

# **Blood Vessel Abnormalities and Risk of Bleeding in Alagille Syndrome**

Tina Bales, M.D.

Children's Hospital of Philadelphia

Courtesy of Binita M. Kamath, MBBChir MD

Hospital of Sick Children, Toronto

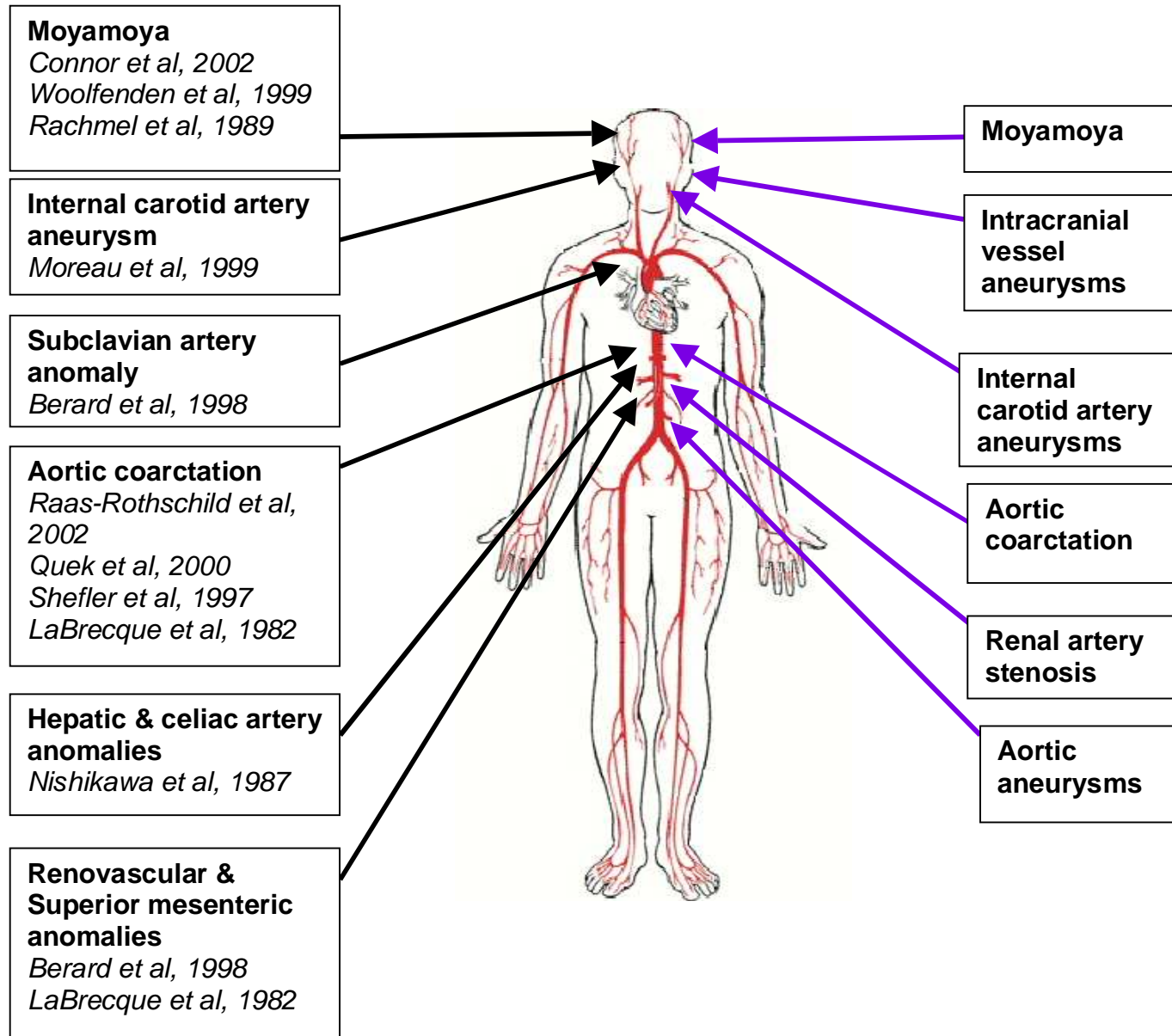
# Introduction

- Blood vessel involvement in AGS has been recognized from the earliest descriptions
- 1973 Watson and Miller describe AGS patients with vascular lesions of heart – mostly pulmonary artery
- Alternate name is Arteriohepatic Dysplasia

# Blood Vessel Abnormalities in AGS

- Vascular anomalies seen of:
  - aorta
  - kidney
  - liver
  - brain
- Large review at Children's Hospital of Philadelphia in 2003 - 9% individuals had some vascular event or bleeding episode

# Spectrum of vascular anomalies in our cohort of AGS patients and in previous reports



# Scientific Evidence for JAG1 Involvement in Vascular Development

- Expression of JAG1
- JAG1 mutant mice die from hemorrhage due to vascular defects
- Other Notch pathway genes implicated in vasculogenesis
- Notch3 mutations cause CADASIL (late-onset strokes caused by vascular changes)

# Blood Vessel Abnormalities of the Brain

- Most common abnormality in vessels of the brain is narrowing of the internal carotid arteries
- Sometimes with increased small vessels to compensate
- Rare aneurysms

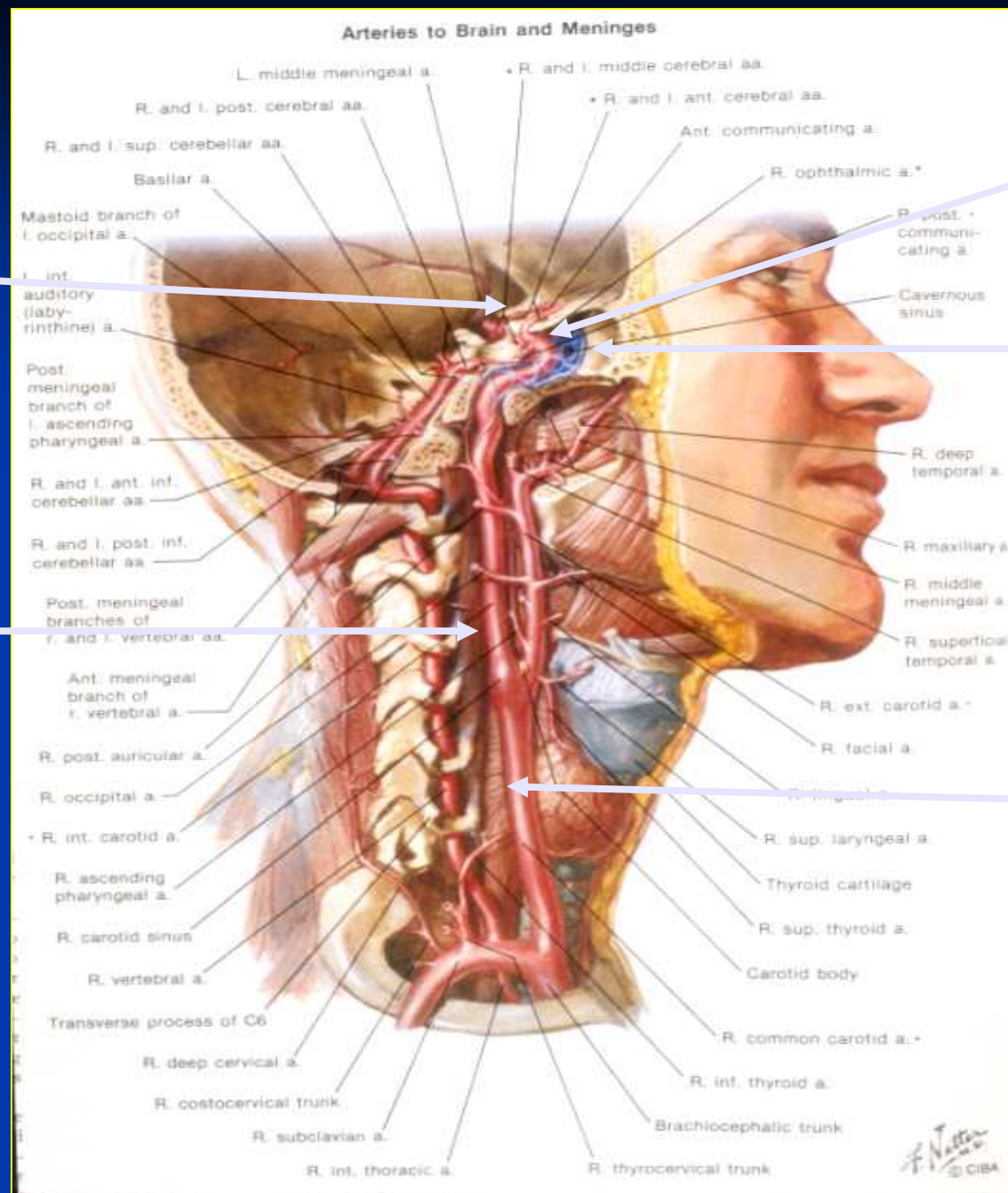
**Middle cerebral and Anterior cerebral**

**Internal carotid**

**Supraclinoid area**

**Cavernous sinus**

**Common carotid**



# Moyamoya

- Narrowing of the internal carotid artery in some AGS patients has led to the diagnosis of Moyamoya
- Moyamoya means hazy or vague referring to the smoky appearance of the collaterals on angiography

# Moyamoya

To diagnose Moyamoya:

1. Stenosis or blockage of internal carotid artery at end portion
2. Proliferation of vessels beyond a narrowing (collaterals)
3. Involvement of both sides

# Moyamoya

- May start as one side and progress to both over years
- Use Positron emission tomography (PET) and Single photon emission CT (SPECT) to assess blood flow to brain
- If very poor perfusion present then bypass surgery is indicated

# Moyamoya

- Usually detectable on MRA
- Needs to be followed for progression
- Cause unknown
- Approximately 5-10 individuals with AGS and Jagged1 mutations

# AGS anomalies

- Not all AGS patients meet criteria for diagnosis of Moyamoya
- Some patients may have birth anomalies which are unchanging
- There may be several different types of anomalies
- Will require following patients with identified lesions to see what happens

# Intracranial Bleeding: What has been seen?

- Intracranial bleeding has been reported in many studies and occurs in approximately 15% individuals with AGS
- Some, but not all of these have a documented structural vessel abnormality
- Not all associated with trauma or clotting disorder
- Mortality associated with intracranial bleeds is high: 30-50%

# What has been seen?

- Strokes - narrowing of the internal carotid artery on arteriogram
- Small bleeds without anomalies on arteriogram
- Slight increase likelihood of bleeding after trauma

# Presentation of Stroke or Bleeds

- Headache after trauma
- Sudden weakness of arms or legs
- Slurred speech
- Seizures
- No symptoms

# Management of Intracranial Vessel Involvement

- Value of MRA is not clear
  - Patients with normal MRAs have gone on to have an intracranial bleed
  - Patients with a normal MRA have developed symptoms and had anomalies identified on subsequent scans – progressive lesions?
- Current recommendation is for a baseline MRA in children who do not require sedation

# Management of Intracranial Vessel Involvement

- Recommend aggressive evaluation and investigation in the event of
  - Head trauma
  - New onset neurologic symptoms - limb weakness, slurred speech, numbness, severe headache

# Summary

- Vascular anomalies and events are a potentially under-recognized complication of AGS
- Intracranial bleeding occurs in 15% individuals
- Vascular anomalies may account for one-third of the deaths in AGS individuals
- Any clinical suspicion of vascular compromise should be aggressively worked up in children and adults with AGS