin.

We are looking forward to welcoming you in Berlin.

Prof. Dr. Peter Vajkoczy  
Congress President

## Organization

### Congress President

Prof. Dr. Peter Vajkoczy  
Charité- Universitätsmedizin Berlin  
Department of Neurosurgery  
Augustenburger Platz 1  
13353 Berlin, Germany

### Congress Secretary

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Department of Neurosurgery  
Augustenburger Platz 1  
13353 Berlin, Germany

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### Congress Organization

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### Venue

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10115 Berlin, Germany  
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## Programme Overview

### Thursday, July 2, 2015

#### "How I do it"-Workshop

|               |                                             |
|---------------|---------------------------------------------|
| 11.45 - 12.00 | Introduction                                |
| 12.00 - 12.30 | Part I                                      |
| 12.30 - 14.00 | Part II Indirect Revascularization          |
| 14.00 - 14.45 | Part III Direct Revascularization           |
| 14.45 - 15.30 | Coffee break with industrial exhibition     |
| 15.30 - 16.15 | Part III Direct Revascularization           |
| 16.15 - 17.00 | Part IV Combined Revascularization          |
| 17.15 - 18.00 | Part V Rescue Strategies for Repeat Surgery |

### Friday, July 3, 2015

|               |                                                            |
|---------------|------------------------------------------------------------|
| 08.30 - 10.40 | Vascular Biology and Plasticity                            |
| 10.40 - 11.00 | Coffee break with industrial exhibition and poster viewing |
| 11.00 - 13.00 | Epidemiology and Natural Course                            |
| 13.00 - 14.00 | Lunch break with industrial exhibition and poster viewing  |
| 14.00 - 16.00 | Diagnosis and Classification                               |
| 16.00 - 16.30 | Coffee break with industrial exhibition and poster viewing |
| 16.30 - 18.45 | Treatment Concepts and Controversies                       |
| 19.30 - 22.30 | Get Together                                               |

### Saturday, July 4, 2015

|               |                                                            |
|---------------|------------------------------------------------------------|
| 08.30 - 10.30 | Pediatric MMD                                              |
| 10.30 - 11.00 | Coffee break with industrial exhibition and poster viewing |
| 11.00 - 13.00 | Genetics and Molecular Biology of MMD                      |
| 13.00 - 14.00 | Lunch break with industrial exhibition and poster viewing  |
| 14.00 - 15.50 | Moyamoya-Syndrom and Atypical MMD / Free Topics            |
| 15.50 - 16.30 | Coffee break with industrial exhibition and poster viewing |
| 16.30 - 18.30 | New Experimental Approaches                                |

## Scientific Programme

**Thursday, July 2, 2015, 11:45 - 18:15 hrs**

### "How I do it" – Workshop

#### Surgical Techniques in Moyamoya Vasculopathy – Tricks of the Trade

Chair Peter Vajkoczy (Berlin/D)

11:45 TH.01.01 Introduction  
Peter Vajkoczy (Berlin/D)

#### Part I

12:00 TH.01.02 General Principles of Direct BypassSurgery  
Marcus Czabanka (Berlin/D)

12:15 TH.01.03 General Principles of indirect BypassSurgery  
Satoshi Kuroda (Toyama/J)

#### Part II: Indirect Revascularization

12:30 TH.01.04 Multiple burr holes  
Thomas Blauwblomme (Paris/F)

12:45 TH.01.05 Encephalomyosynangiosis (EMS)  
Peter Vajkoczy (Berlin/D)

13:00 TH.01.06 Encephaloduroarteriosynangiosis (EDAS) – pediatric  
Edward Smith (Boston/USA)

13:15 TH.01.07 Encephaloduroarteriosynangiosis (EDAS) – adult  
Nestor Gonzalez (Los Angeles/USA)

13:30 TH.01.08 Encephaloduroarteriomyosynangiosis (EDAMS)  
N.N.

13:45 TH.01.09 Bifrontal Encephaloduroperiostalsynangiosis  
Luca Regli (Zurich/CH)

#### Part III: Direct Revascularization

14:00 TH.01.10 STA-MCA bypass  
Peter Vajkoczy (Berlin/D)

14:15 TH.01.11 Double barrel STA-MCA bypass  
John E. Wanebo (Phoenix/USA)

14:30 TH.01.12 Occipital artery posterior cerebral and middle cerebral artery  
bypass  
Ken Kazumata (Sapporo/J)

14:45 ..... Coffee break with industrial exhibition

## Scientific Programme

15:30 TH.01.14 Superficial temporal artery-anterior cerebral artery /middle  
cerebral artery double bypasses with long graft for Moyamoya  
disease – surgical technique and angiographical evaluation  
Akitsugu Kawashima, Takakazu Kawamata, Koji Yamaguchi, Yoshika-  
zu Okada (Chiba/J, Tokyo/J)

15:45 TH.01.15 Double anastomosis using only one branch of STA  
Fady T. Charbel (Chicago/USA)

#### Part IV: Combined Revascularization

16:00 TH.01.16 STA-MCA bypass + EMS  
Peter Vajkoczy (Berlin/D)

16:15 TH.01.17 STA-MCA bypass + EMS/EDMS  
Kiyohiro Houkin (Sapporo/J)

16:30 TH.01.18 STA-MCA bypass + pansynangiosis  
Satoshi Kuroda (Toyama/J)

16:45 TH.01.19 STA-MCA bypass + Encephaloduroperiostalsynangiosis  
Sepideh Amin-Hanjani (Chicago/USA)

#### Part V: Rescue Strategies for Repeat Surgery

17:00 TH.01.20 Omentum transposition  
Gary K. Steinberg (Stanford/USA)

17:15 TH.01.21 ECA-MCA bypass with radial artery graft  
Satoshi Hori (Berlin/D)

17:30 TH.01.22 OA-MCA / OA-PCA bypass  
Gary K. Steinberg (Stanford/USA)

17:45 TH.01.23 Auricular artery / MCA bypass  
Luca Regli (Zurich/CH)

## Scientific Programme

**Friday, July 3, 2015, 08:30 - 10:40 hrs**

### FR.01 Vascular Biology and Plasticity

|                |                                                                                                                                                                                                                                                                                                                                                                           |
|----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chair          | Peter Vajkoczy (Berlin/D)                                                                                                                                                                                                                                                                                                                                                 |
| 08:30 FR.01.01 | Vascular Development and Plasticity<br>Hellmut Augustin (Mannheim/D)                                                                                                                                                                                                                                                                                                      |
| 08:55 FR.01.02 | Ischemia as a driving force in sprouting angiogenesis<br>Holger Gerhardt (Berlin/D)                                                                                                                                                                                                                                                                                       |
| 09:20 FR.01.03 | Arteriogenesis in cerebral ischemia<br>Ivo Buschmann (Berlin/D)                                                                                                                                                                                                                                                                                                           |
| 09:45 FR.01.04 | In vitro and in vivo evidence on inhibition of angiogenesis by the Moyamoya susceptible gene and its mutation, RNF213 R4810K<br>Akio Koizumi, Hatasu Kobayashi, Yoshiko Matsuda, Toshiaki Hitomi, Hiroko Okuda, Hirotomo Shioi, Tetsuya Matsuda, Hirohiko Imai, Masakatsu Sone, Daisuke Taura, Kouji H. Harada, Yasushi Takagi, Susumu Miyamoto, Toshiyuki Habu (Kyoto/J) |
| 10:10 FR.01.05 | Functional characteristics of endothelial cells in Moyamoya disease<br>Kinga G. Blecharz, Dietmar Frey, Tobias Schenkel, Michael Fromm, Irina Kremenetskaia, Marcus Czabanka, Peter Vajkoczy (Berlin/D)                                                                                                                                                                   |
| 10:20 FR.01.06 | Pathogenesis of Moyamoya disease: the role of angiogenesis, extracellular-matrix remodeling and endothelial progenitor cells<br>Anna Bersano, G. Bedini, S. Nava, G. Alessandri, Francesco Acerbi, Paolo Ferroli, M. Ranieri, D. Riva (Milano/I)                                                                                                                          |
| 10:30 FR.01.07 | Analysis the response of angiogenic factors in endothelial cells derived from iPS cells of Moyamoya disease patients<br>Shuji Hamauchi, Hideo Shichinohe, Masaki Ito, Naoki Nakayama, Ken Kazumata, Kiyohiro Houkin (Sapporo/J)                                                                                                                                           |

**10:40 - 11:00 Coffee break with industrial exhibition and poster viewing**

## Scientific Programme

**Friday, July 3, 2015, 11:00 - 13:00 hrs**

### FR.02 Epidemiology and Natural Course

|                |                                                                                                                                                                                                                                                                 |
|----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chair          | Gary K. Steinberg (Stanford/USA)                                                                                                                                                                                                                                |
| 11:00 FR.02.01 | Epidemiology and Natural Course of Asymptomatic Adult MMD<br>Satoshi Kuroda (Toyama/J)                                                                                                                                                                          |
| 11:20 FR.02.02 | Unilateral MMD – different disease entities or the same as classical MMD<br>Kentaro Hayashi, Yuki Matsunaga, Yoichi Morofuji, Nobutaka Horie, Tsuyoshi Izumo, Takayuki Matsuo (Nagasaki/J)                                                                      |
| 11:40 FR.02.03 | Predictors of clinical and imaging deterioration in adult Moyamoya angiopathy<br>Dominique Hervé, Stephen Delorme, Christian Stapf, Abbas Taleb, Hugues Chabriat (Paris/F)                                                                                      |
| 12:00 FR.02.04 | Contralateral progression and its risk factor in surgically treated unilateral adult moyamoya disease with a review of pertinent literature<br>Sang-chul Lee, Jin Pyeong Jeon, Jeong Eun Kim, Young Seob Chung, Hyun-Seung Kang, Chang Wan Oh (Seongnam-si/ROK) |
| 12:10 FR.02.05 | Progressive occlusion of intracranial arteries and worsening of ischemic event among patients with adult Moyamoya disease<br>Akihito Sato, Takumi Kudo, Motoki Inaji, Yoji Tanaka, Kiishi Ishiwata, Kenji Ishii, Taketoshi Maehara, Tadashi Nariai (Tokyo/J)    |
| 12:20 FR.02.06 | Management of Moyamoya-associated aneurysms<br>Sepideh Amin-Hanjani (Chicago/USA)                                                                                                                                                                               |
| 12:30 FR.02.07 | Adult Moyamoya phenomenon in North of France: epidemiology, characteristics and management<br>Laurent Thines, H. Henon, Charlotte Cordonnier (Lille/F)                                                                                                          |
| 12:40 FR.02.08 | Moyamoya disease: A view from Russia<br>Margarita Khristoforova (St.-Petersburg/RUS)                                                                                                                                                                            |
| 12:50 FR.02.09 | Profiling of circulating microRNAs in patients with Moyamoya disease: differential expressions in discordant monozygotic twins<br>Haruto Uchino, Masaki Ito, Ken Kazumata, Shuji Hamauchi, Naoki Nakayama, Hidenao Sasaki, Kiyohiro Houkin (Sapporo/J)          |

**13:00 - 14:00 Lunch break with industrial exhibition and poster viewing**

**Friday, July 3, 2015, 14:00 - 16:00 hrs**

### FR.03 Diagnosis and Classification

- Chair Satoshi Kuroda (Toyama/J)
- 14:00 FR.03.01 Update on clinical and research topics regarding adult Moyamoya disease  
Jeong Eun Kim (Seoul/ROK)
- 14:20 FR.03.02 Suzuki's angiographic staging and surrounding topics  
Teiji Tominaga, Miki Fujimura (Sendai/J)
- 14:40 FR.03.03 Japan Adult Moyamoya (JAM) Trial and its up-to-date subsequent analyses  
Jun Takahashi, Takeshi Funaki, Susumu Miyamoto (Suita/J, Kyoto/J)
- 15:00 FR.03.04 Decrease of white matter apparent diffusion coefficient and improvement of executive functions after burr-hole surgery in Moyamoya adults  
Lionel Calviere, P. Loubiere, Isabelle Catalaa, Jean-Christophe Sol, Fabrice Bonneville, Vincent Larrue (Toulouse/F)
- 15:10 FR.03.05 Periventricular anastomosis in Moyamoya disease: noninvasive scoring of fragile collaterals with sliding-thin-slab maximum-intensity-projection MR angiography  
Yohei Mineharu, Takeshi Funaki, Jun Takahashi, Kazumichi Yoshida, Yasushi Takagi, Yasutaka Fushimi, Susumu Miyamoto (Kyoto/J, Suita/J)
- 15:20 FR.03.06 Aberrant regional homogeneity of resting-state executive control, default mode and salience networks in adult patients with Moyamoya disease  
Yu Lei, Jiabin Su, Wei Ni, Yuxiang Gu, Ying Mao (Shanghai/RC)
- 15:30 FR.03.07 The Berlin grading system stratify for clinical onset and perioperative complications in adult Moyamoya disease  
Daina Kashiwazaki, Masaki Koh, Naoki Akioka, Naoya Kuwayama, Kiyohiro Houkin, Satoshi Kuroda (Toyama/J, Sapporo/J)
- 15:40 FR.03.08 Validation and application for a new grading system of Moyamoya disease in adult patients  
Mario Teo, Sunil Furtado, Osamu F. Kaneko, Tej D. Azad, Jeremiah Johnson, Huy M. Do, Gary K. Steinberg (Stanford/USA)
- 15:50 FR.03.09 3D-planned EC-IC-bypass-operation for Moyamoya patients  
Eike Schwandt, Ali Ayyad, Alf Giese (Mainz/D)

**16:00 - 16:30 Coffee break with industrial exhibition and poster viewing**

**Friday, July 3, 2015, 16:30 - 18:45 hrs**

### FR.04 Treatment Concepts and Controversies

- Chair Sepideh Amin-Hanjani (Chicago/USA)
- 16:30 FR.04.01 Pro Conservative treatment Moyamoya Disease  
Martin Brown (London/UK)
- 16:45 FR.04.02 Pro Surgical treatment Moyamoya Disease  
Gary K. Steinberg (Stanford/USA)
- 17:00 Discussion
- 17:10 FR.04.03 Targeted revascularization surgery for MMD  
Satoshi Kuroda (Toyama/J)
- 17:25 FR.04.04 Non-targeted revascularization surgery for MMD  
Kiyohiro Houkin (Sapporo/J)
- 17:40 Discussion
- 17:50 FR.04.05 Utilizing flow measurements to optimize donor flow and extent of revascularization in Moyamoya Disease  
Fady T. Charbel (Chicago/USA)
- 18:05 FR.04.06 Changing patterns of cerebral hemodynamics after EC-IC revascularization in Moyamoya disease: multi-modality evaluation  
Yujun Liao, Bin Xu, Yuxiang Gu, Ying Mao (Shanghai/RC)
- 18:15 FR.04.07 Revascularisation surgery in juvenile Moyamoya syndrome – own experiences and review  
Peter Ulrich, Elke Januschek (Offenbach/D)
- 18:25 FR.04.08 Revascularization for moyamoya angiopathy in older adults  
Richard W. Williamson, Adib Abila, Joseph M. Zabramski, Peter Nakaji, Robert F. Spetzler, John E. Wanebo (Phoenix/USA)
- 18:35 FR.04.09 Outcome of revascularization surgery for elderly patients with Moyamoya disease over the age of 60 years: Single institute experience  
Miki Fujimura, Kuniyasu Niizuma, Hidenori Endo, Hiroyuki Sakata, Teiji Tominaga (Sendai/J)

**Saturday, July 4, 2015, 08:30 - 10:30 hrs**

### SA.01 Pediatric MMD

- Chair Kiyohiro Houkin (Sapporo/J)
- 08:30 SA.01.01 Ischemic stroke in pediatric patients beyond MMD  
Kees Braun (Utrecht/NL)
- 08:50 SA.01.02 Cognitive functions in children and adults with moyamoya vasculopathy: a systematic review and meta-analysis.  
Annick Kronenburg, Esther van den Berg, Albert van der Zwan, Kees P.J. Braun, Lionel Calviere, Catharina J.M. Klijn (Utrecht/NL, Toulouse/F, Nijmegen/NL)
- 09:10 SA.01.03 Pro - direct revascularization strategies in pediatric MMD  
Marcus Czabanka (Berlin/D)
- 09:25 SA.01.04 Pro - indirect revascularization in pediatric Moyamoya disease  
Edward Smith (Boston/USA)
- 09:40 Discussion
- 09:50 SA.01.05 Moyamoya disease in children – new insights from imaging and surgical treatment  
Thomas Blauwblomme, Bertrand Mathon, Hervé Lemaitre, Olivier Naggara, Manoelle Kossorotof, Marie Bourgeois, Stephanie Puget, Philippe Meyer, Francis Brunelle, Michel Zerah, Nathalie Boddaert, Christian Sainte-Rose (Paris/F)
- 10:00 SA.01.06 Combined direct/indirect anastomosis in Moyamoya disease: results of 358 surgeries in Hokkaido University  
Kiyohiro Houkin (Sapporo/J)
- 10:10 SA.01.07 Characteristics and treatment for young patients with Moyamoya disease  
Toshiaki Hayashi, Reizo Shirane, Hiroshi Karibe, Miki Fujimura, Teiji Tominaga (Sendai/J)
- 10:20 SA.01.08 Encephaloduromyosynangiosis treating moyamoya disease in young children  
W. Shen (Shanghai/RC)

**10:30 - 11:00 Coffee break with industrial exhibition and poster viewing**

**Saturday, July 4, 2015, 11:00 - 13:00 hrs**

### SA.02 Genetics and Molecular Biology of MMD

- Chair Elisabeth Tournier-Lasserre (Paris/F)
- 11:00 SA.02.01 Molecular regulation of angiogenesis  
Ralf H. Adams (Münster/D)
- 11:25 SA.02.02 Moyamoya genetics beyond RNF 214  
Elisabeth Tournier-Lasserre (Paris/F)
- 11:50 SA.02.03 Effects of EDAS surgery on the circulating angiogenic factors of patients with Moyamoya disease and intracranial atherosclerosis  
Nestor Gonzalez, Azim Laiwalla, Raymond Liou, Yinn Ooi, Jeffrey Saver (Los Angeles/USA)
- 12:00 SA.02.04 Temporal profile of magnetic resonance angiography of RNF213, moyamoya disease susceptibility gene, deficient mice with immunologic adjuvant administration  
Atsushi Kanoke, Miki Fujimura, Kuniyasu Niizuma, Taku Fujimura, Shigeo Kure, Teiji Tominaga (Sendai/J)
- 12:10 SA.02.05 Analysis of genetic variant RNF213 (c. 14576G>A) in 5 pairs of Japanese identical twin with Moyamoya disease of juvenile onset  
Maki Mukawa, Tadashi Nariai, Takumi Kudo, Kazuki Sumita, Hideaki Onda, Hidetoshi Kasuya, Taketoshi Maehara, Hiroyuki Akagawa (Tokyo/J)
- 12:20 SA.02.06 Significance of narrow carotid canal and the RNF213 risk variant for the diagnosis of Moyamoya disease and middle cerebral artery occlusion  
Yohei Mineharu, Takaaki Motimoto, Yasushi Takagi, Toshiaki Hitomi, Hatasu Kobayashi, Shoichi Tani, Yasushi Ueno, Hirotoshi Imamura, Kenichi Todo, Takeshi Funaki, Akio Koizumi, Nobuyuki Sakai, Susumu Miyamoto (Kyoto/J)
- 12:30 SA.02.07 Investigation of RNF213 p.R4810K and A4399T in a high-prevalence town of Moyamoya disease in China  
Hanqiang Jiang, Wei Ni, Yu Lei, Yanjiang Li, Yuxiang Gu, Ying Mao (Shanghai/RC)
- 12:40 SA.02.08 Genetic analysis of RNF213 variant in Moyamoya disease, Quasi-moyamoya disease and various cerebrovascular diseases  
Satoru Miyawaki, Hideaki Imai, Masahiro Shimizu, Shinichi Yagi, Hideaki Ono, Akitake Mukasa, Hirofumi Nakatomi, Tsuneo Shimizu, Nobuhito Saito (Tokyo/J, Kumagaya/J)

## Scientific Programme

12:50 SA.02.09 Genome-wide CNV array analysis in parent-offspring pairs with Moyamoya disease with and without clinical anticipation  
Masaki Ito, Ken Kazumata, Haruto Uchino, Yuuka Hama, Syuji Hamachi, Hidenao Sasaki, Kiyohiro Houkin (Sapporo/J)

**13:00 - 14:00 Lunch break with industrial exhibition and poster viewing**

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## Scientific Programme

**Saturday, July 4, 2015, 14:00 - 15:50 hrs**

**SA.03 Moyamoya Syndrom and Atypical MMD/ Free Topics**

Chair Satoshi Kuroda (Toyama/J)

14:00 SA.03.01 Clinical and radiological features of quasi-Moyamoya disease  
Kentaro Hayashi, Yuki Matsunaga, Yoichi Morofuji, Nobutaka Horie, Tsuyoshi Izumo, Takayuki Matsuo (Nagasaki/J)

14:20 SA.03.03 Diagnosis and Treatment of Moyamoya Syndrome  
Satoshi Kuroda (Toyama/J)

14:40 SA.03.04 Moyamoya Syndrome in Caucasians  
Güliz Acker, Susanne Goerdes, Peter Schmiedek, Marcus Czabanka, Peter Vajkoczy (Berlin/D, Mannheim/D)

15:00 SA.03.05 Surgical outcomes following encephaloduroarteriosynangiosis in adult moyamoya disease associated with type 2 diabetes  
Lian Duan, Bin Ren, Zheng-Shan Zhang (Beijing/RC)

15:10 SA.03.06 Individualized EC-IC revascularization in the treatment of advanced Moyamoya disease: surgical techniques and mid-term follow-up results  
Bin Xu, Yujun Liao, Yuxiang Gu, Ying Mao (Shanghai/RC)

15:20 SA.03.07 Attempt of quantitative evaluation of cerebral blood flow using estimated arterial spin labeling method for Moyamoya disease  
Yoshifumi Higashino, Makoto Isozaki, Ken-ichiro Kikuta, Hirohiko Kimura, Hidehiko Okazawa (Fukui/J)

15:30 SA.03.08 The importance of blood pressure control to prevent cerebral hyper- or hypoperfusion syndrome after direct revascularisation surgery for moyamoya steno-occlusive cerebrovascular disease  
Elke Januschek, Peter T. Ulrich (Offenbach)

15:40 SA.03.09 Rescue strategies for failed revascularization in MMD and MMS  
Gary K. Steinberg (Stanford/USA)

**15:50 - 16:30 Coffee break with industrial exhibition and poster viewing**

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**Saturday, July 4, 2015, 16:30 - 18:30 hrs**

| <b>SA.04</b>   | <b>New Experimental Approaches</b>                                                                                                                                                                                                                                                                       |
|----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chair          | Marcus Czabanka (Berlin/D)                                                                                                                                                                                                                                                                               |
| 16:30 SA.04.01 | Experimental stroke treatment – implications for MMD<br>Matthias Endres (Berlin)                                                                                                                                                                                                                         |
| 16:55 SA.04.02 | Biomarkers in Moyamoya disease<br>Edward Smith (Boston/USA)                                                                                                                                                                                                                                              |
| 17:20 SA.04.03 | Therapeutic angiogenesis using myoblast-mediated gene therapy in experimental EMS model of mouse<br>Aiki Marushima, Nils Hecht, Melina Nieminen-Kelhä, Irina Kremenetskaia, Roberto Gianni Barrera, Johannes Woitzik, Andrea Banfi, Peter Vajkoczy (Berlin, Basel/CH)                                    |
| 17:30 SA.04.04 | Predicting cerebral hyperperfusion syndrome following STA-MCA bypass based on 3.0T intraoperative perfusion-weighted MRI<br>Fengping Zhu, Yuxiang Gu, Bin Xu, Itsu Sen, Wei Zhu, Ying Mao (Shanghai/RC, Sydney/AUS)                                                                                      |
| 17:40 SA.04.05 | Significance of hemodynamic stress distribution as a possible clinical marker of ischemic symptom in patients with moyamoya disease<br>Satoshi Takahashi, Yoshio Taniyaki, Kazunori Akaji, Tadashige Kano, Kazunari Yoshida, Ban Mihara (Tokyo/J, Iseaki/J)                                              |
| 17:50 SA.04.06 | Serial measurement of cerebral hemodynamics with ASL-MRI after indirect bypass surgery for patients with Moyamoya disease<br>Naoki Taira, Yoji Tanaka, Motoki Inaji, Takumi Kudoh, Taketoshi Maehara, Tadashi Nariai (Tachikawa/J, Tokyo/J)                                                              |
| 18:00 SA.04.07 | Amelioration of brain metabolism and higher brain function by surgical re-vascularization against adult Moyamoya disease – A positron emission tomography study<br>Takumi Kudo, Tadashi Nariai, Motoki Inaji, Chihiro Hosoda, Shihori Hayashi, Taketoshi Maehara, Kiishi Ishiwata, Kenji Ishii (Tokyo/J) |
| 18:10 SA.04.08 | Postoperative executive function in adult Moyamoya disease: a preliminary study of its functional anatomy and behavioral correlates<br>Yu Lei, Hanqiang Jiang, Bin Xu, Yuxiang Gu, Ying Mao (Shanghai/RC)                                                                                                |

- P 01 Moyamoya disease: Two different techniques in the same patient – case report and surgical considerations  
Alexandre Canheu, Carlos Alexandre Zicarelli, Marcio Francisco Lehmann, Sergio Murilo Georgeto, Marcos Antonio Dias, Fahd Haddad, Paulo Henrique Pires de Aguiar (Londrina/BR)
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- P 03 Distinct chromosomal rearrangements in two novel Moyamoya syndromes  
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### Registration

Registration prior to the meeting can be made online via [www.moyamoya2015.com](http://www.moyamoya2015.com) and on site at the meeting office.

### Registration Fee

| Entire meeting participation          | From May 4, 2015 |
|---------------------------------------|------------------|
| Specialists                           | 350 €            |
| Specialists EANS members <sup>1</sup> | 335 €            |
| Residents <sup>2</sup>                | 250 €            |
| Residents EANS members <sup>12</sup>  | 240 €            |
| Students <sup>2</sup>                 | 75 €             |
| Get Together                          | 35 €             |

<sup>1</sup> Only for EANS Individual Members. Please mention that you are an individual member of the EANS when you register. All registrations will be double-checked with the EANS office and if necessary rectified.

<sup>2</sup> Residents, nurses and students need to send a valid certificate (official certificate of the head of department or student ID) via fax (+49 30 284499-11) or email ([moyamoya2015@porstmann-kongresse.de](mailto:moyamoya2015@porstmann-kongresse.de)) to Porstmann Kongresse GmbH. Late submission will not be accepted. Please send your certificate at your earliest convenience after online registration.

The registration fee for the meeting includes:

- Meeting documents
- Final programme including abstracts
- Coffee & lunch breaks

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Rooms at the below mentioned hotels can be booked via the PCO - Porstmann Kongresse GmbH. Please send your reservation request via email to: moyamoya2015@porstmann-kongresse.de

| Hotel                     | Address                        | Distance to venue |
|---------------------------|--------------------------------|-------------------|
| Mercure Hotel Berlin City | Invalidenstr. 38, 10115 Berlin | 5 min walking     |
| Nordic Hotel              | Invalidenstr. 98, 10115 Berlin | 4 min walking     |

### Instructions for Presentations

All speakers are requested to be at the registration counter at least 15 minutes before the session starts. Powerpoint presentations have to be checked in at the media technician desk (directly in the lecture hall), not later than one hour before the session starts if possible at the last break ahead the session. Personal laptops will not be allowed. Speakers are kindly asked to strictly adhere to the allocated presentation time.

### Poster Presentations

Poster authors are responsible for setting up their poster at the beginning of the meeting on Friday, July 3, 10.00 hrs. The posters have to be removed at the last day of the meeting (Saturday, July 4, 2015, 18.00 hrs at the latest). The congress organization is not responsible for lost or damaged posters, which are not removed.

### Congress Language

The congress language will be English. No simultaneous translation.

### Get Together

**Friday, July 3, 2015 from 19.30 – 22.30 hrs**

**at the Hörsaalruine der Charité | Lecture hall ruin of the Charité**



Price per person: 35 €  
Snacks and drinks will be served. With Live music from the Duo "Stand-Arts"  
Guided tours through the Berlin Museum of Medical History will start at 20.00 and 20.30 hrs.

Address:  
Campus Charité Mitte  
Berliner Medizinhistorisches Museum  
Charitéplatz 1 (Virchowweg 17)  
10117 Berlin | Germany

Approx. 5 minutes walking distance from the Kaiserin-Friedrich-Haus



## Abstracts

### Fr.01.01

### Vascular development and plasticity

Hellmut G. Augustin and co-workers<sup>1,2,3</sup>

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The field of angiogenesis research has primarily focussed on the mechanisms of sprouting angiogenesis. Yet, vessel sprouts need to anastomose to establish a three dimensional vascular network that is hierarchically structured in arteries, capillaries and veins in order to facilitate directional blood flow. Moreover, the growing vasculature is extensively remodeled. This 'trimming' includes distinct processes of vascular pruning, the regression of selected vascular branches. Angiopoietin and Wnt signaling play key roles in the later steps of the angiogenic cascade as it relates to vessel maturation, remodeling, and pruning. This presentation will summarize the state-of-the-art of current Ang/Tie research with a focus on novel aspects of Ang/Tie biology relating to angiocrine signaling, the microenvironmental control through paracrine acting endothelial cell-derived growth factors. Moreover, a possible molecular link between Wnt and NFAT signaling in the pathogenesis of Moyamoya disease will be disclosed.

FR.01.04

### ***In vitro* and *in vivo* evidence on inhibition of angiogenesis by the Moyamoya susceptible gene and its mutation, RNF213 R4810K**

Akio Koizumi<sup>1</sup>, Hatasu Kobayashi<sup>1</sup>, Yoshiko Matsuda<sup>2</sup>, Toshiaki Hitomi<sup>1</sup>, Hiroko Okuda<sup>1</sup>, Hirotomo Shioi<sup>1</sup>, Tetsuya Matsuda<sup>3</sup>, Hirohiko Imai<sup>3</sup>, Masakatsu Sone<sup>4</sup>, Daisuke Taura<sup>4</sup>, Kouji H. Harada<sup>1</sup>, Yasushi Takagi<sup>2</sup>, Susumu Miyamoto<sup>2</sup>, Toshiyuki Habu<sup>5</sup>

<sup>1</sup>Department of Health and Environmental Sciences, <sup>2</sup>Department of Neurosurgery, <sup>3</sup>Department of Systems Science, <sup>4</sup>Department of Diabetes, Endocrinology and Nutrition, <sup>5</sup>Radiation Biology Center, Kyoto University, Kyoto, Japan

**Objective:** RNF213 (myosin), which is an AAA+ ATPase, is the susceptibility gene for moyamoya disease (MMD) and its p.R4810K polymorphism (rs112735431) is a founder polymorphism for East Asian patients. Because its penetrance is very low and only limited numbers of carriers develop MMD, environmental factors are speculated to trigger MMD development. However, the role of RNF213 R4810K and associated environmental factors in MMD etiology remains unknown.

**Methods and Results:** RNF213 was upregulated by interferon (IFN)- $\beta$  in endothelial cells (ECs) through STATx in the promoter. Induction of RNF213 wild type by IFN- $\beta$  lowered angiogenesis in ECs, while upregulation of R4810K lowered angiogenesis without exposure to IFN- $\beta$ . We then investigated the effects of mutagenesis of glutamic acid of the Walker B motif and deletion of the first AAA+ in ECs on angiogenesis. We found the former inhibited angiogenesis while the latter did not, suggesting that oligomers once formed inhibited angiogenesis, but failure of oligomerization did not. We investigated the effects of R4810K on ATPase activity and found that RNF213 R4810K, similar to WEQ, decreased ATPase activity, suggesting that it impairs angiogenesis by stabilizing oligomers. To confirm the lowered angiogenic effect of RNF213 upregulation on angiogenesis *in vivo*, vascular EC- or smooth muscle cell (SMC)- specific RNF213 R4757K (R4810K orthologue) or wild type transgenic mice were exposed to hypoxia for 2 weeks. Cerebellar angiogenesis was suppressed in mice overexpressing RNF213 R4757K in ECs ( $p < 0.05$ ), although none of other mice showed suppressed cerebellar angiogenesis.

**Conclusions:** Our study suggests the importance of inflammatory signals as environmental factors and predicts that R4810K carriers are more susceptible to cerebral hypoxia than the wild type. Further study is needed to investigate the roles of angiogenesis in the entire pathological process of MMD.

FR.01.05

### **Functional characteristics of endothelial cells in Moyamoya disease**

Kinga G. Blecharz<sup>1</sup>, Dietmar Frey<sup>2</sup>, Tobias Schenkel<sup>1</sup>, Michael Fromm<sup>3</sup>, Irina Kremenetskaia<sup>1</sup>, Marcus Czabanka<sup>2</sup>, Peter Vajkoczy<sup>1,2</sup>

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Moyamoya disease (MMD) is a rare stenooclusive cerebrovascular disorder which often results in hemorrhagic and ischemic strokes. In contrast to atherosclerotic cerebrovascular disease (ACVD) MMD is characterized by a highly plastic and at the same time instable pathological neovascularization which is prone to rupture, although the same ischemic stimulus has been implicated for both disorders. To understand the molecular mechanisms underlying the cerebrovascular instability in MMD, we analyzed MMD and ACVD patients' sera for levels of vessel destabilizing factors and investigated the effect of these sera on cerebral endothelial cells (ECs) *in vitro*. We found an induction of endothelial expression and secretion of VEGF, angiopoietin-2 and MMP-9 in cerebral ECs by MMD sera when compared to ACVD, while systemic concentrations of these cytokines in both patient groups did not differ. In addition, MMD sera induced a down-regulation of endothelial cell-cell contacts (tight junctions and adherens junctions) accompanied by a loss of EC integrity. These effects were absent or inverse in ECs of non-brain origin suggesting brain endothelium specificity. Finally, these destabilizing responses of brain ECs to MMD sera could be suppressed by the inhibition of the VEGF/VEGFR-2 signaling pathway. These data define brain ECs as the potential source of vessel destabilizing mediators inducing the high plasticity state and disintegration of the cerebrovascular system in MMD in a paracrine manner. Our findings help to understand the high incidence of cerebrovascular hemorrhagic and ischemic events in MMD and may provide the basis for future preventive treatment strategies

FR.01.06

### Pathogenesis of Moyamoya disease: the role of angiogenesis, extracellular-matrix remodeling and endothelial progenitor cells

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The pathogenesis of moyamoya disease (MMD) is unknown. Many research projects have focused on angiogenic and vasculogenic mechanisms, which are believed to be induced by ischemic and hypoxic phenomena. Increased expression of angiogenic factors such as hypoxia-inducing factor-1 $\alpha$  (HIF-1 $\alpha$ ), vascular endothelial growth factor (VEGF), basic fibroblast growth factor (b-FGF), granulocyte colony stimulating factor (G-CSF), transforming growth factor-b1 (TGFb1), and hepatocyte growth factor (HGF) was observed both in CSF and serum of MMD patients as well as around the affected vasculature and in glial cells. An impaired balance between matrix metalloprotease (MMPs) and their tissue inhibitors has been also observed in MMD patients supporting the hypothesis that an excessive accumulation of smooth muscle cells (SMCs) and an abnormal production of extracellular matrix (ECM) components may induce vessel stenosis or occlusion. Furthermore endothelial progenitor cells (EPCs), that are a subset of bone-marrow derived cells, that, following endothelial damage, home to sites of neovascularization have been investigated to better understand and characterize MMD pathogenesis. Although the results of preliminary studies are controversial a possible role of these cells in the development of vessel occlusions as well as in inducing vasculogenesis and angiogenesis has been highlighted. However, the research on pathogenic mechanism of MMD is still in its infancy. Although the results from studies on EPCs as well as research on several angiogenic, vasculogenic and cellular proliferative pathways changes might provide some insights into the disease pathophysiological mechanisms, these findings are still inadequate to clarify the pathogenesis of MMD.

FR.01.07

### Analysis the response of angiogenic factors in endothelial cells derived from iPS cells of Moyamoya disease patients

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**Objective:** Past research reported several angiogenic factors are upregulated in various parts of the body in patients with moyamoya disease. However, whether these upregulated factors are causal agents of Moyamoya disease or simply reflect the cerebral ischemia have not been investigated. We analyzed the responsibilities of angiogenic factors to endothelial cells derived from iPS cells of moyamoya disease.

**Methods:** Three iPS cell lines are established from PBMCs of Moyamoya disease patients carrying RNF213 R4810K. Pre-established three iPS cell lines from healthy persons are used for control. Endothelial differentiation was conducted on matrigel layer with the treatment of BMP4, VEGF, bFGF, SB431542 for 6 days. CD31+VE-cadherin+ cells were purified by cell sorter. These endothelial cells were tested for CCK8-cell proliferation assay, scratch cell migration assay, and *in-vitro* angiogenesis assay. These experiments were performed on the either conditions of no growth factor, VEGF 50ng/ml, bFGF 50ng/ml, TGF-beta 50ng/ml, or BMP4 50ng/ml. Student's t-test was used for data analysis. Endothelial cells were also analyzed by DNA microarray.

**Results:** Endothelial proliferative activity after three days of culture and cell migration rate after 12hours showed no significant difference between controls and Moyamoya disease groups on any conditions. On the contrary, *in-vitro* angiogenesis was significantly impaired in Moyamoya disease on all conditions even in no treatment of angiogenic factors ( $p<0.05$ ) implicating the impaired response to some angiogenesis inducing agents such as extracellular matrix rather than angiogenic factors. In microarray analysis, KEGG pathway analysis of genes downregulated in Moyamoya disease by more than three-fold (Welch's t-test,  $P<0.01$ ) showed extracellular matrix receptor related genes were significantly downregulated in moyamoya disease.

**Conclusions:** Angiogenic activity was impaired in endothelial cells of moyamoya disease, although moyamoya disease specific response to angiogenic factors couldn't be detected. Angiogenic response to ECM should be investigated in the future.

## FR.02.01

**Epidemiology and Natural Course of Asymptomatic Adult MMD**

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Recent development of a non-invasive MR examination has increased the opportunity to identify asymptomatic patients with moyamoya disease who have experienced no cerebrovascular events. Previous nation-wide survey in Japan revealed that 7 of 34 conservatively treated patients developed any cerebrovascular events, including TIA in three patients, ischemic stroke in one, and hemorrhagic stroke in three. As the results, the annual risk of any cerebrovascular events and stroke was 5.7% and 3.2%, respectively. Disturbed cerebral hemodynamics at initial diagnosis was significantly linked to ischemic episodes ( $P < 0.05$ ). Disease progression during follow-up periods also highly caused ischemic episodes. However, their clinical features, prognosis, and treatment strategy are still unclear because of small number of subjects and short follow-up periods. Therefore, we have designed Asymptomatic Moyamoya Registry (AMORE) Study in Japan. The objectives of this nation-wide, multi-center prospective study are to clarify long-term prognosis of asymptomatic patients with moyamoya disease and to determine the risk factors to cause ischemic and hemorrhagic stroke in them. In this lecture, we review the published data on asymptomatic moyamoya disease and report the on-going multi-center prospective cohort study, Asymptomatic Moyamoya Registry (AMORE) study. We would like to emphasize the importance to determine the clinical features, prognosis, and treatment strategies of asymptomatic moyamoya disease in very near future.

## FR.02.02

**Unilateral MMD – different disease entities or the same as classical MMD**

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**Objective:** To estimate total number of patients, the annual incidence rate and prevalence of MMD, unilateral MMD and quasi-MMD in Japan, nationwide epidemiological survey was conducted. Furthermore, to identify the clinical features of unilateral MMD, second survey was conducted.

**Methods:** The questionnaire was directly mailed to 2998 departments of neurosurgery, neurology and pediatrics. Secondary, the questionnaire was directly mailed to 241 departments that reported treating unilateral MMD and quasi-MMD patients in a primary survey. We ascertained the sex, age, family history, clinical manifestation, radiological findings, treatments, course of the disease, and daily activity of unilateral MMD.

**Results:** A total of 1183 department replied to the questionnaire (response rate; 39.5%) It is estimated that 6670.9 MMD patients, 840.5 unilateral MMD patients and 430.4 quasi-MMD patients exist in Japan. The annual incidence rate of MMD, unilateral MMD and quasi-MMD are 1.13, 0.23 and 0.11/100,000 respectively, and the prevalence is 5.22, 0.66 and 0.34/100,000 respectively. A total of 114 departments replied to the second survey. The data of 203 patients (118 female and 85 male; female to male ratio 1.4) were registered and analyzed. Mean age was 40.2 years old with a peak of the fifties. Twenty-one patients (10.7%) exhibited familial MMD. Their imaging study type included ischemic type in 64 patients (32.5%), bleeding type in 51 (25.9%), and normal in 82 (41.6%). The development of moyamoya vessels were mild in 78 cases (43.9%) and most cases (81.1%) were accompanied with cerebral hypoperfusion. Medical treatment or vascular reconstruction were employed for the more than half of the patients.

**Conclusions:** This nationwide study reports the current epidemiologic status of MMD, unilateral MMD and quasi-MMD in Japan. Unilateral MMD was predominant in adult and the development of moyamoya vessel was relatively less.

FR.02.03

### Predictors of clinical and imaging deterioration in adult Moyamoya angiopathy

*Dominique Hervé, Stephen Delorme, Christian Stapf, Abbas Taleb, Hugues Chabriet  
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**Objective:** The clinical course of moyamoya angiopathy (MMA) in adults appears widely variable. Some patients develop severe disability over a few months while others remain clinically asymptomatic over decades. Although a past history of stroke has been recognized as a prognostic factor in MMA, no other predictor of clinical deterioration has been validated in non-operated adult patients.

To evaluate various potential predictors of clinical and radiological deterioration in a cohort of MMA adult patients who were not operated.

**Methods:** Clinical and imaging parameters potentially predicting the progression of symptoms or brain lesions in MMA were investigated in an ongoing prospective mono-centric cohort of MMA patients using a standardized protocol. Analysis was performed for determining in MMA patients the predictors of any incident stroke (outcome 1) and of any incident stroke or ischemic or hemorrhagic lesion on MRI (outcome 2). The analysis was performed separately in the whole population of non-operated MMA patients and in patients with bilateral MMA having a past history of stroke.

**Results:** 53 non-operated patients with MMA were followed over a mean duration of  $3.7 \pm 2.8$  years. Univariate analysis showed that hypercholesterolemia ( $p=0.02$ ) and short delay since last stroke ( $p=0.05$ ) were associated with incident stroke or vascular lesion on MRI. In the subgroup of patients who already had a stroke and with bilateral MMA ( $n=26$ ), alterations of cerebrovascular reserve ( $p = 0.03$ ) was the only predictor of incident stroke events. Multivariate analysis did not show any significant result most likely due to the small size of our sample and insufficient power.

**Conclusions:** These preliminary results suggest that vascular risk factors and the delay since last stroke predict stroke events and accumulation of cerebrovascular lesions in MMA. In patients with bilateral MMA and a past history of stroke, alterations of cerebrovascular reserve are also found predicting MMA worsening. A larger sample will help confirming that these predictors should be actually considered in the management of patients with MMA.

FR.02.04

### Contralateral progression and its risk factor in surgically treated unilateral adult moyamoya disease with a review of pertinent literature

*Sang Chul Lee, Jin Pyeong Jeon, Jeong Eun Kim, Young Seob Chung, Hyun-Seung Kang, Chang Wan Oh  
Department of Neurosurgery, Seoul National University College of Medicine, Seoul, Korea*

**Objective:** The incidence and natural history of unilateral moyamoya disease(MMD) in a general MMD population have not been fully described. Particularly, the fate of the contralateral unaffected side of the unilateral MMD after revascularization surgery in adults has not been well described in detail. The aim of the study was to reveal the angiographic progression rate and the risk factors associated with the unaffected contralateral side in unilateral adult MMD patients who underwent surgical revascularization for hemodynamic insufficiency in the affected side.

**Methods:** Patients who were diagnosed as unilateral MMD between 2001 and 2011 at a single institution were retrospectively evaluated. A total of fifty-seven (8.5%) unilateral MMD patients were recruited. Among them, 41 (72%) underwent surgical treatment for hemodynamic impairment on the affected side and were included in our analysis. We reviewed medical and radiological records including gender, age, hypertension (HTN), diabetes mellitus (DM), dyslipidemia, history of smoking, familial history of MMD, initial presenting symptoms, surgical treatment methods, radiologic data including Suzuki stage, and the presence of disease progression. Univariate and multivariate analyses were conducted to determine risk factors.

**Results:** Thirty-one patients were female (75.6%) and mean age at diagnosis was  $41.1 \pm 10.5$  years. Contralateral minimal abnormality on initial angiography occurred in 18 patients (43.9%). Among them, 6 patients (33.3%) experienced contralateral angiographic progression during the mean follow-up of 34 months. The presence of a contralateral angiographic abnormality on initial angiography was a statistically significant risk factor for progression (OR, 49.00;  $p=0.04$ ). Younger age at diagnosis ( $p=0.046$ ) was statistically significant in the univariate analysis, but age was not a significant factor in the multivariate analysis ( $p=0.82$ ). Other variables did not show statistical significance.

**Conclusions:** The presence of contralateral angiographic abnormality on initial angiography is a statistically significant risk factor for contralateral angiographic progression in unilateral adult MMD patients who have undergone revascularization surgery for hemodynamic insufficiency in the affected side.

FR.02.05

### Progressive occlusion of intracranial arteries and worsening of ischemic event among patients with adult Moyamoya disease

Akihito Sato<sup>1</sup>, Takumi Kudo<sup>1</sup>, Motoki Inaji<sup>1</sup>, Yoji Tanaka<sup>1</sup>, Kiishi Ishiwata<sup>2</sup>, Kenji Ishii<sup>1</sup>, Taketoshi Maehara<sup>1</sup>, Tadashi Nariai<sup>1</sup>

<sup>1</sup>Department of Neurosurgery, Tokyo Medical and Dental University, <sup>2</sup>Research Team for Neuroimaging, Tokyo Metropolitan Institute of Gerontology

**Objective:** To assess the frequency of progressive intracranial arterial occlusion in patients with adult moyamoya disease.

**Methods:** From January 1981 to December 2013, we have treated 330 patients with adult moyamoya disease of 18 years or older. We conducted indirect bypass surgery in 100 patients who were recognized to have hemodynamic deficiency determined with DSC-MRI and/or 150 gas PET. The other 230 were conservatively followed up. 163 of them were repeatedly followed up by MRI/A in outpatient clinic. Occurrence rate of progressive vessel occlusion and worsening of ischemic event were assessed in both the operated and the non-operated groups.

**Results:** Among 100 operated patients, 7 presented re-worsening of ischemic symptom after amelioration of cerebral circulation by the initial surgery. 6 presented with TIA and 1 presented with infarction. 2 were caused by progression of internal carotid artery occlusion of non-operated side and 5 were caused by occlusion of posterior cerebral artery (PCA) of the operated side. Interval from the initial operation to the event was 50 months in average (10-120 months). Among 163 conservatively observed cases, 19 (12%) presented cerebrovascular event. 14 were hemorrhagic event and the other 5 (3%) presented ischemic event due to progressive occlusion of cerebral vessels. All of 5 presented occlusion of PCA and 4 of them presented cerebral infarction. The other 144 (88%) did not experience any cerebrovascular event after mean follow-up period of 66 months (5-245 months). Overall, among 263 followed up cases, 12 (4.5%) presented progressive occlusion of cerebral vessels in adulthood and 10 (83%) of the occluded vessel were PCA.

**Conclusions:** In both the operated and non-operated cases, further worsening of cerebral vessel occlusion may occur in some adult patients. It should be noted that progressive occlusion of PCA may be the major cause of worsening of ischemic symptom in adulthood.

FR.02.07

### Adult Moyamoya phenomenon in North of France: epidemiology, characteristics and management

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**Objective:** Moyamoya disease has been only scarcely described in France. We therefore attempted to study its epidemiology, characteristics and management in our region.

**Methods:** Lille University Hospital is covering an area of 4 million people. We started to prospectively register all moyamoya patients referred to our institution since 2009. Their demographic, clinical and radiological characteristics were recorded. All patients were assessed and then followed-up with a standardized radiological work-up using brain MRI-MRA, high-resolution transcranial Doppler and SPECT with acetazolamide challenge, and 6 vessels cerebral angiography. Management decisions were made during multidisciplinary cerebrovascular meetings and patients were offered cerebral revascularization in case of recurring or crescendo symptoms in association with severe cerebral hypoperfusion. Combined technique (direct EC-IC bypass + indirect encephalosynangiosis) was the first line treatment option.

**Results:** Thirty-nine patients were followed-up. The estimated incidence was 0.14 per 100,000 person-years. The female to male ratio was 2.3:1 and mean age was 40. Typical bilateral moyamoya (definite case) was found in 18 patients (46%). Unilateral moyamoya (probable case) was found in 8 cases (21%) and Moyamoya-like (M1 occlusion) was identified in 13 cases (33%). Two patients had a syndromic form: 1 unidentified dysmorphism and 1 with a deficit in brcc3 deubiquitinase. Four patients died during follow-up (10%), 1 postoperatively and 1 post-embolization. The mode of presentation was ischemic in 56%, hemorrhagic in 28%, mixed in 10% and 5% of patients were asymptomatic. Sixteen patients (41%) were surgically treated: 12 with a combined technique (75%) and 3 with an indirect technique alone.

**Conclusions:** Initially thought to be an exotic disease occurring primarily in Asian countries, the number of patients diagnosed and treated in North of France is improving probably due to an increased awareness of the condition leading to appropriate radiological identification and therapeutic management.

FR.02.08

### Moyamoya disease: A view from Russia

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**Objective:** The etiology of moyamoya disease is unknown, although the disease is much more widespread in Asia, the Japanese in particular. This may be explained by the interplay of the genetic and the ethnic factors. Cases of moyamoya disease exist in America, Europe and Russia but are less frequent.

**Methods:** Complex investigation and treatment of 40 patients with moyamoya disease at the Russian A.L.Polenov Neurosurgical Institute between 1991 and 2014. The patients were diagnosed using cerebral angiography and MR imaging according to the guidelines-2001. Cases of unilateral disease in children and moyamoya syndrome were excluded from the study group. The follow-up period was 1 to 14 years (on average 7,5 years). We register 2 new patients annually. The patients are aged from 3 to 55. The study group includes 17 children (aged 3-17) and 23 adults (aged 18-55). Ethnic distribution within the study group was: 36 Europeans to 4 Asian patients. Generally, there was a 1.5:1,0 female/male distribution, but in children 1,8:1 (1.6:1 in European children). The initial symptoms in children were: ischemia- in 11 cases (64.8 %), hemorrhage- in 3 cases (17.6%), headache- in 3 cases (17,6%). In adult patients the clinical presentation was: hemorrhage - in 8 cases (34,7%), ischemia- in 15 cases (65, 3%). In all children and several adults hemorrhage onset develops into ischemia, and they represent a combined type of disease. Out of 40 moyamoya patients 28 (70%) were operated on and 12 (30%) patients were treated conservatively . The most effective operation was a combined revascularization applying STA-MCA anastomosis + EMS or (in case the former was technically impossible) EDAS and EMS using a temporal muscle fragment split in two parts.

**Results:** There are differences in the clinical course of the disease in our study group. In our series the symptoms of the disease have been more severe in children. Indications for surgical treatment of moyamoya patients require a clearer definition. The described differences of moyamoya clinical course in distinct territories and ethnic groups require verification, so a worldwide database of moyamoya patients is required and should be used to study the eventual influence of genetic differences on the incidence and course of moyamoya disease and to establish new treatment strategies.

FR.02.09

### Profiling of circulating microRNAs in patients with Moyamoya disease: differential expressions in discordant monozygotic twins

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The pathogenesis of moyamoya disease (MMD) may involve genetic and nongenetic factors, but its etiology remains unknown. We hypothesized the epigenetic alterations of patients may be related to the development of MMD and screened plasma microRNA (miRNA) profiles to identify biomarkers for MMD. This study included a pair of monozygotic twins discordant for MMD and 10 adult MMD patients along with 10 healthy volunteers. We conducted genome-wide microarray analysis of the plasma samples and examined the difference in the expression of miRNAs between the patients and the controls. Then, we identified several differentially expressed plasma miRNAs in the monozygotic twin suffering from MMD and the other adult patients in common. The predicted target genes of these miRNAs included several MMD associated genes such as RNF213, PDGFRB, TGFBI, TIMP2, and BRCC3. Furthermore, several miRNAs differentially expressed have been proven to be involved in the function of endothelial cells in previous literatures. Our preliminary results suggest that several plasma miRNAs differentially expressed may play important roles in the development of MMD and they could be potential biomarkers of MMD.

FR.03.01

## Update on clinical and research topics regarding adult Moyamoya disease

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Moyamoya disease (MMD) is an idiopathic steno-occlusive disease of the bilateral internal carotid arteries with characteristic abnormal vascular networks. Although many reports have been published, a lot of questions are still being raised in the clinical and research field of this disease, especially for adult patients. The author will present several topics of adult MMD in Korea including demographic features, natural course, treatment outcome, and research data. The nationwide population-based study, the incidence of MMD in Korea was 1.7 to 2.3 per 100 000 from 2007 to 2011, and the prevalence was 16.1 per 100 000 in 2011. The incidence for men and women was 1.3 to 1.7 and 2.1 to 3.0 per 100 000, respectively, and the prevalence for men and women was 5.8 to 11.5 and 10.7 to 20.6 per 100 000, respectively. As for natural course of the adult MMD, two interesting topics such as the fate of the contralateral unaffected side of the surgically treated unilateral MMD, and natural course of hemodynamically stable adult MMD without revascularization surgery will be presented. Although the pathogenesis is not yet known, revascularization surgery has shown satisfactory results in pediatric and adult MMD. In adult MMD, however, there is still controversy about the effectiveness of some types of revascularization surgeries. The author quantitatively evaluated the long-term outcomes of combined revascularization for adult MMD patients in their institute in terms of clinical, angiographic, and hemodynamic states, and the result will be also reported. The elevation of cellular retinoic acid binding protein-I (CRABP-I) has been suggested as a candidate in the pathogenesis of pediatric MMD. However, few studies have addressed CRABP-I in adult MMD. After examining the expression of CRABP-I in the cerebrospinal fluid (CSF) of adult MMD with regard to its association with clinical presentation and postoperative hemodynamic change, the author concluded that higher CRABP-I in the CSF can be associated with typical bilateral MMD pathogenesis in adults, and that postoperative basal collateral change may be related to the degree of CRABP-I expression. Smooth-muscle cells are one of the major cell types involved in this disease process. The characteristics of circulating smooth-muscle progenitor cells (SPCs) in MMD are poorly understood. SPCs could be established from the peripheral blood of MMD patients with adequate culture conditions. These cells showed specific differentially-expressed genes compared with healthy control volunteers. This study provides a novel experimental cell model for further research of MMD.

FR.03.02

## Suzuki's angiographic staging and surrounding topics

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Moyamoya disease (MMD) is a chronic, occlusive cerebrovascular disease with unknown etiology characterized by steno-occlusive changes at the terminal portion of the internal carotid artery and an abnormal vascular network at the base of the brain. MMD has compensatory nature to convert their vascular supply from internal carotid (IC) system to external carotid (EC) system, so called 'IC-EC conversion', which is clearly demonstrated by the Suzuki's angiographic staging. For the definitive diagnosis of MMD in early stage of the angiographic staging, however, following modern diagnostic tools are useful to identify the characteristics of MMD. Recent advance in high resolution MRI such as CISS imaging allow us to detect the early morphological change of intracranial artery such as vascular wall thinness and outer diameter narrowing of the affected vessels in MMD, which could provide supplementary information to the findings of catheter angiography. Taken together with the recent advance in genetic analysis of MMD including RNF213 gene variant, an attempt to perform screening MRA in the three-generation cohort of the Tohoku Medical Megabank project may further contribute to the detection of the patients with the early form of MMD in the future. In light of the increasing number of the elderly patients with MMD, it is alternatively critical to make accurate differential diagnosis between MMD and atherosclerotic occlusive cerebrovascular diseases. In fact, recently revised diagnostic criteria of MMD in Japan require catheter angiography for the definitive diagnosis of MMD if the patients accompany atherosclerotic background. Combined use of the catheter angiography, high resolution MRI focusing on intracranial vascular wall, and genetic analysis in RNF213 among East Asian population, would provide promising information for the diagnosis of MMD in the elderly patients with atherosclerosis.

FR.03.03

### Japan Adult Moyamoya (JAM) Trial and its up-to-date subsequent analyses

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**Objective:** The purpose of the JAM Trial is to determine whether extracranial-intracranial bypass can reduce incidence of rebleeding and improve patient prognosis.

**Methods:** This study was a multi-centered prospective randomized controlled trial conducted by 22 institutes in Japan. Adult patients with hemorrhagic moyamoya disease were given either conservative care or bilateral extracranial-intracranial direct bypass and were observed for 5 years. Primary and secondary endpoints were defined as all adverse events or rebleeding attacks, respectively.

**Results:** Eighty patients were enrolled (surgical, 42; nonsurgical, 38). Adverse events causing significant morbidity (primary endpoint) were observed in 14.3% of the surgical group and 34.2% of the nonsurgical group. Kaplan-Meier survival analysis revealed significant differences between the two groups (3.2%/year vs 8.2%/year,  $p = 0.048$ ). The hazard ratio of the surgical group calculated by Cox regression analysis was 0.391 (95% CI: 0.148–1.029). Rebleeding attacks (secondary endpoint) were observed in 11.9% of the surgical group and 31.6% of the nonsurgical group, significantly different in the Kaplan-Meier survival analysis (2.7%/year vs 7.6%/year,  $p = 0.042$ ). The hazard ratio of the surgical group was 0.355 (95% CI: 0.125–1.009).

**Conclusions:** JAM Trial revealed the significant preventive effect of direct bypass against rebleeding. The subsequent analysis is now ongoing to test the prespecified subgroup hypothesis that the natural course and surgical effects vary depending on the hemorrhage site at onset.

FR.03.04

### Decrease of white matter apparent diffusion coefficient and improvement of executive functions after burr-hole surgery in Moyamoya adults

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**Objective:** Previous studies in Moyamoya patients found a correlation between increased apparent diffusion coefficient (ADC) in normal-appearing white matter (WM), impairment of cerebrovascular reserve (CVR) and executive dysfunction. Thus, raising of ADC may be related to subtle structural changes in WM secondary to chronic hypoperfusion. The aim of this study was to assess the effect of burr-hole surgery on ADC values and executive functions in Moyamoya adults.

**Methods:** ADC was measured before and 6 months after burr hole surgery in 8 patients with bilateral Moyamoya disease or syndrome (6 women, mean age  $\pm$  SD 38.1  $\pm$  9.6 years). Each hemisphere was studied independently. ADC was obtained from regions of interest located in normal-appearing frontal WM. We calculated CVR using cerebral blood volume ratio and the acetazolamide challenge. Impairment of CVR was defined by CVR negative or nul. 6/8 patients had available neuropsychological data before and after surgery.

**Results:** Sixteen hemispheres were studied. Frontal CVR was impaired in 12/16 hemispheres (75 %) before surgery. Trail making test part B was impaired in 5/6 cases. After surgery, ADC values decreased in 11 /16 hemispheres (68.8 %). Mean ADC values were significantly lower than before surgery (804.1 vs 786.1;  $p = 0.03$ ). TMT B improved significantly in all patients ( $p = 0.03$ ). In the same time, frontal CVR increased in 9/ 16 hemispheres (56.3 %) and became positive in 6/12 (50%).

**Conclusions:** In Moyamoya adults, WM ADC decreased after burr-hole surgery, approaching normal values in WM. This evolution seems to be associated with improvement of hemodynamic parameters and executive functions. Thus, subtle WM changes and cognitive troubles may be related to hypoperfusion, and in part reversible after surgery.

FR.03.05

### Periventricular anastomosis in Moyamoya disease: noninvasive scoring of fragile collaterals with sliding-thin-slab maximum-intensity-projection MR angiography

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**Objective:** To test whether periventricular anastomosis, an abnormal collateral specific to moyamoya disease, is associated with hemorrhage and to assess accuracy and reliability of the finding in differentiating hemorrhagic type.

**Methods:** This cross-sectional study sampled consecutive patients with moyamoya disease or syndrome who visited our institute since 2009. Periventricular anastomoses were detected with MR angiography reformatted as sliding-thin-slice maximum-intensity-projection coronal images and were scored according to the three classifications: lenticulostriate, thalamic, and choroidal types.

**Results:** Of 136 eligible patients, 122 were actually analyzed. Eighteen (14.8%) patients was determined as hemorrhagic type. The proportion of the hemorrhagic type increased in response to periventricular score: 2.8% for score 0, 8.8% for score 1, 18.9% for score 2, and 46.7% for score 3 ( $P < 0.01$  for trend). Univariate analysis revealed that age ( $P = 0.02$ ) and periventricular anastomosis score ( $P < 0.01$ ) were a tentative factor associated with the hemorrhagic type. Periventricular anastomosis score remained statistically significant after adjustment of age (odds ratio, 3.38 [95% confidence interval, 1.84 to 7.00]).

**Conclusions:** Periventricular anastomosis is associated with the hemorrhagic moyamoya disease. Noninvasive scoring of periventricular anastomosis can differentiate hemorrhagic moyamoya disease with substantial accuracy and reliability.

FR.03.06

### Aberrant regional homogeneity of resting-state executive control, default mode and salience networks in adult patients with Moyamoya disease

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**Objective:** Aberrant local connectivity within cerebral intrinsic connectivity networks (ICNs) at rest has not been reported in adult moyamoya disease (MMD). The aim of the present study was to examine the regional homogeneity (ReHo) of resting-state executive control (ECN), default mode (DMN) and salience networks (SN) in adult MMD with executive defects, thus to explore its underlying mechanism.

**Methods:** Twenty-six adult patients and 24 normal control (NC) were recruited. Executive function was evaluated by two tests (TMT-B and MES-EX). Using resting-state fMRI and independent component analysis, the whole brain and ICNs specific ReHo mappings were compared between the case and NC groups in a voxel-wise approach. Then a correlation analysis was performed to explore the relationship between ICNs' averaged ReHo and executive functioning in the case group.

**Results:** Compared with NC, the case group exhibited significant ReHo decrease mainly in the frontal and parietal gyrus, while increase only in the left middle temporal gyrus. Subsequent ICNs analysis indicated that compared with NC, patients exhibited significantly decreased ReHo in the dorsolateral prefrontal cortex (DLPFC) and inferior parietal gyrus (IPG) of left ECN, the IPG, superior frontal gyrus and DLPFC of the right ECN, the right precuneus, left medial superior frontal gyrus, and right medial orbitofrontal gyrus of the DMN, as well as the left middle frontal gyrus and right supplemental motor area of SN. Of note, only bilateral ECNs exhibited significant correlation of averaged ReHo values with executive performance.

**Conclusions:** Our results focused on abnormal regional coherence of spontaneous neuronal activity in adult MMD with executive function, thus providing a new insight into the pathophysiological nature of this disease.

FR.03.07

### The Berlin grading system stratify for clinical onset and perioperative complications in adult Moyamoya disease

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**Objective:** The grading system on cerebral angiography does not allow stratifying for clinical symptomatology and surgical risk in adult moyamoya disease. Recently, Czabanka et al. from Berlin proposed a new grading system for adult moyamoya disease and proved its validity to stratify for clinical symptomatology. This study was aimed to externally validate whether the Berlin grading system can stratify for the onset and perioperative complications in adult moyamoya disease in Japan.

**Methods:** This study included totally 89 adult patients (161 hemispheres) who were diagnosed as moyamoya disease in Hokkaido University Hospital (2000-2011) and Toyama University Hospital (2012-2014). Clinical data including DSA, MRI and regional cerebral blood flow studies were assessed. Grading system included: DSA (stenosis/occlusion = 1 point; stenosis/occlusion + intracranial compensation = 2 points; stenosis/occlusion + intracranial compensation + extra-intracranial compensation = 3 points), MRI (no sign of ischemia = 0 points; signs of ischemia = 1 point) and cerebrovascular reserve capacity (normal CVR = 0 points; impaired CVR = 2 points). Totally 82 of 161 hemispheres underwent STA-MCA anastomosis and EDMAPS. Perioperative complications included ischemic and hemorrhagic stroke and hyperperfusion syndrome within 30 days after surgery.

**Results:** Preoperative examination defined 87 hemispheres as grade I, 39 as grade II, and 50 as grade III. Statistical analysis revealed a significant correlation between Berlin Grading System and clinical onset ( $P < 0.001$ ). Perioperative complications occurred in 12 (14.6%) of 82 operated hemispheres. Berlin Grading System was closely related to the occurrence of perioperative complications ( $P = 0.001$ ).

**Conclusions:** The Berlin Grading System can stratify for clinical onset and perioperative complications in adult moyamoya disease in Japan, suggesting its universal validity in clinical practice.

FR.03.08

### Validation and application for a new grading system of Moyamoya disease in adult patients

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**Objective:** 1. To validate the new moyamoya preop symptomatology grading system proposed by Berlin group. 2. To determine the clinical application in predicting radiological and clinical outcome after surgical revascularization.

**Methods:** 96 MMD patients (192 hemispheres) with all 3 investigations (DSA, MRI, Xenon CT) performed preop at Stanford (2007-2013) were included. The imaging findings were independently graded by 2 clinicians according to the criteria proposed (Czabanka et al 2013). Patients' mRS score (preop, postop, at last follow-up), postop infarct (radiological, clinical) were collected and statistical correlation performed using SPSS. To correlate the grading system with patients as individuals (instead of per hemisphere) the highest score was assigned (if both hemispheres were differently affected), and mRS 0-1 was considered excellent outcome.

**Results:** 157 direct STA-MCA bypass procedures were performed on 96 patients (mean age 41 years (18-65), mean follow-up 52 months (1- 90). DSA, MRI and CVRC were independent factors associated with the occurrence of clinical symptoms. 45 hemispheres were graded as mild (grade I), 71 as moderate (grade II), 76 as severe (grade III); 33% of grade I, 92% of grade II, 100% of grade III hemispheres were clinically symptomatic ( $p < 0.0001$ ). 2% of grade I, 11% of grade II, 20% of grade III hemispheres showed postoperative radiological DWI positive ischemic changes or hemorrhage on MRI ( $p = 0.018$ ). A strong trend was also found when correlating with clinical postop stroke (0% of grade I, 1.4% of grade II, 6.6% of grade III hemisphere,  $p = 0.077$ ). Correlation with mRS The new grading system did not correlate with patients' preop mRS status, but correlated well to dichotomized mRS outcome at 4-6 weeks post op (excellent outcome in 92% of grade I, 78% of grade II, 55% of grade III,  $p = 0.016$ ) and at last follow-up (100% of grade I, 78% of grade II, 66% of grade III,  $p = 0.025$ ).

**Conclusions:** The moyamoya grading system proposed by the Berlin group is now validated with a larger patient cohort as an important tool to stratify preop hemispheric symptomatology. Furthermore, it also correlated with postop new ischemic changes on MRI, and showed a strong trend in predicting clinical postop stroke. When assessing the patients holistically (instead of per hemisphere) using mRS, the grading system did not correlate with patients' clinical state preop, but was highly predictive of postop and long-term outcome.

FR.03.09

### 3D-planned EC-IC-bypass-operation for Moyamoya patients

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**Objective:** Minimally invasive neurosurgical procedures have the potential to result in a better outcome by minimizing the surgical trauma. For that purpose 24 EC-IC-bypass-operations, including 5 operations in moyamoya-patients, were planned by Dextroscope since 2008. By fusion of high-resolution-datasets from CT and MRI the Dextroscope-software facilitates an exact operation-planning, generating a three-dimensional model of the patient's head in virtual reality. The advantages of 3D-operation-planning for EC-IC-bypass surgery in moyamoya-patients will be demonstrated.

**Methods:** The Dextroscope-unit (Volume Interaction, Singapore) is used routinely for planning of minimal invasive approaches and operations in our neurosurgical department. In the selected moyamoya-cases high-resolution images from CT and MRI (including CT- and MR-angiography) were used to create the 3D-objects. Donor and recipient vessels were selected and the optimal position of craniotomy was identified. Measurements on virtual skin surface were matched to patients' anatomy as means of navigation. Additional use of Dexport-software in the last case allowed us to export Dextroscope-processed images in DICOM-format and superimpose virtual craniotomy during operation using iPlan-software and Brainlab navigation-system (Brainlab, Feldkirchen, Germany).

**Results:** Accuracy and precision of the system could be quantified in mm by alignment of either postoperative CT- /MRI-scan or intraoperative microscope-screenshots with the dextroscope-dataset. Operation techniques have been elaborated and approaches have been minimized. The virtual preselection of donor- and recipient-vessels allowed prompt intraoperative identification of the recipient vessel and a minimally invasive craniotomy of 28,64mm (s.e.m. 2,51) in diameter to reach the recipient vessel and to successfully complete the procedures in all Dextroscope-planned bypass-operations in moyamoya-patients.

**Conclusions:** Dextroscope-planning enables the surgeon to prepare optimally for individual operations. Extent of skin incision was optimized individually, tissue trauma and size of the bone flap were minimized. By transferring the virtual surface measurements on patients head, bypass-operations were feasible without additional use of navigation systems. If navigation system was used, dextroscope-tailored craniotomy was easily gone over in the operation by superimposing the craniotomy-outline.

FR.04.01

### Pro Conservative treatment Moyamoya Disease

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**Objective:** Randomised trials of extra-cranial bypass surgery in adults with atherosclerotic obliterative arteriopathy have shown that the risk of surgery outweighs the benefits and patients treated conservatively have better outcomes. The only randomized trial in moyamoya disease recruited only adult patients with intracranial haemorrhage and found only a marginally significant benefit of bypass surgery, but did not define conservative management. We therefore reviewed the outcome of patients attending the adult moyamoya clinic at the National Hospital, Queen Square, London with the objective of determining the value of conservative treatment.

**Methods:** Patients attending the clinic had comprehensive investigations. Less than half the patients had received bypass surgery as a child, while only a minority of patients had bypass surgery as an adult. Conservative management included stopping all antiplatelet agents, blood pressure monitoring and treatment to maintain blood pressure below 135/90, statin therapy and life style advice. Patients had follow up imaging at approximately 2 yearly intervals.

**Results:** 98 moyamoya patients attended the clinic from 2003 up to May 2015. Around half the patients had recurrent symptoms, including headache and transient episodes of neurological disturbance, but the rates of recurrent stroke and progressive imaging abnormalities were very low. There was no significance difference between patients who had bypass surgery and those who did not have bypass surgery in the rate of recurrent symptoms.

**Conclusions:** Adult patients with moyamoya disease can be safely managed with conservative treatment alone. Stopping antiplatelet therapy and intensive management of hypertension is not hazardous.

## FR.04.02

**Pro-Surgical Treatment for Moyamoya Disease**

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While the natural history of Moyamoya Disease (MMD) is not completely defined and it can have a variable course with slow or rapid neurologic decline, the majority of patients demonstrate inevitable disease progression. At least 7 retrospective studies have shown recurrent annual stroke rates of 3-15% in patients presenting with TIAs, ischemic stroke or hemorrhagic stroke treated with medical management alone. Other retrospective studies have suggested that 2/3 of medically treated MMD patients suffer symptomatic progression over 5 years, with generally poor outcomes. Our Stanford series of 265 patients undergoing 450 bypasses demonstrated that surgical revascularization reduced the stroke risk to 1.1%/yr (including peri-operative strokes) and a meta-analysis of 1156 MMD patients revealed a 2.6% annual symptomatic progression with surgical treatment, much lower than the risk with medical therapy alone. Asymptomatic MMD may be a misnomer since these patients have a 3.2%/yr stroke risk and 20% show "silent" infarcts. Furthermore, a Stanford study reported that pre-surgical neuropsychological assessment in 30 adult MMD patients with no MR evidence of stroke (either ischemic lesions or hemorrhage) demonstrated a 23% incidence of significant cognitive impairment and 37% incidence of significant emotional distress (depression or anxiety). We have followed some asymptomatic MMD patients or asymptomatic hemispheres, and been dismayed to watch them experience strokes during the observation period.

Until recently, the evidence that surgical revascularization was efficacious for hemorrhagic MMD was less compelling than for ischemic MMD. However, the 2014 publication of the prospective, randomized JAM Trial of 80 hemorrhagic MMD patients showed that direct bypass surgical revascularization was superior to medical therapy, with surgery having a 2.7%/yr bleed rate c/w 7.6%/yr for medicine ( $p=.042$ ) and a total morbidity of 3.2%/yr for surgery c/w 8.2%/yr medical treatment ( $p=.048$ ).

Surgical revascularization is the treatment of choice for symptomatic MMD patients and even for many asymptomatic patients with MR infarcts, poor angiographic collaterals and impaired hemodynamic reserve on CBF tests.

## FR.04.03

**Targeted Revascularization Surgery for MMD**

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Direct STA-MCA anastomosis can improve cerebral hemodynamics just after surgery and thus is believed to reduce the incidence of perioperative ischemic complications in patients with moyamoya disease. In fact, their TIA and headache attack quickly decrease in frequency or resolve after surgery. Direct STA-MCA anastomosis is useful especially in adult patients, because indirect bypass procedures induce effective collaterals in about half of them. Recent randomized clinical trial, Japan Adult Moyamoya (JAM) Trial, has shown that direct STA-MCA anastomosis significantly reduce the incidence of re-bleeding in adult patients with hemorrhagic-type moyamoya disease. However, direct STA-MCA anastomosis is sometimes challenging in infants and requires careful post-operative managements to avoid hyperperfusion-related complications. For these 18 years, we have performed STA-MCA single or double anastomosis combined with encephalo-duro-myo-arterio-pericranial synangiosis (EDMAPS) for more than 200 patients with moyamoya disease. The EDMAPS procedure is quite useful to provide collateral blood flow to the wide region, including the frontal lobe, because the vascularized frontal pericranium can widely cover the frontal lobe. In this lecture, we precisely present the surgical technique, short- and long-term prognosis after STA-MCA anastomosis and EDMAPS.

FR.04.06

### Changing patterns of cerebral hemodynamics after EC-IC revascularization in Moyamoya disease: multi-modality evaluation

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**Objective:** To explain reduced rehemorrhagic risk after ec-ic revascularization in moyamoya disease in terms of cerebral hemodynamics.

**Methods:** 32 patients (20 female, 12 male, mean 39.3y) of hemorrhagic moyamoya disease were enrolled. All patients received superior temporal artery-middle cerebral artery bypass combined with encephaloduro-myosynangiosis (STA-MCA bypass + EDMS) on the affected hemisphere. Multi-modality evaluation were conducted to identify the changing patterns of cerebral hemodynamics, including traditional angiogram (Preoperative and six-month follow-up) trans-cranial color Doppler (TCCD, Preoperative, one-week and six-month follow-up), intraoperative Indocyanine green (ICG) angiogram and NOVA study.

**Results:** Follow-up angiogram was available in 30 hemispheres, all demonstrated cerebral blood flow re-distribution to various extents, reconstructive vascular network fed the MCA distribution area, resulted in shrink of moyamoya vessels (MMVs), anterior or posterior choroidal artery collaterals, pial collaterals and hemodynamic-related aneurysms. TCCD revealed an "intracranialized trend" in STA with elevated peak systolic velocity (PSV,  $57.55 \pm 17.00$  vs  $84.27 \pm 21.85$ ), end-diastolic velocity EDV,  $18.36 \pm 6.50$  vs  $37.82 \pm 10.64$  and decreased resistance index RI,  $0.68 \pm 0.10$  vs  $0.55 \pm 0.06$ , whereas intracranial arteries such as ipsilateral ICA and basilar artery (BA) exhibit an opposite trend with elevated RI ( $0.51 \pm 0.09$  vs  $0.58 \pm 0.08$  in ICA,  $0.46 \pm 0.06$  vs  $0.52 \pm 0.07$  in BA), which indicated an increase in vessels bed resistance induced by revascularization. NOVA study with MR scan revealed an decrease in ipsilateral ICA blood flow after operation ( $102.4 \pm 12.3$ ml vs  $202.4 \pm 20.9$ ml), which was consistent with previous study. In addition, an interesting borderline was observed between blood flow from the direct bypass and spontaneous collaterals with intraoperative ICG angiogram, and the velocity of former was much more higher, we believe this phenomenon maybe an intuitively reflect of "watershed shift", which maybe the reason of post-operation transient neurological deficit.

**Conclusions:** Hemodynamically speaking, EC-IC revascularization may cause blood flow redistribution between extra- and intra-cranial arteries, thus reduce the blood flow stress of MMVs and spontaneous collaterals, result in lower risk of re-haemorrhage risk.

FR.04.07

### Revascularisation surgery in juvenile Moyamoya syndrome – own experiences and review

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**Objective:** Ischemic brain injury predominates in children and adolescents, while intracerebral hemorrhage is the leading cause of stroke in adults. The benefit of revascularisation surgery is only proven in the juvenile type of this disease. Due to its low incidence in western countries, the alertness of physicians towards this entity should be improved.

**Methods:** From 1984 to 2011 87 revascularisation procedures were performed in 52 patients with Moyamoya syndrome. There were 21 children or adolescents and 31 adults, 37 females and 15 males. One third of the patients had an Asian origin in at least 1 parent. The mean age of the juvenile group was 8.5 years (range 1-18). The mean follow-up was 23 years and 5 months (range 4 - 31 years). Two patients were lost for follow-up. Our protocol for preoperative work up included cerebral angiography (DSA), computerized tomography (CT) or magnet resonance imaging (MRI) for all patients. The cerebrovascular reserve capacity (VRC) was measured in 87%. For follow-up patient condition were documented by a questionnaire every 12 months and by physical examination in the hospital. At least 1 postoperative angiography was done in 57%, repeated VRC measurements in 68% of the patients.

**Results:** DSA revealed obstructions in the basal arteries on both sides in 85% of the patients. Leading symptoms in the juvenile group were epilepsy, transient ischemic attacks, mental retardation. Revascularisation was done in the juvenile patients as end-to-side anastomoses in 26 cases, encephalo-myosynangiosis in 4 cases and encephalo-duro-arterio-synangiosis in 57 cases. In follow-up all symptoms disappeared in 58% of the patients, improved in 37% and did not change in 5%. We had no perioperative mortality or permanent morbidity in the juvenile group.

**Conclusions:** In accordance with the literature the ischemic symptoms were eliminated by the revascularisation surgery in 96% of our cases with a very low rate of complications. Early diagnosis and surgical treatment seem to potentiate the benefit independently of the type of the revascularisation procedure.

FR.04.08

### Revascularization for moyamoya angiopathy in older adults

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**Objective:** Moyamoya angiopathy most often presents in young people in the second and third decade of life. Though uncommon, it can present itself later in life. Here we present our results of moyamoya patients over the age of 50 treated with surgical revascularization via either direct bypass or indirect bypass (encephaloduroarteriosynagiosis).

**Methods:** A retrospective review was conducted to identify all patients with moyamoya disease treated with surgical revascularization at our institution from 2002 to present.

**Results:** We identified 18 patients with moyamoya angiopathy over the age of 50 treated with surgical revascularization for 26 affected hemispheres. The average age was  $57 \pm 7$  years. Sixteen of the affected hemispheres were treated with indirect bypasses while the other 8 were treated with direct bypasses. One patient (5.5%) suffered a surgical complication. Average follow-up was 63 months and 5 patients were lost to follow-up. At last follow-up, six of the eight direct bypasses were patent. One patient had a new ischemic stroke in a treated hemisphere with a new event rate of 3.8%. With regards to functional outcome, there was one mortality (7.1%), four patients (28.6%) were the same, and eight patients (57%) improved.

**Conclusions:** Though uncommon, moyamoya angiopathy can present in older adults. Our results suggest that surgical revascularization is an excellent treatment option with good functional outcomes and an acceptable complication rate.

FR.04.09

### Outcome of revascularization surgery for elderly patients with Moyamoya disease over the age of 60 years: Single institute experience

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**Objective:** Superficial temporal artery-middle cerebral artery (STA-MCA) anastomosis prevents cerebral ischemic attack by improving cerebral blood flow in patients with moyamoya disease (MMD). STA-MCA anastomosis is generally recommended for adult MMD patients with ischemic symptom, but its efficacy for elderly patients with MMD is undetermined due to the limited number of elderly MMD patients. We sought to clarify the outcome of revascularization surgery for them based on our single institute experience.

**Methods:** Among 186 consecutive cases with MMD undergoing STA-MCA anastomosis with pial synangiosis for 256 hemispheres, 13 patients (14 hemispheres) were over the age of 60 years old (mean 64.5 years old). Incidence of surgical complications including cerebral infarction and cerebral hyperperfusion (CHP) was compared to those of the patients under 60 years old.

**Results:** In 13 elderly patients undergoing revascularization surgery for 14 hemispheres, the incidence of symptomatic CHP was as high as 21.4% (3/14) despite the intensive peri-operative care, and two of the three patients developed delayed intracranial hemorrhage in the acute stage. One patients developed cerebral infarction at the remote area during the blood pressure lowering against CHP (7.1%, 1/14). The incidence of symptomatic hemorrhage due to CHP was significantly higher in elderly patients (14.3%, 2/14) compared to younger patients (1.7%, 4/242) ( $p=0.0023$ ). Regarding final outcome of elderly patients, eleven patients showed improvement of modified Rankin Scale, and two patients temporarily deteriorated but recovered to the preoperative status 3 months after surgery.

**Conclusions:** Outcome of revascularization surgery for elderly patients with MMD is favorable in general, although they may potentially have higher risk of intracranial hemorrhage due to CHP compared to younger patients. Surgical indication should be carefully decided for elderly MMD patients, and intensive peri-operative management is essential to avoid surgical complications including CHP and ischemia.

## SA.01.01

**Ischemic stroke in pediatric patients beyond MMD**

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Cerebral arteriopathies are the underlying cause in at least half of all children with arterial ischemic stroke (AIS). In young adults with AIS, arteriopathies are diagnosed in approximately 25%. In contrast to what is often believed, well recognized vasculopathies – such as moyamoya disease (MMD), dissection and vasculitis – only account for a minority of arteriopathic stroke syndromes in children. In a pooled analysis of two large pediatric stroke series, MMD was diagnosed in 9% of cases, dissection in 8% and vasculitis in 4%. The most frequently diagnosed childhood arteriopathic entity was ‘transient cerebral arteriopathy’ (TCA), which may be diagnosed in as many as 20-30% of children with AIS, and in 30-40% of those who were previously healthy. TCA is a monophasic, presumably inflammatory, strictly unilateral, and intracranial disease of the distal internal carotid artery and/or its branches. It causes mainly lenticulostriatal infarction. The diagnosis requires longitudinal vascular imaging. Repeated MRA shows eventual stabilization (with a residual arterial scar), improvement, or even normalization of the arterial abnormalities. After initial evaluation in the acute stage, the arteriopathy is often labelled as FCA (focal cerebral arteriopathy) until follow-up vascular imaging has demonstrated its non-progressive time course. Only then can TCA can be diagnosed with certainty. TCA and its variants also occur in the posterior circulation. More than 40% of children with TCA had chickenpox within 1 year prior to stroke (so called post-varicella angiopathy). Although the course of the arteriopathy is monophasic and benign, many children are left with hemiparesis and dystonia. Recurrence rate is around one in five, mainly occurring during the first weeks to months after diagnosis. Although TCA seems to be specific for the pediatric population, its occurrence in young adults has recently also been reported. The difference and overlap between presumed “unilateral MMD” and occlusive non-progressive TCA will be discussed.

## SA.01.04

**Pro-indirect revascularization in pediatric Moyamoya disease**

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**Introduction:** Moyamoya is a major cause of stroke in the pediatric population, yet optimal management strategies remain controversial. For patients who undergo operative treatment, two major techniques of surgical revascularization are widely employed: direct and indirect bypass. Both commonly utilize branches of the external carotid artery to provide an alternative source of blood supply to the cortex distal to the arteriopathy, but selection of a particular operative approach often is determined by individual practice patterns. Evidence-based data may be useful in guiding operative decision-making.

**Methods:** Literature review and institutional review board (IRB) approved case-series analysis of moyamoya patients at a pediatric hospital.

**Results and Conclusion:** Moyamoya remains a complex entity to diagnose and treat. Indirect revascularization, such as pial synangiosis, has demonstrated efficacy as a safe, durable method of reducing stroke risk in children, with applicability in any age group and with marked reductions in stroke rate sustained over decades.

SA.01.05

### Moyamoya disease in children – new insights from imaging and surgical treatment

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**Objective:** Pediatric Moyamoya (pMMD) is a progressive stenosis of the internal carotid arteries (ICA) requiring cerebral revascularization to prevent ischemic strokes. The surgical outcomes of pMMD are rarely reported. We aimed to evaluate the clinical outcome after multiple burr-hole surgery and to compare cerebral blood flow (CBF) obtained using pulsed arterial spin labeling MRI (pASL-MRI), before and after surgery.

**Methods:** We retrospectively performed clinical assessment of all patients operated in our center between 1999 and 2013. Clinical endpoints included any recurrence of stroke or transient ischemic attack (TIA). In addition, since 2011, pASL-MRI was prospectively done before, three-, and twelve months after surgery. We used a statistical voxel-based approach under SPM8 to compare pre- and post-operative CBF at the individual and group levels.

**Results:** 53 children were operated, with no perioperative mortality or severe morbidity. 46/53 (86.5%) patients had no recurrence of stroke or TIA (mean follow-up 3.8 ± 3.2 years). Two patients required a second revascularization procedure because of recurrent TIA. Preoperative clinical or radiological strokes were significantly associated with a higher risk of postoperative stroke or TIA on multivariate analysis. Statistical analysis of ASL-MRI showed at the group level a significant preoperative hypoperfusion in the MMD middle cerebral artery territory ( $p < 0.05$ , FWE corrected), and a significant increase of CBF three months and one year after surgery in the same arterial territory ( $p < 0.05$ , FWE corrected). The individual analysis demonstrated for each patient a preoperative significant decrease of CBF, colocalized with arterial stenosis on DSA. Postoperatively, SPM analysis showed dramatic improvement of cerebral perfusion, except in one patient with recurrent TIA who required further targeted surgery.

**Conclusions:** Multiple burr hole surgery is safe in pediatric MMD and resulted in satisfactory improvement in clinical, angiographic, and hemodynamic states, as demonstrated on pASL-MRI and prevention of recurrent stroke.

SA.01.06

### Combined direct/indirect anastomosis in Moyamoya disease: results of 358 surgeries in Hokkaido University

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**Objective:** Although combined direct and indirect anastomosis in patients with moyamoya disease immediately increases cerebral blood flow, the surgical procedure is more complex. Data pertinent to the efficacy as well as postoperative complications associated with combined bypass are relatively scarce compared with those associated with indirect bypass. We investigated the efficacy of the bypass as well as incidence and characteristics of postoperative stroke in combined bypass.

**Methods:** A total of 358 revascularization procedures in 236 patients were retrospectively assessed by reviewing their clinical charts and radiological data.

**Results:** 1) Surgical indication; symptomatic hemisphere and asymptomatic hemisphere with severe hemodynamic compromise. 2) modality of hemodynamic assessment; acetazolamide loading rCBF study using SPECT/resting state rCBF and FLAIR/MRI (ivy sign)/OEF using PET, 3) surgical procedures; mostly STA-MCA bypass plus indirect procedure, occasionally STA-ACA bypass or OA-PCA/MCA bypass, 4) surgical complications; 17 instances of postoperative stroke were observed in 16 patients [4.7% per surgery, 95% confidence interval (CI), 2.8–7.5]. Postoperative stroke was more frequent (7.9% per surgery) in adults than in pediatric patients (1.7% per surgery) [odds ratio (OR), 4.07; 95% CI, 1.12–14.7;  $p < 0.05$ ]. 5) Dural growth of direct/indirect anastomosis was the most frequent angiographic representation both in pediatrics and adults.

**Conclusions:** Combined direct/indirect bypass requires complex procedures, however, it maximizes neovascularization and reduces postoperative complications.

SA.01.07

### Characteristics and treatment for young patients with Moyamoya disease

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**Objective:** Young patients with moyamoya disease frequently exhibit extensive cerebral infarction at the time of initial presentation, and even in the early postoperative period. These cerebral infarctions are more frequent in younger age group. To investigate clinical characteristics of the young moyamoya patients, the authors analyzed clinical findings of the patients and discuss the treatment strategy.

**Methods:** Forty-four patients (72 hemispheres) with moyamoya disease, younger than 18 years of age (y.o.), were surgically treated between January 2004 and December 2013. The clinical findings and radiological data were retrospectively reviewed.

**Results:** The patient group was divided into 3 groups by age (group 1: <3 y.o. 9 cases 14 hemispheres, group 2: 4-6 y.o. 10 cases 20 hemispheres, group 3: 7 y.o.- 25 cases 38 hemispheres). The patients who suffered cerebral infarction at the diagnosis were 5/8 in group 1, 4/10 in group 2, 1/25 in group 3. In contrast, 4 patients in the group 3 suffered intracerebral hemorrhage but none in the group 1 and 2. Surgical treatment was performed as an initial treatment in 66 hemispheres. Surgery for additional treatment was performed in 6 hemispheres. The almost all the surgical treatment was direct and indirect bypass but two that performed only indirect bypass. Perioperative complications were seen in 9 patients. Seven patients in group 3 showed temporary neurological deficit due to postoperative hyperperfusion that resolved completely at the time of discharge. Two patients in group 1 showed cerebral infarction due to watershed shift.

**Conclusions:** In young patients, moyamoya disease exhibits rapid progression, resulting in poor clinical outcome. The patient under 3 y.o. has a high risk of cerebral infarction at the time of diagnosis and early postoperative period. The patient over 6 y.o. who performed direct bypass surgery has a high risk of perioperative temporary neurological deficit due to hyperperfusion. Direct bypass can provide prompt improvement in cerebral circulation of moyamoya disease that thought to be suitable for rapidly progressive moyamoya disease. The findings in this study showed that direct bypass is not completely safe in patients with moyamoya disease because it causes dynamic change in postoperative cerebral hemodynamics. We recently induced STA-MCA double bypass as an initial treatment for the patients under 3 y.o.. The surgical strategy for the young moyamoya patients is further discussed.

SA.01.08

### Encephaloduromyosynangiosis treating moyamoya disease in young children

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**Objectives** To evaluate the therapeutic effect of encephaloduromyosynangiosis (EDMS) in children younger than 6 years old for moyamoya disease (MMD).

**Methods** 27 MMD children confirmed by digital subtraction angiography (DSA) or magnetic resonance angiography (MRA) in our center were admitted between January 2011 and September 2013. The clinical manifestation was described as below: 1 with cerebral hemorrhage history, 26 with ischemic history. 8 left brain hemispheres, 6 right hemispheres and 13 bilateral hemispheres were operated. All the procedures were performed in 136 ± 22 min with 21 ± 3 ml blood loss.

**Results** The mean period of follow-up after surgery was 15.8 months, with a range of 6-38 months. 1 The cerebral blood flow in the effected regions increased 3 months after the operations all cases got vascularization. Spontaneous revascularization from the deep temporal artery, superficial temporal artery and the middle meningeal artery was found in DSA or MRA. 2 27 SPECT reviewed cases had better perfusion after the operations. 3 The ischemic symptoms were relieved in 31 (77.5%) hemispheres, while stabilized in 8 (20.0%) hemispheres. There were 4 cerebral infarctions (10%) within one month post-op, 1 located in the operated hemisphere while 3 located in the contralateral sites.

**Conclusions** EDMS is a safe, effective and secluded treatment for MMD young children, the extracranial vessels could revascularization in a multi-layered extensively manner, which significantly improved patients' neurological function.

## SA.02.01

**Molecular regulation of angiogenesis**

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Angiogenesis is the main process mediating the expansion of the blood vessel network during development, tissue regeneration or in pathological conditions such as cancer. The formation of new endothelial sprouts, a key step in the angiogenic growth program, involves the selection of endothelial tip cells, which are highly motile, extend numerous filopodia, and lead new sprouts. Angiogenic sprouting is induced by tissue-derived, pro-angiogenic signals such as vascular endothelial growth factor (VEGF), which activates and triggers signaling by cognate receptor tyrosine kinases in the endothelium. However, this response is strongly modulated by intrinsic signaling interactions between endothelial cells, which involve the Notch pathway. Our work is providing further insight into the regulation of sprouting angiogenesis such as the distinct functional roles of different Notch ligands or the modulation of growth factor receptor activity by endocytosis.

Mouse genetics is a powerful tool for the characterization of the molecular processes controlling blood vessel morphogenesis. As the global or constitutive endothelial cell-specific inactivation of genes controlling angiogenesis frequently lead to embryonic lethality at midgestation, we have focused on the generation of tamoxifen-inducible CreERT2 transgenic mice. To ensure robust and faithful expression of the resulting transgenic mice, we preferentially use large genomic DNA fragments in BAC or PAC vectors together with recombineering techniques. Successful examples include the Cdh5(PAC)-CreERT2 line that can be used for functional studies in the developing and adult endothelium. Bmx(BAC)-CreERT2 transgenics enable gene inactivation experiments in arterial endothelial cells without affecting veins or capillaries. To investigate the role of tip cells in endothelial sprouting, we have generated Esm1(BAC)-CreERT2 transgenics. The Pdgfrb(BAC)-CreERT2 line enables genetic experiments in mural support cells, namely pericytes and vascular smooth muscle cells, that stabilize the vessel wall.

We will provide examples of ongoing studies involving these transgenic lines, which provide insight into the regulation of blood vessel growth in the central nervous system and in bone.

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## SA.02.03

**Effects of EDAS surgery on the circulating angiogenic factors of patients with Moyamoya disease and intracranial atherosclerosis**

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**Objective:** To evaluate the levels of circulating pro and antiangiogenic factors among patients with moyamoya disease (MMD), intracranial atherosclerosis (ICAS), and controls, and the effects of indirect revascularization with encephaloduroarteriosynangiosis (EDAS) in their levels.

**Methods:** Prospective longitudinal study of circulating angiogenic factors in 22 patients with MMD, ICAS, and controls. Patients with MMD and ICAS underwent EDAS surgery. Control cases had cranial surgery for non-vascular or tumor pathology. Circulating angiogenic factors were measured at baseline and 7 days after surgery. Log-corrected levels were compared at baseline and 7 days after surgery between groups. Multivariate analysis of variance (MANOVA) was used to examine differences within pairs and between groups. Regression mixed models were built to account for intrasubject correlation to evaluate the association of angiogenic levels with group and treatment.

**Results:** Mean age in the MMD group was 41(SD 11) vs. 65(SD 16) in ICAS, and 51(SD 19) in controls. 83% of MMD patients were female, 44% in ICAS, and 43% in controls. Patients with MMD had significantly higher levels of PDGFAA (568.8 pg/ml), vs ICAS (165.9pg/mL), and controls (38.4 pg/mL)  $p=0.007$ ; PDGFBB (1449.7 pg/mL), vs. ICAS (141.2 pg/mL), and controls (65.2 pg/mL)  $p=0.03$ ; TGFβ1 (24.5 ng/mL), vs. ICAS (13.8 ng/mL), and controls (6.2 ng/mL)  $p=0.006$ ; TSP1 (128.5 ng/mL), vs. ICAS (91.7 ng/mL), and controls (9 ng/mL)  $p=0.0007$ . After surgery (EDAS for MMD and ICAS vs. cranial surgery for controls) levels of PDGFAA, PDGFBB, and TGFβ1 increased on the ICAS and control groups eliminating the baseline differences. EDAS, independently from etiology, affected the levels of pro-angiogenic TGFβ2 (EDAS: 290 pg/mL, controls: 161 pg/mL), and BMP2 (EDAS: 153 pg/mL, controls: 109 pg/mL)  $p<0.02$ . Interestingly, EDAS also increased the levels of the anti-angiogenic TSP2 (EDAS: 54.5 ng/mL, controls: 29 ng/mL)  $p=0.02$ .

**Conclusions:** This is the first report of a broad-spectrum investigation of angiogenic factors in intracranial steno-occlusive disorders and the effects of EDAS. Our study demonstrates that patients with MMD have baseline higher levels of pro-angiogenic factors PDGFAA, PDGFBB, and TGFβ1, involved in vessel maturation. EDAS, independent from etiology, affected the levels of TGFβ2, BMP2 and TSP2, cytokines involved in vessel maturation, increased vascular permeability, and modulation of cell migration, respectively.

## SA.02.04

### Temporal profile of magnetic resonance angiography of RNF213, moyamoya disease susceptibility gene, deficient mice with immunologic adjuvant administration

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**Objective:** Moyamoya disease (MMD) is a chronic, occlusive cerebrovascular disease with abnormal vascular network at the base of the brain. Recent genome-wide and locus-specific association studies identified the RNF213 gene (RNF213) as an important susceptibility gene of MMD among East Asian population. However the mechanism underlying RNF213 abnormality relates to MMD is still unknown. Regarding the environmental factors, an immunologic reaction such as autoimmunity has been implicated in the pathogenesis of MMD, as suggested by an association between MMD and autoimmune diseases. In this study, we sought to evaluate the role of immunologic stimulation as a supplementary insult to the target disruption of RNF213 in the pathophysiology of MMD.

**Methods:** We generated conventional RNF213 knock-out mice (RNF213-KO) by deleting exon 32 of RNF213 with the Cre/loxP system. To expose the mice to immunologic stimulation in addition to the genetic alteration of RNF213, the mice were subjected to subcutaneous injection with complete Freund's adjuvant (CFA) and muramyl dipeptide (MDP)-Lys (L18) that was a synthetic NOD2 agonist acting as a powerful immunologic adjuvant. The temporal profile of intracranial arteries was evaluated by 9.4-T magnetic resonance angiography (MRA) continuously in the same individual of wild-type mice, RNF213-KO, and RNF213-KO exposed to immunologic adjuvants.

**Results:** RNF213-KO grew normally, and no significant difference was observed MRA findings or the anatomy of the circle of Willis between RNF213-KO and wild-type littermates under normal conditions up to 64 weeks of age. CFA or MDP administration did not affect this result, and immunologic adjuvant administration failed to develop MMD in RNF213-KO up to 40 weeks.

**Conclusions:** RNF213-KO did not develop MMD under normal condition. Immunologic adjuvant administration did not affect the vascular anatomy in RNF213-KO, and further evaluation is required to address the role of immunologic reaction supplementary to RNF213-deficiency in the pathophysiology of MMD.

## SA.02.05

### Analysis of genetic variant RNF213 (c. 14576G>A) in 5 pairs of Japanese identical twin with Moyamoya disease of juvenile onset

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**Objective:** The genetic variant RNF213 (c. 14576G>A) has recently been reported as a susceptibility gene mutation for moyamoya disease (MMD) in eastern Asian population. The role of this variant, however, in relation to the onset of MMD is still ambiguous. The variant of c. 14576G>A in 5 pairs of identical twins was examined to consider the role of this genetic variant.

**Methods:** We treated 6 pairs of Japanese identical twins one or both of whom were diagnosed as having MMD during childhood. Both of 4 pairs and one of a pair agreed to be examined with their peripheral blood for DNA sampling. Type of RNF213 (c. 14576G>A) mutation was examined.

**Results:** 1) RNF213 (c. 14576G>A) variant of three pairs were wild type (GG). In two of these pairs, only one of pairs presented MMD at the age of 2 and 8. Their twin sisters have had normal MRA 15 or 3 year after the diagnosis. Both of one pairs were diagnosed as having MMD at the age of 11. One of them died due to intraventricular hemorrhage soon after diagnosis and DNA analysis was impossible. 2) Two pairs had heterogeneous mutation (AG). Both of one pair presented MMD at the age of 5, but in the other pair, only one presented MMD and his twin brother had normal MRA.

**Conclusions:** Identical twin with MMD is very rarely observed, but must be important subjects to be analyzed to clarify the genetic background of MMD. Further analysis of samples using whole genome or exon sequencing may be necessary to detect the susceptibility gene mutation other than RNF213.

SA.02.06

### Significance of narrow carotid canal and the RNF213 risk variant for the diagnosis of Moyamoya disease and middle cerebral artery occlusion

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**Objective:** RNF213 has been shown to be associated with both moyamoya disease (MMD) and middle cerebral artery occlusion (MCAO). We investigated the significance of narrow carotid canal in combination with the RNF213 risk variant for the differential diagnosis of MMD and MCAO.

**Methods:** Carotid canal diameter was measured by 0.6mm thin slice computational tomography in 26 patients with MMD, 8 patients with unilateral MMD, 11 patients with MCAO and 60 control individuals. The rs112735431 variant in RNF213 was also genotyped and the association of narrow carotid canal and the RNF213 risk variant with intracranial arterial stenoses was analyzed among 56 MMD, 15 MCAO and 140 control hemispheres.

**Results:** Carotid canal diameter was significantly smaller in patients with MMD than control individuals (4.03 mm vs 5.30 mm,  $p < 0.001$ ). Smaller carotid canal diameter was associated with younger age at onset and more advanced Suzuki's stage. Narrow canal  $\leq 4.5$  mm was only observed in affected hemispheres of unilateral MMD but not in unaffected hemispheres. The rs112735431 variant and narrow carotid canal of  $\leq 4.5$  mm were both associated with an increased risk of MMD and MCAO phenotypes in a multivariate analysis. Combination of narrow carotid canal  $\leq 4.5$  mm and the rs112735431 risk variant dramatically increased the risk of MMD but not MCAO: 60.7% of affected hemispheres of MMD had both risk factors whereas none of the MCAO or control hemispheres had both risk factors.

**Conclusions:** Narrow carotid canal and the RNF213 risk variant were independently associated with an increased risk of MMD and MCAO. Combination of these two factors may help to distinguish MMD from MCAO.

SA.02.07

### Investigation of RNF213 p.R4810K and A4399T in a high-prevalence town of Moyamoya disease in China

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**Objective:** Moyamoya disease (MMD) is characterized by a progressive stenosis or occlusion at the terminal portion of the internal carotid artery and the development of abnormal collateral vessels at the base of the brain. Although the etiology is still unclear, recent genetic studies identified RNF213 p.R4810K and A4399T as susceptible variants among East Asian population. A community-based epidemiological survey has currently discovered a town with a high-prevalence of MMD in China, but whether the aggregated population has the similar genetic predisposition remains unclear. The present study investigated the occurrence of RNF213 p.R4810K and A4399T in patients with MMD who were identified in the same residence.

**Methods:** A community-based epidemiological survey on MMD was carried out in Ciwu Town, Zhuji City, Zhejiang Province, China from January 2013 to June 2014. A total of 297 participants who agreed to participate in this study were enrolled. 1.5-Tesla magnetic resonance angiography (MRA) were arranged to distinguish MMD according to Guidelines for diagnosis and treatment of moyamoya disease (spontaneous occlusion of the circle of Willis) issued by the Ministry of Health and Welfare, Japan. Genotyping of RNF213 p.R4810K and A4399T were carried out immediately and the genotype frequency were further compared between MMD patients and the healthy controls.

**Results:** 40 MMD patients and 257 healthy controls were identified by MRA. According to clinical manifestation, hemorrhage, ischemia and asymptomatic subtypes account for 21 (52.5%), 14 (35%) and 5 (12.5%) respectively. For RNF213 p.R4810K, 6 of 40 MMD patients carried AA+AG mutation with only 2 in 257 healthy controls ( $p < 0.001$ , OR 22.5, 95%CI: 4.3-116.0). For RNF213 p.A4399T, 18 MMD patients carried AA+AG mutation with only 2 in 257 healthy controls ( $p < 0.001$ , OR 104.3, 95%CI: 22.7-479.3). After the stratified analysis by clinical characteristics, AA+AG mutation were identified in 14 MMD patients with hemorrhage, 2 MMD patients with ischemia and asymptomatic respectively ( $p = 0.0048$ , OR 12.0, 95%CI: 2.08-69.1). No significant association between RNF213 p.R4810K mutation and clinical characteristics were observed.

**Conclusions:** Both RNF213 p.R4810K and A4399T polymorphisms were associated with the risk of MMD in Ciwu Town, Zhuji City, Zhejiang Province, China. RNF213 p.A4399T was possibly a strong genetic predictor for hemorrhagic variety in patients with MMD.

SA.02.08

### Genetic analysis of RNF213 variant in Moyamoya disease, Quasi-moyamoya disease and various cerebrovascular diseases

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**Objective:** The c.14576G>A variant in ring finger protein 213 (RNF213) was recently identified as a susceptibility gene variant for moyamoya disease (MMD). We assumed that the c.14576G>A variant could be the cause of a wide spectrum of phenotypes of intracranial major artery stenosis/occlusion (ICASO). In this study, the occurrence of c.14576G>A variant was evaluated in various phenotypes of cerebrovascular diseases.

**Methods:** Study participants were recruited from The University of Tokyo Hospital and Kanto Neurosurgical Hospital. The occurrence rate of c.14576G>A variant was investigated in 678 patients, 93 with definite MMD, 20 with unilateral MMD, 9 with Quasi-MMD (typical unilateral or bilateral MMD angiographic findings associated with inherited or acquired disorders), 192 atherosclerotic ICASO, 80 with extracranial carotid atherosclerosis, 110 with cerebral aneurysm, 25 with intracerebral hemorrhage, and 149 control subjects.

**Results:** RNF213 c.14576G>A variant was found in 83.8% (78/93) of the definite MMD group, and 65.0% (13/20) of the unilateral MMD group. Moreover, the variant was found in 26.5% (51/192) of the atherosclerotic ICASO group. On the other hand, there none in Quasi-MMD group. RNF213 c.14576G>A variant had significant associations with definite MMD, unilateral MMD, and also with atherosclerotic ICASO ( $P < 0.0001$ ; odds ratio, 17.6; 95% confidence interval, 5.37-57.6). There was no significant association with Quasi-MMD, extracranial carotid atherosclerosis, cerebral aneurysm, or intracerebral hemorrhage.

**Conclusions:** Moyamoya disease and related diseases might be classified by genetic analysis of the RNF213 c.14576G>A genotype. A particular subset of patients with atherosclerotic ICASO had RNF213 c.14576G>A, indicating that RNF213 c.14576G>A variant is a high-risk allele for ICASO.

SA.02.09

### Genome-wide CNV array analysis in parent-offspring pairs with Moyamoya disease with and without clinical anticipation

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**Objective:** To investigate the mechanism underlying the association between clinical anticipation in Moyamoya disease (MMD) and Copy Number Variation (CNV) defining a DNA segment 100 kilobases or larger in size and present at variable copy numbers in comparison with a reference genome.

**Methods:** Eighteen (62%) of 29 consecutive parent-offspring MMD pairs treated at the Hokkaido University hospital since 1980 were enrolled in this study. Clinical anticipation, defining a lowering of the age of onset, was confirmed in 10 (56%) of these 18 pairs. Genome-wide CNV array analysis was conducted using a 2.6 M Affymetrix oligonucleotide array. The reference genome was set as per the manufacturer's instruction. The CNV profile was compared between parent-offspring pairs with and without anticipation.

**Results:** The genome-wide CNV array detected 112 CNV loci throughout the genome except for chromosome 21 in 30 samples obtained from the enrolled 18 pairs. Of these, overlapping CNV loci for more than 3 samples were seen in 17 segments. The differences in copy number state between the parent and the offspring in each of the 18 pairs were calculated. The distribution of the difference in copy number state on chr4q13.2 and chr16p13.3 was significantly different between pairs with and without anticipation ( $P = 0.03$  and  $0.04$ , respectively; Man-Whitney test). Of these 2 loci, copy number gain was observed in the offspring with anticipation for chr16p13.3 ( $P = 0.06$ , Wilcoxon's signed rank test), in a region containing 15 genes.

**Conclusions:** Copy number gain on chr16p13.3 may contribute to the anticipation of familial MMD by influencing gene expression or by disrupting genes and altering gene dosage in variable possible forms such as insertions, tandem duplications, and complex gains or losses of homologous sequences at the site in the genome.

## SA.03.01

**Clinical and radiological features of quasi-Moyamoya disease**

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**Objective:** A inherited or acquired disorders and conditions may present in conjunction with moyamoya disease (MMD). This condition is known as quasi-moyamoya disease. To identify the clinical features of quasi-MMD, the cases of quasi-MMD treated in Nagasaki University was reviewed and nationwide survey was conducted.

**Methods:** The questionnaire was directly mailed to 241 departments, which answered treating quasi-MMD patients in the primary survey. We ascertained the sex, age, family history, clinical manifestation, radiological findings, treatments, course of the disease, and daily activity of the patients.

**Results:** A total of 114 departments replied to the questionnaire. The data of 108 patients (66 female and 42 male; female to male ratio 1.57) were registered and analyzed. Mean age was 30.6 years old with a peak of the child. Seven patients (7%) exhibited familial MMD. The initial clinical manifestation was motor weakness, followed by transient ischemic attack, headache. Their imaging study type included ischemic type in 64 patients (63.4%), bleeding type in 7 (6.9%), and normal in 27 (26.7%). Stenoocclusive lesion was seen in internal carotid artery in more than half of the patients. Development of moyamoya vessels was mild in approximately 40% of the patients. Almost all cases were accompanied with cerebral hypoperfusion. About half of them were unilateral lesion. Medical treatment or vascular reconstruction were employed for the approximately 60% patients. The prognosis did not changed significantly. However, the activity of daily living was affected by mental retardation due to associated disorder in our series.

**Conclusions:** Clinical feature of quasi-MMD were revealed in the nationwide study. In quasi-MMD, the development of moyamoya vessels was less and intracranial hemorrhage was less.

## SA.03.03

**Diagnosis and Treatment of Moyamoya Syndrome**

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Diagnosis of moyamoya disease (MMD) and moyamoya syndrome (MMS) has previously been based on the radiological information of intraluminal stenosis in the carotid fork. Even now, therefore, it is not rare to experience the difficulty to distinguish MMD/MMS from atherosclerotic arterial stenosis in a certain population of patients. In this lecture, therefore, we present our recent results on three-dimensional constructive interference in steady state (3D-CISS) images in patients with MMD/MMS. In adult patients with MMD, the outer diameters of C1, M1, and A1 segments were significantly smaller than the control, severe M1 stenosis, and non-involved side in MMD. There are significant correlations between Suzuki's angiographical stage and the outer diameters of C1, M1, and A1. The laterality ratio of C1 and M1 was significantly smaller in unilateral moyamoya disease than the controls and severe MCA stenosis. Therefore, MMD can be characterized by specific shrinkage of the involved arteries. On the other hands, there are two groups in patients with MMS: one group with similar shrinkage of the involved arteries and another group without. Therefore, MMS can be divided into 2 pathophysiologically different subgroups. Further studies would be warranted to determine genetic backgrounds in these 2 groups. We also present surgical results in patients with MMS.

## SA.03.04

**Moyamoya Syndrome in Caucasians**

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**Objektive:** Moyamoya disease (MMD) associated with a potentially underlying disease, such as genetic disorders or other coexisting hematological pathologies, is called moyamoya syndrome (MMS) or quasi-moyamoya. This very rare disease has been characterized mainly in Asian countries, so far. As MMD reveals several significant ethnic differences, the question is raised whether characteristics of MMS would also vary among different ethnic backgrounds. Here, we report a homogenous series of 61 patients with MMS and highlight the specific clinical features of this rare disease among European Caucasians.

**Methods:** We retrospectively identified 61 European Caucasians with MMS who were treated in our institution between 1997 and 2014. We analyzed demographic data, clinical symptoms, associated diseases, angiographic characteristics and functional hemodynamic studies.

**Results:** 32,7% of our patients were juvenile. MMS disease presented with an overall female predominance of 2,8:1. 78,7% presented with a typical MMS with more pronounced unilateral and atypical MMS in pediatric population (unilateral/atypical: pediatric patients 20%/15%, adults 7,3%/7,3%). We identified a wide range of associated diseases. Overall, 83,6% and 8,2% of our cohort presented initially with ischemic and hemorrhagic manifestation, respectively. The hemorrhagic manifestation of MMS occurred however only in adults. Angiographic analysis revealed steno-occlusive involvement of the posterior circulation in 31% with a higher involvement in pediatric patients (40%) compared to adults (26,8%).

**Conclusions:** The characterization of homogenous European Caucasian cohort reveals several differences when compared to reported Asian MMS cohorts and also compared to European Caucasian MMD cohort. We conclude that MMS represents a distinct disease with different ethnic clinical features.

## SA.03.05

**Surgical outcomes following encephaloduroarteriosynangiosis in adult moyamoya disease associated with type 2 diabetes**

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**Objective:** Debate exists regarding merits and shortcomings of indirect bypass procedure for adult patients with moyamoya disease. Considerable variation of neovascularization occurs among different organs with diabetes mellitus. Here we aimed to evaluate the effect of encephaloduroarteriosynangiosis on moyamoya disease associated with type 2 diabetes.

**Methods:** A retrospective and 1:2 matched case-control study in moyamoya patients with or without type 2 diabetes (n=120) was conducted. Postoperative collateral formations were graded according to the modified collateral grading system originated from Matsushima angiographic stage classification. Neurological function outcomes before and after the operation were evaluated according to the modified Rankin scale.

**Results:** There was no significant statistical difference in constituent ratio of initial symptom and preoperative Suzuki stage between patients with and without type 2 diabetes. Progression of the angiopathy around the circle of Willis postoperatively was observed in bilateral internal carotid arteries in both groups. Patients with type 2 diabetes had a higher postoperative Suzuki stage ( $P<0.01$ ) and more frequent development of collateral angiogenesis germinating from the external carotid after indirect revascularization procedures on the surgical cerebral hemisphere (86.3 versus 73.5%,  $P<0.05$ ). The extent of postoperative collateral formation in diabetic group was significantly higher ( $P=0.04$ ). Postoperative clinical improvement in diabetes mellitus group was more common after revascularization procedures ( $P<0.01$ ) and diabetic group had lower scores of modified Rankin scale ( $P<0.05$ ) compared with the nondiabetic cohort.

**Conclusions:** Encephaloduroarteriosynangiosis is an efficacious treatment for adult patients with moyamoya disease. Patients with type 2 diabetes could get better collateral circulation and clinical improvement following surgery.

SA.03.06

### Individualized EC-IC revascularization in the treatment of advanced Moyamoya disease: surgical techniques and mid-term follow-up results

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**Objective:** To evaluate the safety and therapeutic effect of Individualized EC-IC revascularization in the treatment of advanced moyamoya disease.

**Methods:** 72 patients (42 female, 30 male, mean age 42.3y) of advanced moyamoya disease were analysed. The symptoms included Transient ischemic attack (TIA) in 20 cases, cerebral infarction in 28 cases, and intracranial hemorrhage in 24 cases. Angiogram indicated spontaneous anastomoses to various extent, mainly from middle meningeal artery (MMA), superior temporal artery (STA) and occipital artery (OA), all of which were evaluated for individualized surgical planning. Hemodynamic research demonstrated comprised cerebral vessel reserve (CVR) in all cases. Superficial temporal artery-middle cerebral artery bypass combined with an indirect revascularization procedure was recommended. Individualized adjustment was made to preserve pre-existing spontaneous anastomoses. The mean follow-up period was 65.2 months, all clinical data was reviewed.

**Results:** A total of 102 hemispheres of 72 patients were operated. In 96.1% (98/102) of the procedures, the pre-existing spontaneous anastomoses of the distal branches of external carotid artery with the cortical arteries were preserved well. Complication rate was equal to results reported previously by the first author. TIA was effectively reduced or totally arrested. The neurological deficits significantly improved in 35 patients, with the National Institutes of Health Stroke Scale scores lowered by 3-6. There's no rehemorrhage in hemorrhagic group. In the 80 hemispheres with follow-up digital subtraction angiography. 97.8% (88/90) stomas remaining patent until the last follow-up. Additionally indirect anastomosis could be identified with well-persevered pre-existing ones. Hemodynamic follow-up showed improved CVR in most patients.

**Conclusions:** This study showed that individualized EC-IC revascularization is safe and effective in the treatment of advanced moyamoya disease.

SA.03.07

### Attempt of quantitative evaluation of cerebral blood flow using estimated arterial spin labeling method for Moyamoya disease

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**Objective:** This study aimed to introduce our trial method to evaluate cerebral blood flow (CBF) value. It was evaluated by estimated arterial spin labeling ASL(eASL) method and 15O-PET, patients for moyamoya disease (MMD) before bypass surgery.

**Methods:** 8 patients (16 side) who was diagnosed MMD at our university hospital were included in this study. All patients underwent both PET and ASL studies before surgery. 15O-PET was performed to evaluate CBF and metabolism by autoradiographic method. eASL method use a low-resolution, multiple post delay prescan (prescan PLD: 0.7, 1.3, 2.0, 2.5, 3.0 sec). Transit time (TT) map was obtained by the prescan, and CBF map (PLD: 0.7 and 2.0 sec) that was corrected by the TT map. Date of eASL and PET images were registered to a personal computer and analyzed by Dr. View software. 10 regions of interests (ROIs) were selected on the MCA territories on each hemisphere in 2 image slices. Averaged value of ten ROIs were statistically assessed by correlational analysis.

**Results:** Mean age was 45.6 ( $\pm 19.3$ ) years old and 4 patients were female. Coefficient of correlation of PLD: 0.7sec or PLD: 2.0sec were 0.53 ( $Y=1.42X-12.5$ ) and 0.52 ( $Y=1.14X+0.6$ ) respectively. The CBF value of each hemisphere was correlated with both PLD: 0.7 and 2.0 sec. The quantitative value of CBF was slightly overestimated by eASL method.

**Conclusions:** Quantitative CBF value obtained by eASL method corrected by TT map was correlated with real CBF. Further study about the validity of the quantitative performance for MMD will be needed.

SA.03.08

### The importance of blood pressure control to prevent cerebral hyper- or hypoperfusion syndrome after direct revascularisation surgery for moyamoya steno-occlusive cerebrovascular disease

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**Objective:** Hyperperfusion syndrome as a complication after superficial temporal artery-middle cerebral artery (STA-MCA) anastomosis is well known and described. The phenomenon of symptomatic hyper- and hypoperfusion in the same patient is very rare.

**Methods:** A 57-year-old woman suffered from recurrent TIAs (transient ischemic attacks) for 4 years. The left-hander developed a stroke in April 2011 with hemiparesis on the left, motor aphasia and facial palsy. Angiographically a bilateral stenosis of the middle cerebral artery (MCA) with suspicion of moyamoya syndrome was shown and so we planned surgical revascularisation on the symptomatic side. The surgery was performed without complications. In the course of recovery the patient developed again neurological deficits during blood pressure fluctuations, so that a strict blood pressure control (130mmHg) was required to avoid hyper- and hypoperfusion.

**Results:** With systolic blood pressure above or below 130 mmHg the patient developed a hemiparesis and motor aphasia. Only by setting very close blood pressure limits, there was an almost complete remission of neurological deficits.

**Conclusions:** To prevent neurological deficits after STA-MCA (superficial temporal artery-middle cerebral artery) anastomosis an understanding of hyper- and hypoperfusion syndrom is required, as only a very accurate blood pressure control can help resolve or even avoid recurrent neurological deficits.

SA.03.09

### Rescue strategies for failed revascularization in MMD and MMS

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From 1991-2014, 1244 revascularization bypass procedures (1107 direct, 137 indirect) were performed in 765 patients, of whom 57 were repeat revascularizations. The surgeries were done at Stanford Hospital or Lucile Packard Children's Hospital.

Patients with previous indirect bypass: 38 (23F, 15M) underwent 56 repeat revascularizations. 42% (16/38) were pediatric patients. The mean time to repeat surgery was 49 months (3-264). The indications for repeat surgery included TIAs (26 patients, 68%), new strokes (9), and worsening developmental delay with seizure (3). Of the repeat surgeries, 59% (33/56) had direct bypasses (28 STA-MCA, 4 OA-MCA, 1 saphenous-MCA) and 23 had indirect (4 EMS, 6 EDAS, 4 EDAMS, 8 omental-cerebral transpositions, 1 burr holes). Mean follow up was 4.8 years (0-16) and 81% (29/36) of the surviving patients are well with no TIAs/stroke.

Patients with previous direct bypass: 19 (16F, 3M) required 20 repeat revascularizations. 26% (5/19) were pediatric patients. The mean time to repeat surgery was 47 months (0.2-200). The indications for repeat surgery include TIAs (13 patients, 68%), new strokes (4), 1 acute graft occlusion and 1 with persistent steal despite surgery. 55% (11/20) of repeat revascularizations were to augment blood supply in another vascular territory and this was achieved using another direct bypass technique (ie frontal STA branch or occipital artery). Other procedures included 3 EMS, 1 EDAS, 5 omental-cerebral transposition. Mean follow up was 4.7 years (0.5-21), 82% (14/17) of the surviving patients are well with no TIAs/stroke.

When the initial revascularization was performed at Stanford, the rate of repeat revascularization was 4% (5/137) and 1% (12/1107) for indirect and direct bypass, respectively (p=0.0312).

Repeat revascularization is safe and effective in preventing future ischemic events in patients with failed prior revascularization procedures. Initial indirect bypass has a higher rate of requiring repeat revascularization. Over 50% of repeat revascularizations were achieved with direct bypass procedures.

SA.04.02

### Biomarkers in Moyamoya disease

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**Background:** Moyamoya is a progressive arteriopathy of unclear etiology predominantly affecting the major branches of the internal carotid arteries. This disorder was initially characterized by radiographic criteria, as defined by Suzuki. Over time, it has increasingly become apparent that these angiographic findings represent a multitude of distinct pathophysiologic processes that manifest a shared radiographic signature. Initially, this concept of multiple conditions culminating in a common end pathway was acknowledged by the distinction between moyamoya "disease" (bilateral arteriopathy existing in isolation) and moyamoya "syndrome" (either unilateral arteriopathy or arteriopathy found in conjunction with some other medical disorder). This awareness of heterogeneity in clinical presentation has prompted research focused on the development of techniques capable of better defining MMD. One area with the potential to advance the diagnosis, prognosis and understanding of moyamoya is the field of biomarkers.

**Methods:** Laboratory research and literature review

**Results and Conclusions:** Biomarkers are defined as "any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease." In essence, biomarkers are biological "fingerprints" that can be used by clinicians to identify a specific disease. Current biomarkers relevant to the diagnosis of moyamoya, including phenotypes, radiographic findings, proteins, circulating cells and genetic/epigenetic markers are presented, including discussion of how they could be employed in practice.

SA.04.03

### Therapeutic angiogenesis using myoblast-mediated gene therapy in experimental EMS model of mouse

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**Objective:** An encephalomyosynangiosis (EMS) is performed to induce collateral angiogenesis in moyamoya disease. But the angiogenetic effect is not constant in some moyamoya patients, and is rarely seen for patients with occlusive cerebrovascular diseases. Recently, we developed the myoblast-mediated gene therapy to deliver angiogenic genes to the brain/muscle interface and to stimulate angiogenesis after EMS. The purpose of this study is to establish the myoblast-mediated gene therapy to induce mature and functional angiogenesis in ICAO/EMS model.

**Methods:** Control, VEGF, PDGF or VEGF/PDGF-transfected myoblasts were implanted into the temporal muscle following ICAO/EMS in mice. The engraftment of myoblasts were examined by X-gal staining. Time-course change of CBF and CVRC were measured by LASCA. The transplanted angiogenesis, the infarct area and rescued neuronal cells and neuronal apoptosis after transient MCAO were evaluated on day 21, 42 and 84. Expression of pro-angiogenic cytokine was examined in the cerebral cortex after ICAO/EMS and myoblast-mediated gene therapy.

**Results:** The fusion of myoblasts were confirmed the animal model on day 21. The group of VEGF/PDGF-transfected myoblasts implantation showed earlier and higher recovery of CVRC than other groups, and stimulated the transplanted angiogenesis consisting of endothelial cells with pericyte coverage. These collateral angiogenesis with mature vessel structure rescued neuronal cells and decreased the number of neuronal apoptosis and the infarct area after MCAO. It was considered that expression of pro-angiogenic cytokine such as VEGF and Ang-2 were related to the enhanced angiogenesis in the cerebral cortex attached with the temporal muscle after EMS.

**Conclusions:** This novel approach of therapeutic angiogenesis using myoblast-mediated gene therapy could improve the hemodynamic disorder by inducing mature and functional angiogenesis, and might be a promising strategy for patients with hemodynamic disorder by moyamoya disease and atherosclerotic cerebral artery occlusion.

## SA.04.04

**Predicting cerebral hyperperfusion syndrome following STA-MCA bypass based on 3.0T intraoperative perfusion-weighted MRI**

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**Objective:** To use intraoperative magnetic resonance imaging (iMRI) to quantitatively monitor hemodynamic changes after superficial temporal artery-middle cerebral artery (STA-MCA) bypass and explore clinical efficacy of iMRI in STA-MCA bypass surgery.

**Methods:** 25 cases with occlusive cerebrovascular disease (OCVD) treated with STA-MCA bypass in 3.0T iMRI suite were recruited iMRI series, including intraoperative MRA, perfusion weighted imaging (PWI) were performed before and after STA-MCA anastomosis. Postoperative CTA or DSA were performed to assess the judgment of intraoperative MRA about bypass patency. Pre- and intra-operative perfusion parameters, including cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT) of MCA-territory area in the surgical side and contralateral mirroring areas were measured. Relative perfusion values (rCBF, rCBV, rMTT) were also obtained. Differences in pre- and intra-operative perfusion parameters, relative perfusion values were assessed with paired t test or matched-paired signed-ranks test.

**Results:** Patency of bypass graft was displayed using intraoperative 3D MRA images and confirmed by follow-up DSA or CTA within one week. There were no hemorrhagic or ischemic infarction after the operation. Nine cases suffered from postoperative CHS, including headache in two cases, seizure attacks in three cases, aphasia in two cases, transient motor deficits in two cases. All patients recovered well without neurological deficits within two weeks. Postoperative rCBF and rCBV values were significantly higher than those before operation ( $P < 0.05$  for all). Postoperative rMTT was significantly lower than that before operation ( $P < 0.05$ ). Postoperative rCBF values, the change of rCBF values in the MCA-territory of the surgical side in the group with CHS were significantly higher than those without CHS ( $P < 0.05$  for all).

**Conclusions:** High-field iMRI is valuable for the non-invasive assessment of both the graft patency and cerebral hemodynamic changes in the STA-MCA bypass surgery for OCVD by performing intraoperative MRA and PWI analysis.

## SA.04.05

**Significance of hemodynamic stress distribution as a possible clinical marker of ischemic symptom in patients with moyamoya disease**

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**Objective:** Nowadays, the chance for diagnosing asymptomatic moyamoya disease by a medical check up with MRI is increasing. In this study, we considered the less invasive method for predicting future ischemic symptom of the patients.

**Methods:** We reviewed cerebral blood flow (CBF) data obtained by xenon CT imaging (XeCT) in six patients with ischemic type or asymptomatic moyamoya disease. The data were obtained as volume data using 320-row CT, and applied to the automated region-of-interest-determining software (3DSRT) and converted to standardized images. CBF value, cerebrovascular reserve capacity (CVRC), and hemodynamic distribution (hdSD) of 6 asymptomatic hemispheres were compared to those of 4 ischemic hemispheres. The statistical difference was determined by two-sided Mann-Whitney's U test. Difference with  $P < 0.05$  was considered to be significant. When statistically significant difference between parameters of asymptomatic side and ischemic symptomatic side is identified, cut-off points were calculated with receiver operating characteristics (ROC) curves. Transition of hdSD before and after bypass surgery was also assessed.

**Results:** Of six CBF related parameters evaluated, statistically significant differences between asymptomatic sides and ischemic sides were observed in CBF value of MCA region, hdSD at rest, and hdSD after acetazolamide loading. Of the three statistically significant parameters, ROC analysis revealed that hdSD was the most sensitive as well as specific parameter (threshold 1.2, sensitivity 1, specificity 1). In all two patients that have undergone EC-IC bypass surgeries and CBF data were obtained both before and after surgery as well, hdSDs were higher than the threshold of 1.2 before surgery, but decreased lower than the threshold of 1.2 after surgery along with recovery of ischemic symptoms.

**Conclusions:** The data showed that hdSD reflects ischemic symptom of patients with moyamoya disease well, thus could be used as an ischemic symptomatic marker for following up patients with moyamoya disease.

SA.04.06

### Serial measurement of cerebral hemodynamics with ASL-MRI after indirect bypass surgery for patients with Moyamoya disease

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**Objective:** We investigated the utility of arterial spin labeling (ASL) MRI in patients with Moyamoya disease (MMD) who underwent surgical treatment.

**Methods:** 15 patients with MMD (mean age; 19.3 y.o.) who were treated with indirect bypass surgery were serially examined with ASL-MRI before and after surgery. 15O gas PET studies were performed in 5 of 15 patients to confirm the quantitativity of ASL-CBF.

**Results:** ASL-CBF had significant but weak linear correlation with PET-CBF ( $r=0.46$ ). However, abnormally decreased ASL-CBF corresponded well with the area responsible for clinical symptoms. Serial ASL measurement revealed the improvement of hemodynamics after surgery, and the amelioration was detected even around 1 month after surgery.

**Conclusions:** Although ASL-CBF was less quantitative than gold standard CBF value, it can be used sufficiently to detect the relative abnormality of cerebral circulation. It must be useful to serially evaluate cerebral hemodynamics non-invasively before and after surgical treatment of MMD.

SA.04.07

### Amelioration of brain metabolism and higher brain function by surgical re-vascularization against adult Moyamoya disease – A positron emission tomography study

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**Objective:** We have previously presented that the decreased oxygen metabolism of occipital lobe highly correlated with low score of intelligence quotient (IQ) in patients with Moyamoya disease (MMD) (Hosoda et al. Int J Stroke 2010). In this paper, we analyzed if the surgical revascularization against the parieto-occipital area may contribute to the amelioration of cerebral metabolism and IQ of patients with MMD.

**Methods:** We have examined the cerebral oxygen metabolism ( $CMRO_2$ ) among 70 hemisphere of 39 patients with MMD (mean 31.5, 19-58) using <sup>15</sup>O gas technique and positron emission tomography (PET) before and approximately 1 year after the indirect bypass surgery. Patients treated from 1991 to 2000 were operated with EDAS on the sensorimotor area (Phase 1, N=14), and those treated after 2001 were operated with EDPS on the parieto-occipital area in addition to EDAS if occlusion of PCA were observed (Phase 2, N=25). 18 of subject were also evaluated with WAIS-R or -III together with PET examination.

**Results:** In phase 1 patients,  $CMRO_2$  did not increase after the operation. Instead,  $CMRO_2$  significantly decreased in occipital lobe and thalamus. In phase 2 patients,  $CMRO_2$  significantly increased among frontal, parietal and occipital lobe. In 6 of phase two patients and none of phase 1 patients showed increase in IQ score of more than 10 points. In these 6 patients  $CMRO_2$  significantly increased in fronto-parietal lobe. In other 12 patients whose IQ did not change after surgery,  $CMRO_2$  also was unchanged.

**Conclusions:** Surgical revascularization to the parieto-occipital area in patients with PCA lesion may be a key factor for the amelioration of higher brain function in adult patients with MMD.

SA.04.08

### Postoperative executive function in adult Moyamoya disease: a preliminary study of its functional anatomy and behavioral correlates

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**Objective:** The impact of surgical revascularization on executive dysfunction in adult moyamoya disease (MMD) remains unclear. The aim of the present study was to examine the postoperative radiological correlates of cognitive improvement, thus to explore its underlying mechanism.

**Methods:** Fourteen patients who met the inclusion criteria were operated and successfully followed up for 6 months. Cortical perfusion and spontaneous functional activities were examined by single photon emission computed tomography (SPECT) and resting-state BOLD fMRI, separately. Executive function was evaluated by two tests (TMT-B and MES-EX). Follow-up neuropsychological outcomes were correlated with radiological changes to identify nodes of leading contribution to postoperative executive outcomes. This study was registered on ClinicalTrials.gov numbering NCT02305407.

**Results:** All patients received successful unilateral bypasses, and during 6 month follow-up, the different operating sides did not differ significantly at either baseline MES-EX ( $p=0.671$ ) or in the  $\Delta$ MES-EX ( $p=0.930$ ) (1 patient could not complete the TMT-B). The group with good collaterals (9 patients, graded A, Matsushima criteria) exhibited significantly increased postoperative perfusion ( $\Delta$ Hemodynamics) in the left frontal lobe ( $p=0.009$ ), right frontal lobe ( $p=0.003$ ) and left parietal lobe ( $p=0.014$ ), and also a trend of increase in the right parietal lobe ( $p=0.205$ ). Then, spearman's correlation test suggested that only the right frontal lobe exhibited significant positive postoperative radiological correlates with cognitive performance ( $\Delta$ MES-EX vs.  $\Delta$ Hemodynamics,  $r=0.620$ ,  $p=0.018$ ;  $\Delta$ MES-EX vs.  $\Delta$ ALFF,  $r=0.676$ ,  $p=0.008$ ;  $\Delta$ Hemodynamics vs.  $\Delta$ ALFF,  $r=0.547$ ,  $p=0.043$ ). Subsequent regional amplitude of low-frequency fluctuations (ALFF) analysis revealed that the right dorsolateral prefrontal cortex (DLPFC) was the only node lying in the responsible hemisphere to exhibit significant postoperative ALFF changes.

**Conclusions:** The results not only advanced our understanding of dynamic and pathological interactions of executive dysfunction in adult MMD, but also indicated that the right DLPFC amplitude might provide a quantitative prediction of postoperative executive control improvement.

SA.04.09

### Cognitive functions in children and adults with moyamoya vasculopathy: a systematic review and meta-analysis.

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**Objective:** Patients with moyamoya vasculopathy (MMV) may experience cognitive impairment. In a systematic review and meta-analysis, we aimed to assess the presence, severity, and nature of cognitive impairment in children and adults with MMV.

**Methods:** We searched Ovid Medline and EMBASE for studies published between January 1st 1969 and November 7th 2014. Independent reviewers extracted data for mean intelligence quotient (IQ) and standardized z-scores for cognitive tests and determined percentages of children and adults with cognitive deficits. We explored associations between summary measures of study characteristics and cognitive impairment by linear regression analysis.

**Results:** We included 16 studies (12 studies reporting on 362 children, 4 on 104 adults). In children, the median percentage with impaired cognition was 30% (range 13-67%), median IQ was 97 (range 71-107). Median z-score was -0.39 for memory and -0.43 for processing speed. In adults, the median percentage with impaired cognition was 43% (range 0-69%), median IQ was 97 (range 95-99). Median z-score of cognitive domains were between -0.9 and -0.4, with multiple domains affected.

**Conclusions:** A large proportion of children and adults with MMV have cognitive impairment, with modest to large impairments across various cognitive domains. Further research is needed to investigate determinants of cognitive deterioration and the influence of revascularization treatment on cognitive outcome.

P 01

### Moyamoya disease: Two different techniques in the same patient – case report and surgical considerations

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**Objective:** Moyamoya disease is described as hypoplasia of bilateral internal carotid arteries. The vascular network of the disease was considered as being collateral after stenosis or vessel occlusion. The treatment is clinical medical devices, encephalo-duro-arterio-myo-synangiosis, arterial shunts or multiples burr holes to improve the brain vascularization.

**Case Report:** A six-year-old boy presented episodes of right hemiparesis with motor afasia. Imaging studies showed classical features of moyamoya disease at the left side. He had been operated on two years ago in another hospital because he had presented left hemiparesis and drowsiness. The radiologic findings had showed hypodense image in right frontal lobe and occlusion of right middle cerebral artery, beside signs of bilateral moyamoya disease. The performed surgery had being encephalo-duro-arterio-myo-synangiosis at the right side.

**Methods:** Under general anesthesia the patient was prepared and a “T” incision was made for approach left skull convexity. After exposure of temporal muscle and pericranium, several triangular shapes incisions were made in the pericranium in order to allow one-inch burr hole just beneath of each incision. After complete the burr holes the dura mater and arachnoid were opened under magnification to expose the pial vessels. Finally we slipped each leaf of pericranium into the respective burr hole allowing the contact between pial vessels and pericranium. We've done eight burr-holes covering the entire left skull convexity.

**Results:** The patient has been followed up for 72 months showing no symptom of motor or language dysfunction. The cerebral angiography shows better pial anastomosis at the left side as well as more intense arterial irrigation.

**Conclusions:** Surgical treatment offers the best results and benefits for moyamoya disease, but no standard surgical treatment is established. At least for this case, multiples burr holes technique improved brain vascularization better than encephalo-duro-arterio-myo-synangiosis and provide a greater field of arterial irrigation.

P 02

### Whole exome sequencing in a Korean family including 2 MMD cases

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**Objective:** A genetic determinism is highly suspected in MMD, based on the 10% rate of familial cases. A susceptibility variant in RNF213 gene (p.R4810K) has been strongly associated with MMD in Japan and East Asia but is not detected in Caucasian MMD cases.

**Methods:** A French MMD family originating from Korea, including two affected sisters born from unaffected non-consanguineous parents. Sanger sequencing was used to screen for the R4810K variant. Whole Exome Sequencing (WES) was performed in both sisters and their 2 parents.

**Results:** Both sisters presented a child-onset bilateral anterior moyamoya angiopathy, and the youngest exhibited severe arterial hypertension and renal artery stenosis. Sanger sequencing excluded the p.R4810K variant in RNF213 gene in the two sisters. No other RNF213 candidate variant was detected using WES data. WES data were then filtered using an autosomal recessive and a *de novo* models (mosaics hypothesis). We excluded intronic (except splice-affecting), 3'UTR and 5'UTR variants, variants frequently found in the ESP and 1000 genomes databases ESP, and in an in-house database. We chose an allelic frequency threshold of 0.1% for the *de novo* dominant model and 1 % for the recessive model. Four candidate *de novo* variants were shared by both sisters. According to the autosomal recessive model, we identified 13 candidate genes (6 homozygous variants and 7 genes with compound heterozygous variants). Among these candidate mutations, 11 variants might be false positive, because of a poor coverage (X<8), poor quality (Q<20) or conflicting data when checking the BAM files. Confirmation of these candidate variants by Sanger sequencing is ongoing. Variants located in one of these candidate genes or in a gene involved in a same pathway- will be further searched for in a cohort of 20 MMD probands using WES.

**Conclusions:** These 2 MMD cases and family originating from Korea did not harbor a candidate RNF213 mutation. WES identified several candidate variants which are currently validated by Sanger analysis and will be checked in a series of 20 additional MMD patients who are undergoing WES.

P 03

### Distinct chromosomal rearrangements in two novel Moyamoya syndromes

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**Objective:** Physiopathological mechanisms of Moyamoya angiopathy are so far unknown. The identification of the various genes involved in familial moyamoya disease and moyamoya syndromes with a high penetrance of this angiopathy provides clues to identify the pathways leading to this vasculopathy.

**Methods:** Detailed clinical and MRI characterization of 2 unrelated families including 3 MMS affected brothers (F1) and one female MMS child (F2). High throughput genotyping analysis including high-density Affymetrix 6.0 DNA chips and FISH were performed in both families.

**Results:** Family F1's MMS has not been reported so far and is characterized by a moyamoya angiopathy associated with various rare systemic venous abnormalities in three male children born from non-consanguineous healthy parents. Family F2's affected child shows moyamoya angiopathy, growth retardation, developmental delay, facial dysmorphism, hearing-loss, multiple cutaneous angioma and nephropathy. This young girl is born from unaffected non-consanguineous parents. Both families are of Caucasian origin. Copy number analysis with high-density arrays identified in family F1 a X-chromosome triplication encompassing 7 genes and cosegregating with the disease. FISH showed that this rearrangement is located on Xq28 chromosome. The triplication was shared by the affected children and their mother, who showed a totally skewed X-inactivation. In F2, routine karyotype and high-density array performed in the affected young girl revealed a reciprocal unbalanced translocation resulting in a partial 6p trisomy/18q monosomy. Parental karyotypes and array analyses were normal. Comparison of these chromosomal rearrangements with another pediatric MMS published in 2013 (Rosenberg et al, 2013, Pediatric) sharing some of the features of F2 affected child reduced the candidate interval to a 14 Mb single region located in 6p, duplicated in both cases.

**Conclusions:** We report herein the clinical features of 2 novel MMS. One is caused by a de novo chromosomal anomaly located on 6p and the other one by a most likely recessive X-linked disorder associated with a triplication on Xq28. Molecular analyses of further MMS families with the same phenotype are needed to refine these chromosomal candidate intervals and identify causative genes.

P 05

### Surgical anatomy and preservation of middle meningeal artery during bypass surgery for Moyamoya disease

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**Objective:** The middle meningeal artery (MMA) is known to function as one of important collateral routes in moyamoya disease. However, the anterior branch frequently courses within the lesser wing of sphenoid bone and can easily be damaged during craniotomy for bypass surgery. This prospective study was aimed to study surgical anatomy of the MMA and to establish the technique to preserve it during bypass surgery for moyamoya disease.

**Methods:** Totally 22 patients with moyamoya disease underwent STA-MCA anastomosis combined with indirect bypass on 27 sides. Anatomical relationship between the anterior branch of the MMA and the lesser wing was classified into three types; bridge, monorail, and tunnel types. During surgery, the lesser wing was carefully resected with a rongeur or high-speed diamond drill to preserve the anterior branch of the MMA.

**Results:** The anterior branch of the MMA was classified into bridge type in 5 sides (18.5%), monorail type in 10 sides (37.0%), and tunnel type in 12 sides (44.5%). Patients' age was closely related to the anatomical findings ( $p=0.0168$ ). Careful resection of the lesser wing with a rongeur could preserve the bridge- and monorail-type MMA (100% and 71.4%, respectively). However, drilling out of the lesser wing under a surgical microscope was essential to preserve the tunnel-type MMA. Intraoperative indocyanine green videoangiography was useful to confirm the patency during surgery.

**Conclusions:** It is essential to understand surgical anatomy of the MMA around the pterion in order to preserve its anterior branch during bypass surgery for moyamoya disease.

P 06

### Analysis of risk factors for hyperperfusion syndrome after revascularization surgery for Moyamoya disease

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**Objective:** Cerebral hyperperfusion (CHP) syndrome is a known complication of revascularization surgery for moyamoya disease/syndrome (MMD/S); however, the mechanism remains to be elucidated and analysis of regional CBF (rCBF) study is warranted. The purpose of this study is to evaluate the predicting factor associated with postoperative hyperperfusion syndrome.

**Methods:** We evaluated regional CBF (rCBF) using SPECT and perfusion CT at the site of anastomosis before and after surgery in 14 patients (19 hemispheres) with MMD/S aged between 6 and 64 years (mean, 36). All patients underwent STA-MCA single anastomosis with EDAMS. Intraoperatively, blood flow velocity of recipient artery (M4) was measured with Micro-Doppler, and pre/post-operative regional CBF were compared semiquantitatively ( $rCBF = \text{affected side rCBF} / \text{unaffected side rCBF}$ ).

**Results:** Mean blood flow velocity of recipient M4 (mBFV) before and after anastomosis were 3.5cm/sec and 11.9cm/sec, respectively. rCBFs before and after surgery were 0.95 and 1.42, respectively. Postoperatively, transient neurological deterioration compatible to CHP syndrome was observed in 3 patients. Increase of mBFV and rCBF after anastomosis were higher in the CHP group than no CHP group, even though there were no statistically difference (mBFV: 6.33 vs 4.15 times; rCBF: 1.63 vs 1.47 times).

**Conclusions:** Excessive increase of mBFV and rCBF are possible risk factor of postoperative CHP in MMD/S.

P 07

### Semi-quantitative parameters of analytical digital subtraction angiography before and after STA-MCA bypass

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**Objective:** Recently, parametric imaging of the digital subtraction angiography (DSA) has been developed in clinical use. We aimed to calculate semi-quantitative values of the analytical DSA before and after superficial temporal artery to middle cerebral artery (STA-MCA) bypass and compared each values of both pre and postoperative examinations.

**Methods:** Three patients with symptomatic MCA stenosis or internal carotid artery occlusion underwent standard single STA-MCA bypass. Analytical DSA (iFLOW, Siemens) was conducted before and after the surgery, provided color-coded maps. Region of interests (ROIs) were placed near the anastomosed vessels for following calculation of three semi-quantitative parameters; maximum concentration of the contrast medium (peak height) [%], time to the maximum concentration (peak time) [sec] and area under the curve (AUC); which are calculated from the time-intensity diagram of the ROI. All values were compared between pre and post bypass.

**Results:** Color-coded DSA illustrated excellent resolution images and revealed good bypass patency in all cases. The peak height decreased after the bypass in all patients. The peak time indicated earlier arrival of the contrast medium postoperatively and the AUC had trend to increase after the bypass surgery compared to preoperative DSA in two patients.

**Conclusions:** Although some parameters showed ideal change of flow dynamics, the values could not reach statistical difference due to small number. Adequate position of the ROIs or catheter placement, condition of the injection can not be ignorable for more precise study. Besides, normal values of each parameters should be investigated in non-ischemic patients. Analytical DSA has potential for studying flow dynamics of ischemic strokes.

P 08

### Occipital artery posterior cerebral and middle cerebral artery bypass for symptomatic posterior cerebral artery occlusion in Moyamoya disease

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**Objective:** Posterior cerebral artery (PCA) is involved approximate in 30 % of the patients with moyamoya disease. To explore the feasibility of the direct anastomosis in the posterior brain, the surgical strategies and outcomes were investigated in patients who underwent either occipital artery (OA) - PCA and middle cerebral artery (MCA) bypass.

**Methods:** A total of 428 revascularization procedures in 286 patients were retrospectively assessed by reviewing clinical charts and radiological data.

**Results:** Ten patients (3.5 %) were treated with direct bypass after the anterior revascularization with median interval of 30 months (range; 5 month to 16 years). Seven out of 10 patients were under the age of 18 (average age; 17.5 + 15.6 yrs). Preoperative symptoms were as followed; 1) transient motor deficit in the lower extremities (n=4), 2) visual disturbances (n= 6) and 3) cerebral infarctions (n=6). A favorable outcome (modified Rankin scale < 3) was achieved in 9 patients. The direct anastomosis were performed in 3 hemispheres with OA-MCA bypass and in 8 hemispheres with OA-PCA bypass. Patency of the direct bypass was confirmed on angiogram in 7 out of 7 patients who underwent conventional angiogram performed within 1 year after the surgery. None of the patients demonstrated cerebral infarctions after the posterior revascularization.

**Conclusions:** In MMD, symptomatic PCA regression following anterior revascularization was predominantly observed in children and young adults. Direct anastomosis in the posterior brain can be successfully achieved by OA-PCA/MCA bypass.

P 09

### Long-term results of Moyamoya disease with revascularization and without revascularization – single institute experience

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**Objective:** Moyamoya disease (MMD) is not a rare cerebrovascular disease mainly in South Korea. We analyzed our experience at Busan and Haeundae Paik Hospital. We report on a consecutive series of patients treated for MMD and detail their demographics, clinical characteristics, and long-term surgical outcomes.

**Methods:** Data obtained in consecutive series of 79 patients with MMD treated micro-surgically by one neurosurgeon between 1998 and 2013 were analyzed. Demographic, clinical, and surgical data were prospectively gathered and neurological outcomes assessed in postoperative follow-up using the modified Rankin Scale. Association of demographic, clinical, and surgical data with postoperative outcome was assessed by chi-square, uni- and multivariate logistic regression, and Kaplan-Meier survival analyses.

**Results:** We treated a total of 52 adult patients undergoing 89 procedures (mean age 42.5 years) and 27 pediatric patients undergoing 50 procedures (mean age 11.8 years). Direct revascularization technique was used in 93.4% of adults and 88% of pediatric patients. The surgical morbidity rate was 2.9% and the mortality rate was 0.7% per treated hemisphere. The cumulative 5-year risk of perioperative or subsequent stroke or death was 4.5%. Of the 39 patients presenting with a transient ischemic attack, 92.3% were free of transient ischemic attacks at 1 year or later. Overall, there was a significant improvement in quality of life in the cohort as measured using the modified Rankin Scale ( $p < 0.0001$ ).

**Conclusions:** Revascularization surgery in patients with MMD carries a low risk, is effective at preventing future ischemic events, and improves quality of life. Patients in whom symptomatic MMD is diagnosed should be offered revascularization surgery.

P 10

### Characterization of headache in Moyamoya disease

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**Objective:** Headache is known as a symptom of patients with Moyamoya disease (MMD). So far, only a few studies evaluated the epidemiology of headache in MMD. Literature review showed that no systemic characterization of headaches in MMD exists. Further the clinical treatment is often underestimated and is not enough recognized in the scientific literature.

**Methods:** In order to estimate intensity, characteristics and frequency of headaches, 55 German patients with MMD were asked by using a validated self-administered headache screening-questionnaire and a telephone interview based on the International Headache Society classification. Those patients who received extra-intracranial bypass were asked to remember the frequency and intensity of headache in the year before surgery and after bypass surgery retrospectively.

**Results:** Out of the investigated 55 patients 37 (67,3%) suffered from headaches in the past year. 17 patients (47,9%) fulfilled the diagnostic criteria for migraine, seven (18,9%) without aura and ten (27%) with aura. Headache intensity was rated  $3,2 \pm 1,3$  according to the numeric rating scale with a frequency of  $5,3 \pm 5$  days/month. Tension-type headache character was found in ten patients (27%). Headache intensity was rated  $3 \pm 1,7$  with a frequency of  $7,5 \pm 11$  days/month. A combined headache of migraine and tension-type headache was found in ten patients (27%). Headache intensity was rated  $3,5 \pm 1,3$  with a frequency of  $6,4 \pm 8,7$  days/month. No patient had cluster headache. Out of the 34 patients who underwent bypass surgery 19 had headaches before surgery. Intensity (NRS;  $p < 0.001$ ) and frequency (days/month;  $p < 0.01$ ) of headache was rated as better in the retrospective self-rating questionnaire after surgery.

**Conclusions:** Migraine was found in 47,9% in the patients. In comparison to a German representative sample population, in which episodic migraine was found only in 16,6% (Yoon et al., 2012), the incidence is much higher than expected. Tension-type headache was also found in 27% of the patients which was not reported in MMD before. Moreover, patients who underwent bypass surgery rated headaches significantly being better after surgery compared to those without surgery.

Yoon, M.S., Katsarava, Z., Obermann, M., Fritsche, G., Oezuyurt, M., Kaesewinkel, K., Katsarova, A., Santowski, I., Diener, H., Moebus, S. (2012): Prevalence of primary headaches in Germany: results of the German Headache Consortium Study. J. Headache. Pain. 13, 215-223.

P 11

### A case of aplastic or twiglike middle cerebral artery successfully treated with revascularization

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**Introduction:** An aplastic or twiglike middle cerebral artery (Ap/T-MCA) is rare congenital anomaly related to interference in the normal embryonic development of the MCA. Recent reports suggested that spontaneous middle cerebral artery occlusion with moyamoya phenomenon (MCAO-Mo) is similar to Ap/T-MCA. Here, we present a case of Ap/T-MCA presenting with transient ischemic attack, which was successfully performed with revascularization, and review reported cases of Ap/T-MCA and MCAO-Mo with revascularization.

**Case presentation:** A 19-year-old woman visited our hospital with transient left hemiparesis. Cerebral angiography revealed right proximal M1 occlusion, and M2 was supplied through plexiform form microvascular networks. Left internal carotid angiography showed normal findings and there was no transdural anastomosis. Single photon emission computed tomography indicated misery perfusion in right MCA territory. A right superficial temporal artery (STA) - MCA bypass and encephalo-myo-synangiosis (EMS) was uneventfully performed. Postoperative magnetic resonance angiography showed decrease of the blood flow signal in twiglike networks. She was discharged home without any neurological deficit. Revascularization for Ap/T-MCA might be useful to reduce collateral stress in microvascular networks and prevent selected patients from future stroke.

P 12

### Long-standing misery perfusion in Moyamoya disease compensated with large amount of vasodilation from the early (asymptomatic) stage

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**Objective:** It was well-known that the misery perfusion (defined by an increase of OEF) was observed using O-15 gas PET in patients with ischemic stroke or TIA due to moyamoya disease (MMD). However, compensatory change of cerebral hemodynamics associated with a stenosis of carotid bifurcation and a development of moyamoya vessels (intracerebral collaterals) could be occurred in early (asymptomatic) stage of MMD. In this hemodynamic study for patients with MMD, the role of compensatory mechanisms in response to the progression of hemodynamic cerebral ischemia was investigated using recent O-15 gas PET and CBF-SPECT including acetazolamide-activation.

**Methods:** 10 patients with asymptomatic MMD and 10 patients with symptomatic patients were included in this study. Recent O-15 gas PET provided parametric images of CBF, CMRO<sub>2</sub>, CBV, and OEF. Quantified CBF-SPECT such as 123I-Iodoamphetamine (IMP)-Autoradiography (ARG) method provided cerebrovascular reserve (CVR) and stage of hemodynamic cerebral ischemia. Stage II ischemia was defined by both resting CBF less than 80% of normal mean CBF and CVR (which calculating from (acetazolamide-activated CBF / resting CBF - 1) × 100%) less than 10%. Relationship between CVR-SPECT and OEF-PET, and relationship between CVR-SPECT and CBV-PET were estimated in combined with asymptomatic and symptomatic MMD.

**Results:** A decrease of CVR-SPECT well correlated with an increase of OEF-PET, and significant decrease (<10%) of CVR-SPECT was found in significant increase (+2SD<) of OEF-PET. But, significant decrease (<10%) of CVR-SPECT was also found in less increase (<+2SD) of OEF-PET. On the other hand, a decrease of CVR-SPECT also well correlated with an increase of CBV-PET. However, less decrease (10%<) of CVR-SPECT was found in significant increase (+2SD<) of CBV-PET and significant decrease (<10%) of CVR-SPECT was constantly indicated in extreme increase of CBV-PET.

**Conclusions:** In moyamoya disease, hemodynamic cerebral ischemia was initially compensated with large amount of vasodilation and then could be followed with an increased OEF in response to the degree of progression of hemodynamic cerebral ischemia. Long-standing misery perfusion in MMD should be recognized to have different pattern of the early engagement of vasodilatory reserve capacity associated with a development of intracerebral collaterals in comparison to chronic misery perfusion in atherothrombotic stroke.

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### Time course of flair ivy sign of Moyamoya disease before and after indirect bypass surgery

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**Objective:** Diffuse leptomeningeal high intensity in FLAIR image of MRI of patients with moyamoya disease (MMD) is now well known as "ivy sign". In this study, we aimed to clarify the correlation between FIS and status of cerebral circulation. We also examined time course of perioperative changes in FIS induced by indirect bypass surgery.

**Methods:** 61 patients with MMD underwent indirect bypass surgery since 2011, 38 of them were serially examined with 3T MRI before and 8-12 days (early post) and 4-8 months (late post) after operation. Degree of FIS were evaluated using previously published ivy sign score for each operated hemisphere. We also compared the FIS score and relative regional cerebral blood volume (rCBV) that was detected by DSC MR perfusion.

**Results:** A significant positive correlation was found between FIS score and preoperative rCBV. FIS score significantly ( $p=0.01$ ) increased in early postoperative measurement (mean 3.91, range 0-10) in comparison to preoperative value (mean 2.78, range 0-7). That in late postoperative measurement (mean 2.45, range 0-8) was significantly ( $p=0.03$ ) less than that in preoperative measurement. Late postoperative rCBV was also significantly smaller than preoperative value.

**Conclusions:** We considered that FIS can be a good indicator to represent the severity of hemodynamic deficiency in MMD. It is noticeable that transient increase in FIS was detected in early post-operative measurement after indirect bypass surgery. We need to perform additional investigation to reveal the significance of this phenomenon.

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### A case of Moyamoya disease, basal encephalocele and morning glory disc anomaly in Oro-Facio-Digital Syndrome (OFD1)

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**Objective:** Type 1 oro-facial-digital syndrome (OFD1) is a X-linked dominant male-lethal developmental disorder. Mutations that leads to *Ofd1* transcript inactivation promote several somatic and brain structural abnormalities through a defective sonic hedgehog pathway. Our case presents a new association of moyamoya disease, sphenoidal encephalocele, morning glory disc (MGDA) and coloboma in the context of a missense OFD1 mutation, an occurrence that is never been reported in literature to date.

**Methods:** The patient, aged 6 months, presented bilateral coloboma of optic nerve and sphenoidal encephalocele, MGDA, associated to other mild clinical features of OFD1. At the age of 2 years he reported transitory right hemiparesis. Angio-MRI and digital subtractive angiography showed results consisting with moyamoya, grade 3 of Suzuki. Heparin infusion and subsequent antiplatelet were started. Left indirect revascularization as encephalo-duro-myo-arterio-pericranio-synangiosis (EDAMPS) was carried out. The same procedure was performed contralaterally after three months. Repairing of the encephalocele was scheduled.

**Results:** The postoperative course was uneventful, with neurologic recovery. Follow-up MRA angiography and SPECT showed good patency of intracranial vessels. Electroretinography (ERG) was normal, cortically evoked visual responses (VEP) showed a left decreased amplitude. Genetic consult advised for sequence analysis of OFD1 gene that detected a novel hemizygous missense variant, c.1081T>C, resulting in p.Tyr361His mutation change.

**Conclusions:** Inactivation of *Ofd1* transcript is associated with defective Sonic hedgehog (Shh) pathway and could play a crucial role in the forebrain development, besides being a critical pathway in many developmental processes, as the vessel formation. We describe the surgical treatment of moyamoya disease in a patient with bilateral MGDA, coloboma and sphenoidal encephalocele, reporting a novel missense mutation in OFD1 gene. This contributes to expand the phenotype of OFD1 and make we speculate on a possible pathogenic role of OFD1 gene in this association.

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### Transient middle cerebral artery occlusion in mice induces RNF213 – a susceptibility gene for Moyamoya disease

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**Objective:** Recent genome-wide and locus-specific association studies revealed that ring finger protein 213 (RNF213) gene is a susceptibility gene for moyamoya disease (MMD), while the exact mechanism how the genetic alteration of RNF213 contributes to the development of MMD is undetermined. It was shown by quantitative reverse transcription PCR analysis that constitutive expression of RNF213 gene was very low in both adult and embryonic brain tissue. However, little is known about temporal and spatial expressing pattern of RNF213 gene under the condition of cerebral ischemia which could be one of characteristic pathologies associated with MMD. To address this important issue, Rnf213 mRNA expression was investigated in mice brains subjected to transient middle cerebral artery occlusion (tMCAO).

**Methods:** Male C57BL6/J mice were subjected to tMCAO by intraluminal blockade of MCA. The suture was withdrawn to achieve the reperfusion 60 minutes after the induction of ischemia. The treated mice were perfused through the heart with saline, followed by fixative at a given survival period: 1, 3, 6, or 24 hours. Expression of Rnf213 gene in tMCAO brain was investigated with *in situ* RNA hybridization and real time PCR analysis.

**Results:** By *in situ* RNA hybridization, significant increase in Rnf213 mRNA was detected in the cerebral cortex supplied by affected MCA, especially at penumbra area, as early as 6 hours after tMCAO, which was further increased at 24 hours. The change of Rnf213 gene expression was not observed in non-ischemic hemisphere and control specimens. Double staining of Rnf213 mRNA with NeuN immunohistochemistry indicated Rnf213 hybridization signal expression mostly in neurons. Real time PCR analysis confirmed the induction of Rnf213 gene 24 hours after tMCAO.

**Conclusions:** Rnf213 gene is upregulated in the ischemic brain especially at penumbra area 6 hours after tMCAO. Early increase in RNF213 gene after tMCAO may indicate the involvement of RNF213 gene in cerebral ischemia, which is an underlying pathology of MMD.

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### Direct bypass led immediately and transient effect, after that, indirect bypass kept long-term outcome in Moyamoya disease

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**Objective:** Retrospective analysis of single direct bypass and wider open door “encephalo-duro-arterio-myo-galeo-synangiosis (EDAMGS)” which covers frontal-parietal-occipital lobe area for Moyamoya disease.

**Methods:** Subjects were 30 sides of Moyamoya disease which were treated by the operation mentioned above. Pre- and post-operative angiography and SPECT were analyzed. And hyper-perfusion and ischemic events were also evaluated. From our previous experience, direct bypass became narrow and poor appearance with time. On the other hand, indirect bypasses were growing wider, deeply and incremented vessels with time. We postulated that direct bypass recovered CBF transiently, and indirect bypass recovered CBF permanently. In fact, almost cases showed neovascularization from external carotid system which depended on indirect bypass after 3 months from surgery. By the way, hyper-perfusion flow was revealed in SPECT just after direct bypass surgeries in many cases. We recommended minimum direct bypass and wider indirect bypass, because of protection against hyper-perfusion and for long term neovascularization. So, we have performed single direct bypass and wider open door “encephalo-duro-arterio-myo-galeo-synangiosis (EDAMGS)” which covers frontal-parietal-occipital lobe area.

**Results:** In 30 sides of this operation, one side of 3 year-old girl showed contralateral infarction just after surgery. Although all patients showed increased-cerebral blood flow in SPECT, transient symptomatic hyper-perfusion syndrome was in 5 side (17%). There were no morbidity and mortality. The patency of all direct bypass were confirmed in 3D-CTA or angiography. In mid-term follow-up, there is no ischemic event.

**Conclusions:** The single direct bypass plus wider open door EDAMGS was one of the choices of the treatments for Moyamoya disease.

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### Analysis of cerebral perfusion and vascular reserve after combined revascularization for moyamoya disease

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**Background:** Moyamoya disease is a progressive occlusive disease of the cerebral arteries. Various vascular reconstruction surgeries have been reported, but the most appropriate procedure remains unclear. We have preferred to perform a combined direct and indirect bypass to the Rolandic region to prevent ischemic stroke.

**Objective:** The aim of this study was to evaluate the surgical results of our method using cerebral blood flow (CBF) from single photon emission computed tomography (SPECT).

**Methods:** This study examined 29 hemispheres in 21 patients (6 males, 15 females; mean age,  $33.25 \pm 19.26$  years; range, 9-67 years). All patients underwent combined vascular reconstruction using a superficial temporal artery (STA) -middle cerebral artery (MCA) anastomosis and encephaloduromyosynangiosis. Regional CBF (rCBF) and cerebrovascular reserve (CVR) were measured using N-isopropyl-p-[<sup>123</sup>I]- iodoamphetamine (123I-IMP) SPECT before and after the procedure.

**Results:** Postoperatively, 28 direct bypasses were patent, but one became occluded within 3 months after surgery. Preoperative symptoms completely resolved in all except one case. Three months postoperatively, improvement of rCBF at rest was not evident in the ipsilateral frontal lobe after surgery, but CVR was widely and significantly improved in the frontal lobe involving the motor cortex (preoperative CVR,  $-1.1 \pm 16.1\%$ ; postoperative CVR,  $14.3 \pm 19.7\%$ ,  $p < 0.001$ ) and premotor area (preoperative CVR,  $-2.14 \pm 15.9\%$ ; postoperative CVR,  $10.2 \pm 15.9\%$ ,  $p < 0.001$ ).

**Conclusions:** Our combined direct and indirect bypass effectively reduced ischemic symptoms of moyamoya disease and increased CVR. The possibility that transient ischemic attack was more strongly affected by CVR than by CBF was suggested.

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### CFD analysis for STA-MCA anastomosis

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**Objective:** Quantitative blood flow analysis for the efficacy of STA-MCA anastomosis has not been established yet. The purpose of this study is to simulate MCA blood flow by Computational Flow Dynamics (CFD). We also assessed the difference of anastomosis angle and sites.

**Methods:** 3D vascular images of two ICA obstruction patients who undertook single STA-MCA (M4) anastomosis were created by 3D-DSA DICOM data, which analyzed by ANSYS CFX. Their antegrade flow through ICA mainly came from maxillary arteries. We also made two different angle of anastomosis, and M2 bypass models.

**Results:** Every MCA flow increased in both cases by 59-295% and 2-34%, respectively. The nearer to bypass sites, the larger blood flows through MCA branches. There were no difference in MCA flow between various bypass angles. M2 anastomosis has larger MCA flow than M4 bypass, in spite that less M1 blood flow. This may suggest collision between antero- and retrograde blood flow in M1, which result in cerebral infarction in the area of M1 perforators.

**Conclusions:** There are some differences in MCA blood flow between cases and bypass site. CFD analysis may propose surgical indication and efficacy in STA-MCA anastomosis in the future.

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### Moyamoya disease detected in perinatal period: case presentation

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**Objective:** Pregnancy and delivery is a known trigger of ischemic or hemorrhagic stroke in patients with Moyamoya disease/syndrome (MMD/S). We report a case of MMD/S detected by transient ischemic attack (TIA) during second delivery and underwent vascular reconstruction 12 years later.

**Case presentation:** The patient became pregnant for first time at 25-year-old. At that time, a careful examination was not performed, although she had transient dysarthria. During second delivery at 32-year-old, she had hemiparetic TIA again and MRI/A showed acute ischemic stroke due to MMD/S. Thereafter, antiplatelet therapy was introduced and no neurological deterioration was observed. However, a stage of MMD/S was progressed and cerebrovascular reserve capacity was decreased significantly. She underwent vascular reconstruction surgery at 44-year-old. Currently, 3 years after surgery, she remains well and recent SPECT showed improvement of cerebrovascular reserve capacity.

**Conclusions:** This case is a reminder that we always have to consider a possibility of MMD/S when pregnant patients present ischemic symptoms. Stroke risk is known to increase significantly in perinatal period in MMD/S patients, and the risk is higher in non-diagnosed than in diagnosed patients.

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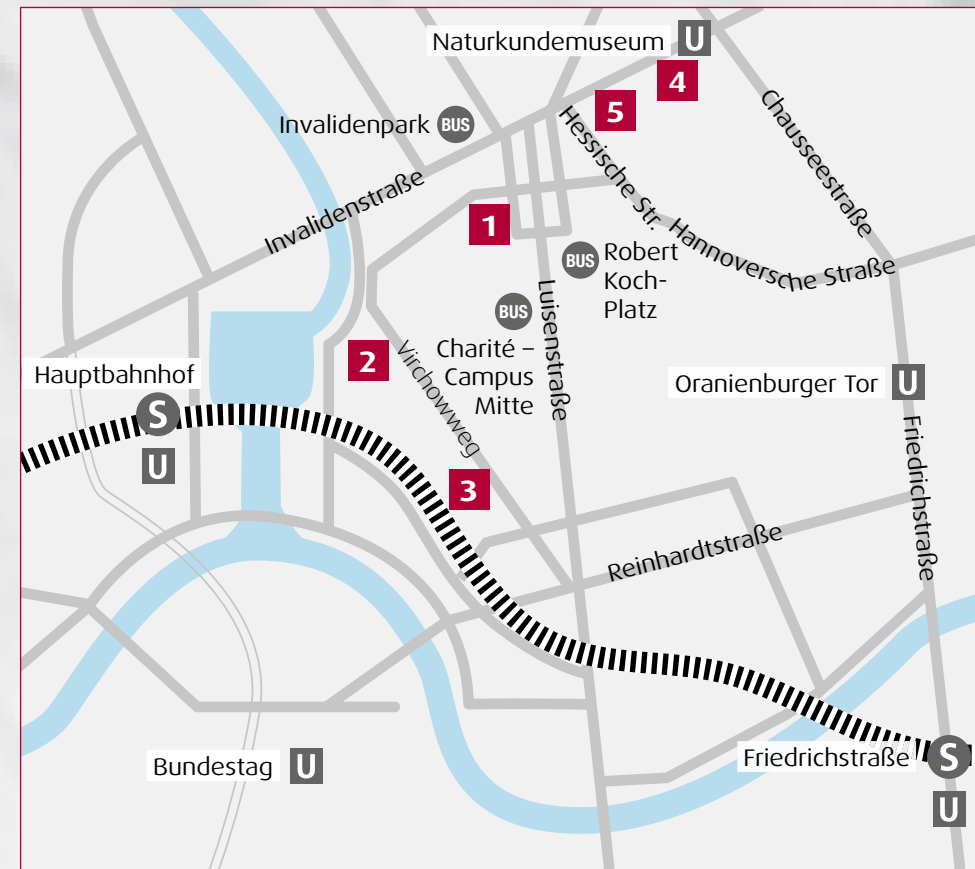
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