Brain Arteriovenous Malformations (AVMs)

- Tangle of abnormal blood vessels (nidus)
  - No intranidal capillary bed
  - Arteriovenous shunting
  - Range of vessel types
- Located randomly throughout brain
- Cause of hemorrhagic stroke

Outcomes following treatment of brain arteriovenous malformations (AVMs) with microsurgery, embolization, stereotactic radiosurgery (SRS), or combinations vary greatly between studies. Case fatality was 0.68 (95% CI, 0.61-0.76) per 100 person-years overall, 1.1 (95% CI, 0.87-1.3; n = 2548) after microsurgery, 0.50 (95% CI, 0.43-0.58; n = 9438) after SRS, and 0.96 (95% CI, 0.67-1.4; n = 1019) after embolization. Intracranial hemorrhage rates were 1.4 (95% CI, 1.3-1.5) per 100 person-years overall, 0.18 (95% CI, 0.10-0.30) after microsurgery, 1.7 (95% CI, 1.5-1.8) after SRS, and 1.7 (95% CI, 1.3-2.3) after embolization. More recent studies were associated with lower case-fatality rates (rate ratio [RR], 0.97; 95% CI, 0.95-0.98) but increased rates of hemorrhage (RR, 1.02; 95% CI, 1.00-1.03).

CONCLUSIONS: Although case fatality after treatment has decreased over time, treatment of brain AVM remains associated with considerable risks and incomplete efficacy. Randomized controlled trials comparing different treatment modalities appear justified.
A Randomized trial of UNRUPTURED Brain Arteriovenous Malformations
NIH/NINDS Grant 1U01 NS051483
JP Mohr, AJ Moskowitz, C Stapf
Best Possible vs. Deferred Invasive Treatment
for those deemed suitable for eradication
Randomization plan 1:1 = 400 cases
Comparison of any invasive therapy to medical management arm (defer
invasive treatment for up to 5 years).
The trial stopped early due to a huge effect in favor of the medical
management arm.

Unlike cancer-related chemotherapy that aims to shrink
abnormal tumor tissue as cytotoxic therapy, the concept for the
treatment of brain AVM would be to stabilize vascular tissue
and thereby decrease the risk of spontaneous ICH.

Identify Specific Targets

- Analyzing surgical specimens
- Modeling brain AVM in animals

Hashimoto, Neurosurgery 54: 410, 2004
Kilic, Neurosurgery 57: 997, 2005
Sure, Neurosurgery 55: 663, 2004
Sonstein, J Neurosurg 85:838, 1996
ZhuGe, Q. et al. Brain 2009
Murphy, PA. Laboratory Investigation 2009
Hereditary Hemorrhagic Telangiectasia (HHT)  
Rendu-Osler-Weber Syndrome

- **Familial**
  - Hereditary Hemorrhagic Telangiectasias (HHT)
    - RASA1 (p120 RasGAP, is a Ras GTPase-activating protein) capillary malformation-AVM
  - Non-HHT
    - 53 patients in 25 families

- **Sporadic**
  - 95-98% no family hx

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Stimulation Results in Brain AVM

- **Autosomal dominant disorder**
- **Mucocutaneous telangiectasia**
- **AVMs in Liver, Lung and Brain**
- 80% of cases have functional heploinsufficiency of Endoglin (HHT1) or ALK1 (HHT2)

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AdCre – Regional Conditional Deletion of Alk1

- **Promoter**
- Exons 4, 5, 6
- loxp

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Alk1 Regional Conditional Deletion Plus VEGF Stimulation Results in Brain AVM

- AdCre + AAV-VEGF
- Alk1
- Angiogenesis
- 8 wks

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VEGF Stimulation is Necessary for Brain AVM Formation

Alk1^+/+ / VEGF

Alk1^-/- / VEGF

Alk1^-/- only


Macrophage Infiltration

A

Mouse Cre VEGF

WT + Alk1^{+/-}

Alk1^{+/-}

Alk1^{+/-}

Alk1^{+/-}

B

Iba1 Cells / mm^2

WT

Alk1^{+/-}

Alk1^{+/-}

Alk1^{+/-}

C

In Iba1 Cell Count

In Iba1 Cell Area

R^2=0.2

Chen et al. ATVB, 2013

Microhemorrhage

Prussian blue

Prussian blue

H&E

Mouse

Human

Chen et al. ATVB, 2013

PDGFB Signaling Regulates Smooth Muscle Recruitment

PDGFB driven vSMC proliferation and migration

Reduced vSMC proliferation and migration

PDGFB or PDGFR^B knock-out

Chen et al. ATVB, 2013

Hellstrom; Development, 1999
ALK1 Knockdown Attenuates the Upregulation of PDGFB in HBMEC in Response to VEGF Stimulation

HBMEC (human brain microvascular endothelial cell) were transfected with control shRNA or shRNA. Cells with >70% reduction of Alk1 gene expression were cultured for 18 h in the presence or absence of VEGF (0, 10, 50, and 100 ng/ml). qRT-PCR was performed for Alk1 (A) and Pdgfb (B). All data are shown as mean and SD. *p<0.05 vs. control.

Gene Mutation in Bone Marrow Transmits the Phenotype

Potential Therapies for Brain AVMs

1. Anti-inflammation: Minocycline
2. Anti-angiogenesis: Avastin, sFLT
3. Increase PDGFB, improve vessel integrity
   Thalidomide
4. Bone marrow transplantation
   Peripheral monocyte/progenitor transfusion
Anti-Inflammation
Doxycycline Treatment Reduces Angiogenesis in VEGF Treated Mouse Brain

Anti-Angiogenesis
Bevacizumab reverse brain AVM phenotype

Anti-Angiogenesis
Stereotactic Injection of AAV2-sFLT Inhibited Brain AVM Formation

Anti-Angiogenesis
Systemic Delivery of AAV9-sFLT Inhibited the Brain AVM Formation
Increase PDGFB

Thalidomide Treatment Reduced the Number of Abnormal Vessels

Prussian blue staining

Summary

1. Invasive therapies are associated with considerable risks
2. No specific medical therapy is available
3. The concept for the treatment of brain AVM is to stabilize vascular tissue and thereby decrease the risk of spontaneous ICH.
4. Novel therapeutic approaches:
   A. Anti-inflammation
   B. Anti-angiogenesis
   C. Improve vascular integrity
   D. Correct gene mutation in BM monocyte/progenitors
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