



# Pediatric Stroke

*Nuances of diagnosis and management, hemoglobinopathies, Sickle cell disease and other specific to children*



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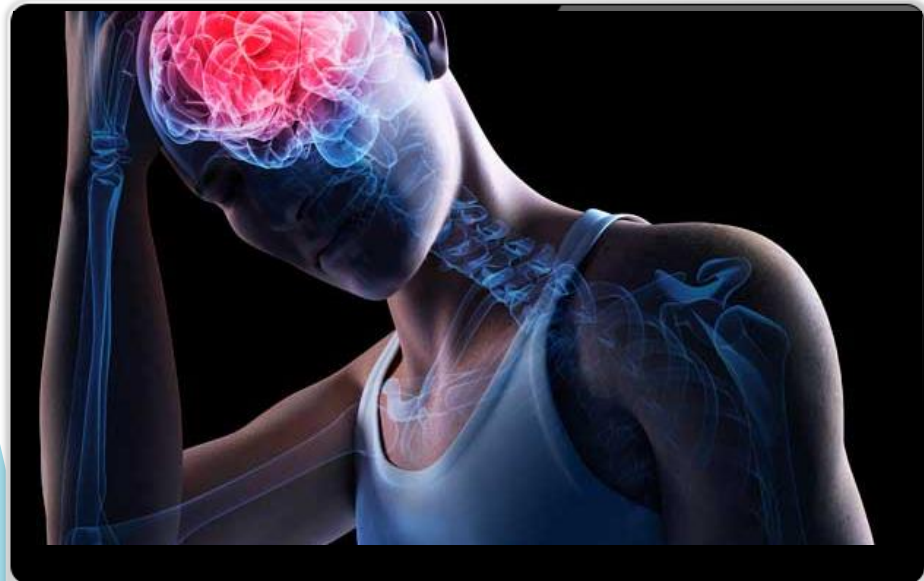
# Presentation Outline

- 1 Introduction to Stroke
- 2 Classification of Pediatric Stroke
- 3 Risk factors for Pediatric Stroke
- 4 Etiologies of Pediatric Stroke
- 5 Presentation, Diagnosis & Management of Pediatric Stroke



# **Introduction to Stroke**

# Stroke definition by WHO



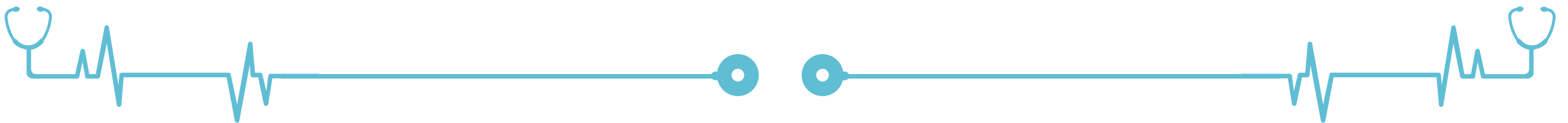
**Disturbance  
of Cerebral  
function  
lasting more  
than 24hrs**

- Clinical syndrome of rapidly developing clinical signs of focal or global nature in cases of coma.
- Leading to death with no apparent cause, other than vascular origin



# Burden of Stroke Globally

- Stroke can happen to anyone anytime.
- Every year, 15 million people worldwide suffer a stroke.
- Of these, 5 million die and another 5 million are left permanently disabled.
- Rare in people under 40 years; if occurs, the main cause is high blood pressure.
- Also occurs in about 8% of children with sickle cell disease.





# More Statistics....

- Stroke leading cause of disability, dementia and death worldwide.
- Approximately 70% of deaths from stroke and 87% of stroke-related disability occur in LMICs.
- Less than a century ago, stroke was relatively uncommon in Africa.





# Rising Stroke Burden

- Most common diseases were communicable diseases, with non-communicable diseases, including stroke, considered rare, particularly in SSA.
- Recent evidence indicates, Africa could have up to 2–3-fold greater rates of stroke incidence and higher stroke prevalence than western Europe and the USA

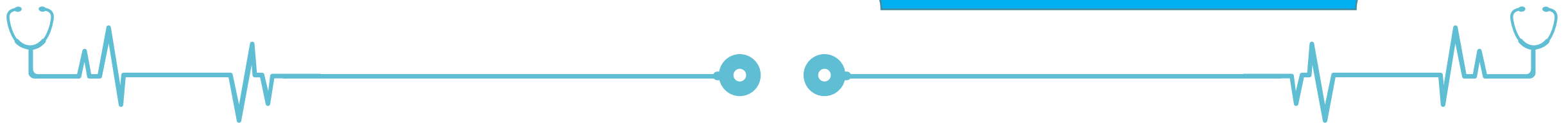
# Stroke in Africa



Annual incidence  
rate of up to 316  
per 100,000

A prevalence  
of up to 1,460  
per 100,000

A 3-year fatality  
rate greater than  
80%.



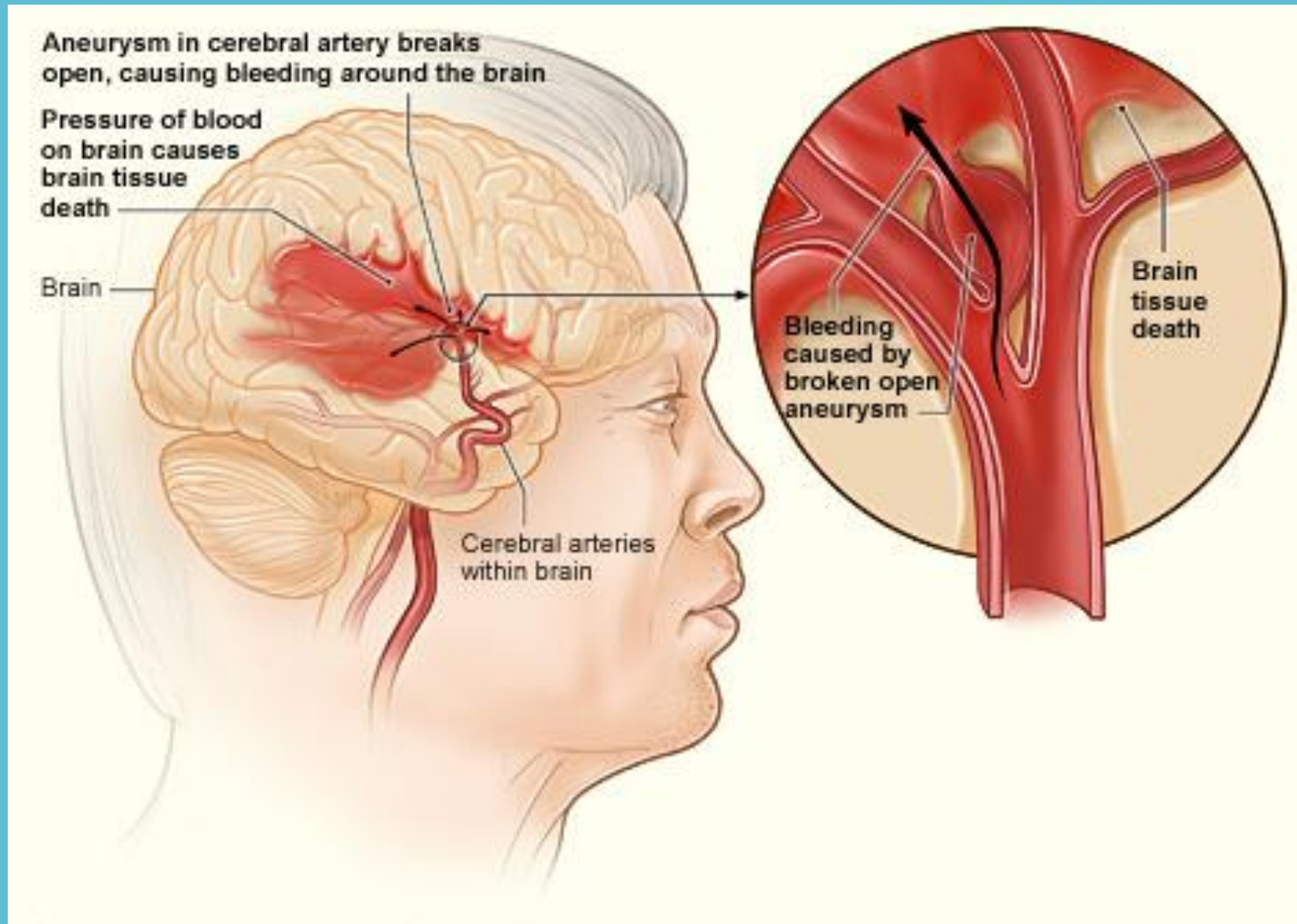


# Types of Stroke:

- **Cerebrovascular accident (CVA)**, otherwise called **a stroke**, is a common cause of morbidity and mortality in many developing countries.
- Stroke can be either **ischemic** or **hemorrhagic** or both.
- **An ischemic stroke** occurs when the blood supply to part of the brain is interrupted or reduced, preventing brain tissue from getting oxygen and nutrients.
- **A Hemorrhagic stroke** is due to bleeding into the brain by the rupture of a blood vessel.



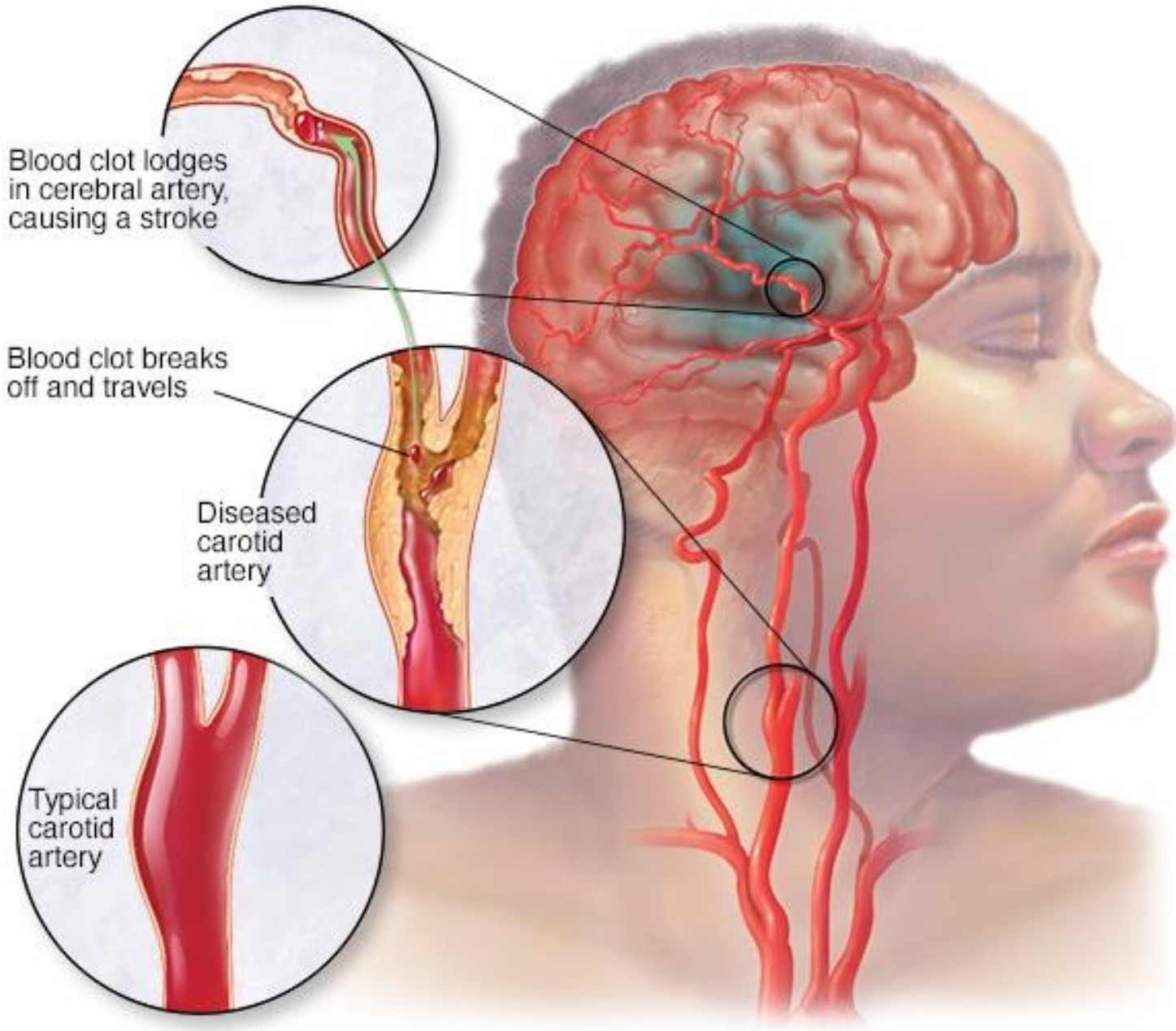
# Hemorrhagic stroke



Source: National Heart Lung and Blood Institute (NIH)

# Hemorrhagic Stroke

- Rupture of a ballooned blood vessel (aneurysms) or leakage of weakened blood vessels that supply blood to brain.
- Less commonly from rupture of the irregular tangling of thin-wall blood vessels (arteriovenous malformation).
- Hemorrhagic stroke may be further subdivided into:
  - ✓ **Intracerebral hemorrhage (ICH)**- bleeding into the brain parenchyma
  - ✓ **Subarachnoid hemorrhage (SAH)**-bleeding into the subarachnoid space.
- Hemorrhagic stroke is associated with severe morbidity and high mortality and responsible for about 40% of stroke-related deaths .



Blood clot lodges in cerebral artery, causing a stroke

Blood clot breaks off and travels

Diseased carotid artery

Typical carotid artery

# Ischemic Stroke

# Ischemic Stroke

- Makes up about 87% of all the stroke cases worldwide, making it the most common type of stroke.
- Usually occurs due to the narrowing or total blockage of the blood vessels by either fatty deposits, blood clots, or debris in the bloodstream.
- Reduction in the blood flow to the brain leads to its starvation of oxygen and nutrients that it requires to function properly
- It is common for children between the ages of two and 10 years to experience an overt ischemic stroke.

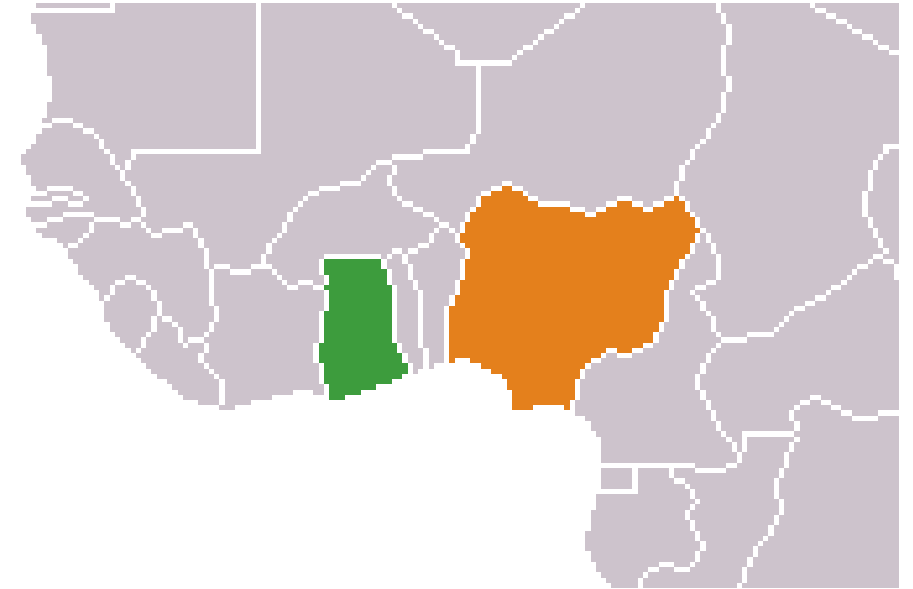


*(National Heart, Lung, and Blood Institute, 2021), (Virani, 2021).*

# Distribution of Stroke types in Africa

## SIREN Study-

- 68% had ischaemic stroke,
- 32% had intracerebral haemorrhage.
- <1% had ischaemic stroke with haemorrhagic transformation.
  
- Other study estimates sub-arachnoid haemorrhage to contribute to ~5% of all strokes in Africa.



Owolabi, M. O. et al, 2018; Ogungbo, B., Mendelow, A. D. & Walker, R, 2004





# Pediatric Stroke

- A stroke or cerebral vascular accident (CVA) in children is typically considered to be a rare event.
- The incidence of pediatric stroke is approximately 1.2 to 13 cases per 100,000 children under 18.
- These figures suspected to be low estimations due to potential misdiagnoses or a lack of clinical suspicion and workup.
- Pediatric acute ischemic stroke (AIS) is classified by age, as :
  - (a) **Perinatal AIS** broadly encompasses 20 weeks of fetal life through day-of-life 28.  
Perinatal AIS is further classified by the timing of presentation-
    - Prenatal.
    - Neonatal
  - (b) **Childhood AIS** encompasses the first month of life and beyond.



# Phases of the Child's Development



# Classification of Pediatric Stroke



**PRE NATAL  
PHASE**



**NEONATAL  
PHASE**



**INFANCY TO  
18 YEARS  
PHASE**

# Risk of AIS in Children

- Highest risk in children under one year of age with a dramatic decline after one year.
- Risk remains low through mid-adolescence, at which time risk begins to increase.
- Black children reported to maintain an increased risk of AIS when compared to white children, and this discrepancy persists after controlling for sickle cell disease.
- Male sex reported to be associated with a higher incidence of both childhood and perinatal AIS, and this discrepancy persists after controlling for trauma.

## MATERNAL FACTORS

Infertility
PROM
Pre-eclampsia
Smoking
IUGR
Infection
Maternal Fever

## FETAL FACTORS

Hypoglycemia
Perinatal Asphyxia
Infection
Resuscitation Efforts
5 min APGAR < 7

## PLACENTAL FACTORS

Chorioamnionitis
Placental infarcts
Weight < 10 percentile

# Risk factors for Perinatal AIS

Due to pregnancy-related risk factors, including hypercoagulability and complex circulation interactions.

# CASCADE Criteria (1)

- The International Pediatric Stroke Study (IPSS) developed the Childhood AIS Standardized Classification and Diagnostic Evaluation (CASCADE) criteria to categorize strokes according to the underlying causes.
- The IPSS defines childhood AIS as follows:
  - (1) Neurological deficit of acute onset;
  - (2) Radiographic image(s) (MRI or CT) showing cerebral parenchymal infarct(s) conforming to known arterial territory(ies) and corresponding to clinical manifestations; and
  - (3) Occurring in children 29 days to 18 years of age.



# CASCADE Criteria (2)

- According to Cascade criteria arteriopathies are recognized as the most significant risk for childhood AIS.
- These blood vessel abnormalities can be chronic or acute/transient changes, and they regularly appear on vascular imaging.
- The CASCADE criteria are not designed to classify perinatal stroke, defined as stroke occurring before 29 days of life, which has unique risk factors.

; Bohmer, M.; et al, 2019; Ganesan, V.; et al, 2003; Wintermark, M.; et al, 2014

# Childhood AIS Risk factors (1)



## Arteriopathies

FCA, TCA

Cranio-cervical  
arterial dissection

Fibromuscular  
dysplasia

Moyamoya  
disease

Primary CNS  
angiitis

## Cardiac Disease

Congenital heart  
disease

Cardiomyopathy

Arrhythmia

Catheterization,  
Surgery

ECMO

## Inherited Thrombophilia

Protein C, S,  
Anti-thrombin  
deficiency

Factor V Leiden

Prothrombin  
G20210A

Lipoprotein A  
elevation

## Acquired Thrombophilia

Antiphospholipid  
syndrome

Drug Induced

# Childhood AIS Risk factors (2)



## Inborn Errors of Metabolism

Mitochondrial disease

Fabry disease

## Rheumatologic Disease

Systemic lupus erythematosus

Systemic vasculitis

## Other

Sickle Cell Disease

Malignancy

Congenital vascular syndromes

Child abuse

Head Trauma



# **Etiologies of Ischemic Stroke in Children**

# Sickle cell disease (SCD)

Highest risk of first overt ischemic stroke is within the first decade of life.

SCD is an umbrella term that defines a group of inherited diseases (including SCA, HbSC and HbS $\beta$ -thalassaemia).

01

04

Highest risk in the most severe and prevalent sickle type, homozygous S disease (HbSS).

Characterized by mutations in the gene encoding the haemoglobin subunit  $\beta$  (*HBB*)

02

05

SCD brain vasculopathy causes both overt stroke and “silent” cerebral infarcts, affecting neurological and cognitive function..

Most common inherited disorder in sub-Saharan Africa (SSA)

03

06

SCD cerebral vasculopathy is mediated by defects in vascular hemodynamics, hemolysis-associated oxidative stress, hemostatic activation, and cellular adhesion.

# Stroke in SCD (1)

- Strokes may occur as early as 18 months of age, but most children present after five years of age.
- AIS is more common in the younger age group whereas hemorrhagic strokes occurs more frequently in older children and adults.
- Risk most significant during the 1st decade of life, then drops in the second decade, and rises again in the 3rd decade
- Strokes may occur in the absence of pain or aplastic crises.
- Low steady-state hemoglobin and acute severe anemia have been shown to increase stroke risk.

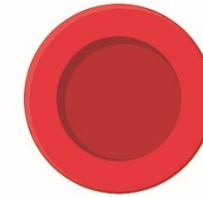




# Stroke in SCD (2)

- Other most consistent risk factors for ischemic stroke in children with SCD include:
  - History of transient ischemic attack,
  - Acute chest syndrome,
  - Degree of anemia, and
  - Elevated systolic blood pressure.
- Sickle cell beta-thalassemia (Hb S/ $\beta$  Th), a subtype of SCD, has the lowest stroke incidence.

## Sickle Cell Disease



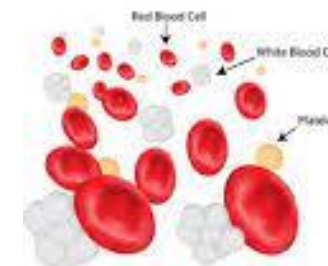
Normal Blood Cell



Sickle Cell

## Thalassemia

Normal



Thalassemia



# Cardiac Causes (1)



- A common cause of stroke in childhood, accounting for up to a third (30%) of all AIS cases.
- Acquired and congenital heart diseases resulted in a 16.1-fold increased risk of AIS when compared to the general pediatric population.
- Children with cardiac etiologies of AIS present at an earlier age.
- Children with a cardiac repair or catheterization, nearly 50% of strokes occur within 72 hours.

# Cardiac Causes (2)

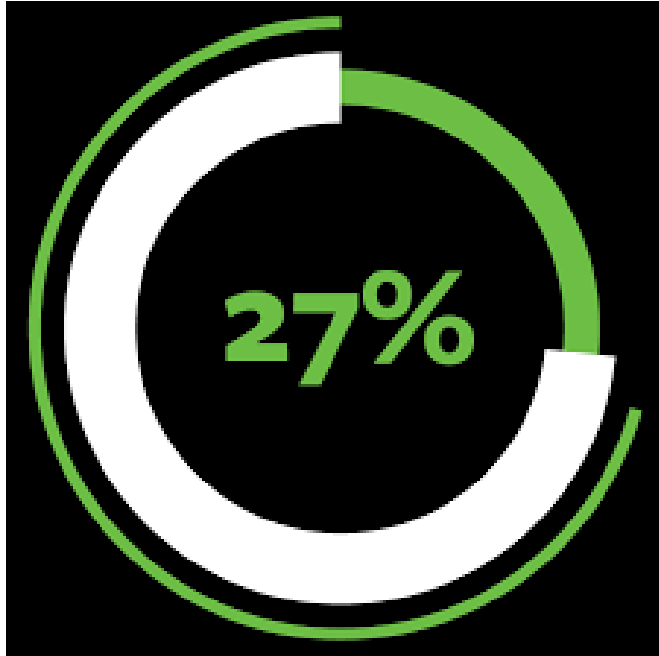
Long-standing cyanotic lesions cause polycythemia and anemia, which both increase the risk of thromboembolism and cerebral infarction.

Embolic clots can arise in children with cardiomyopathies, rheumatic heart disease, prosthetic valves, or valvular vegetation from endocarditis.

A patent foramen ovale (PFO) may serve as a portal for venous embolic events to pass from the right to left side of the heart.



# Recurrent AIS episodes



- Recurrent AIS among childhood patient population a major concern.
- 27% of patients with cardiac causes of AIS have another event within 10 years.
- Recurrent AIS is associated with mechanical valves, thrombophilia, anticoagulation treatment and acute infection.



# Infection

- Varicella infection within the past year can result in basal ganglia infarction.
- HIV infection can cause stroke secondary to HIV-induced vasculitis, vasculopathy with subsequent aneurysms, or hemorrhage in the context of immune thrombocytopenia.
- Five to twelve percent of children with bacterial meningitis, TB meningitis, and viral encephalitis will have a stroke due to local vasculitis and thrombosis.
- Other commonly associated organisms include mycoplasma and chlamydia, as well as enterovirus, parvovirus 19, influenza A, coxsackie, etc

# Malignancy

Children with cancer are at increased risk for AIS as a result of:

- **The disease**, e.g.-Leukemia and lymphoma create a hypercoagulable and hyperviscous state
- **Subsequent treatment**, e.g. Treatment with L-asparaginase decreases antithrombin levels, and may trigger venous thrombosis in leukemic children concurrently receiving prednisone.

Radiation therapy for optic chiasm gliomas or other sellar or suprasellar region tumours can cause vasculopathies that result in strokes.

- **Susceptibility to infection**.-reduced immunity from the disease and medications



# Craniocervical Arterial Dissection(1)

- Occurs in 2.5 children per 100,000 annually.
- Accounts for 5–25% of all acute ischemic strokes in the pediatric population.
- Dissections can be traumatic or spontaneous in nature and is an under-recognized consequence of trauma.
- Many of the head and neck injuries that precede dissections are mechanical or penetrating.



# Craniocervical Arterial Dissection(2)

- Hyperextension or rotational injuries, motor vehicle collisions, sports such as wrestling, or even chiropractic manipulation other causes.
- Whiplash injuries are another mechanism there have been some reports of strokes in children after amusement park rides.
- Adult dissections nearly all traumatic in nature, in children a substantial incidence of spontaneous dissections occur without preceding trauma .
- Approximately 5–20% of children with a spontaneous dissection have an underlying connective tissue or genetic disorder, or bony or vascular anatomic variations.

# Drugs



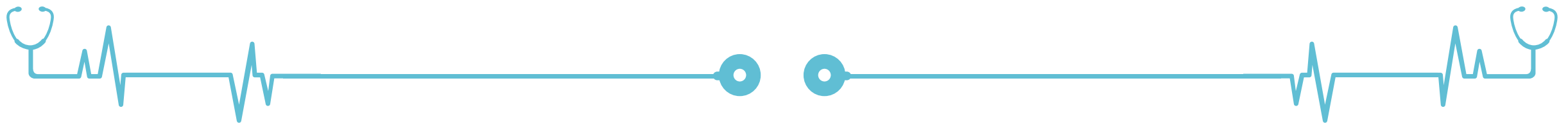
- May occur from use of both illicit and prescribed drugs.
- Cerebral infarcts and hemorrhage reported in patients abusing drugs such as amphetamines, ecstasy, cocaine, phencyclidine (PCP), and glue sniffing [85].
- Stimulants and heroin can also cause vasculopathies predisposing to infarction [83].
- Adolescent girls using oral contraceptives are at higher risk of cerebral venous thrombosis [86].
- Overuse of ergot alkaloids for acute migraine treatment, associated with increased risk of ischemic events [87].



# **Etiologies of Hemorrhagic Stroke in Children**

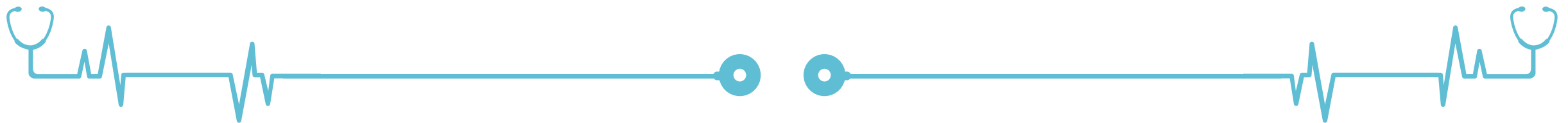
# Hemorrhagic stroke (1)

- Hemorrhagic stroke accounts for 35–54% of all childhood stroke.
- Contrasts with its incidence in adults, where hemorrhagic stroke only accounts for 7.5–19% of all strokes.
- Arteriovenous malformations (AVM) are the most common cause of hemorrhagic stroke after infancy, but can also cause thrombotic stroke .

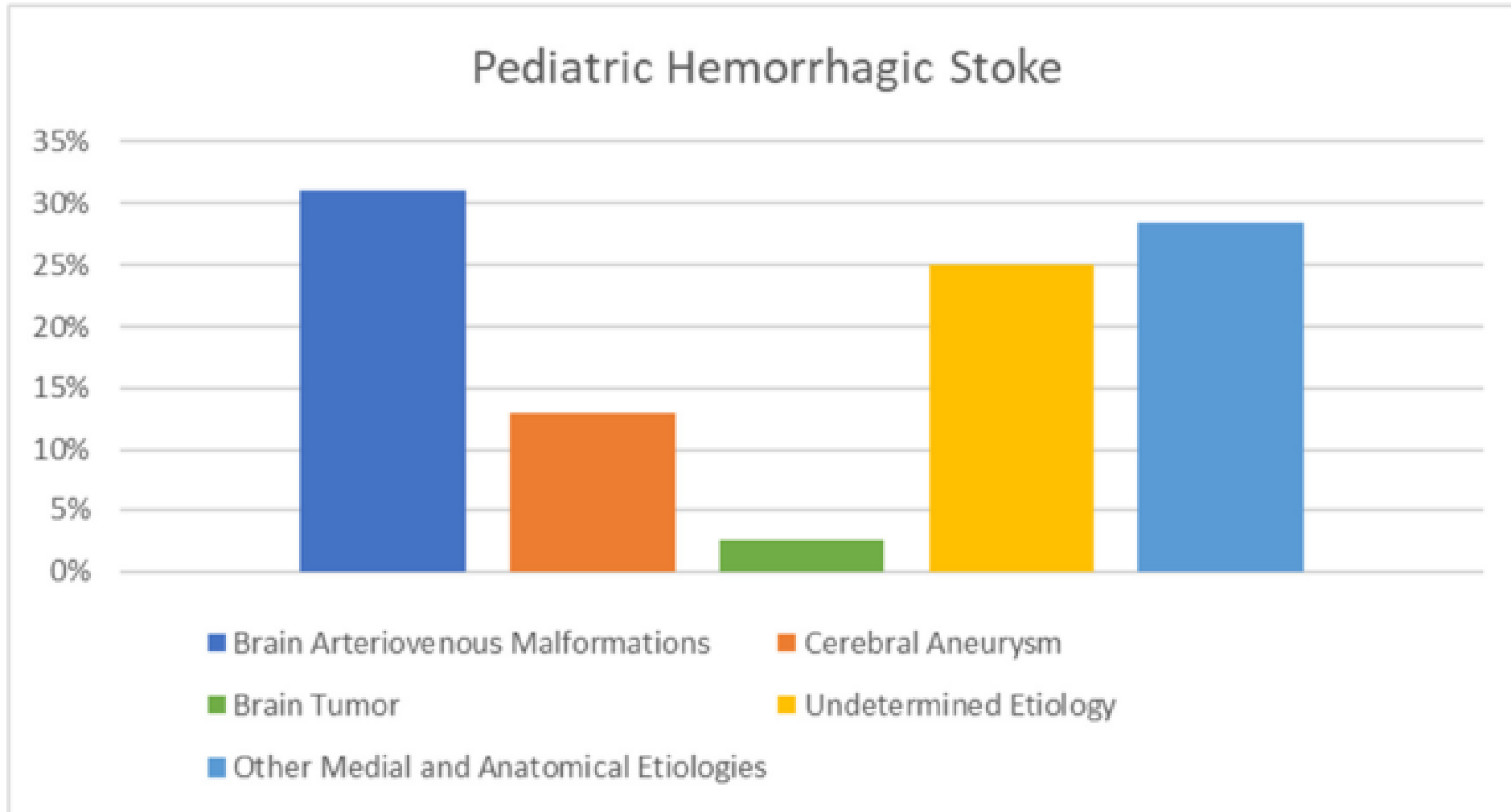


# Hemorrhagic stroke (2)

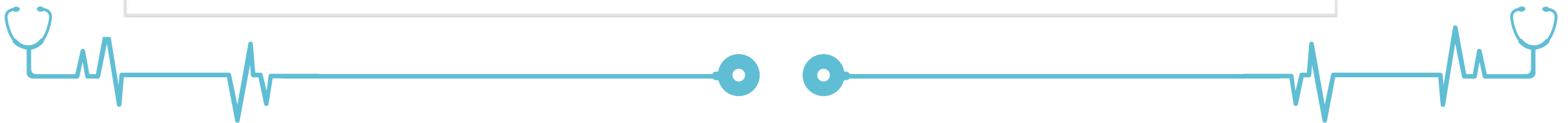
- AVM may be associated with neurocutaneous syndromes such as Osler-Weber-Rendu syndrome (i.e., hereditary hemorrhagic telangiectasia), Sturge-Weber disease, neurofibromatosis.
- Moyamoya is another important vascular cause of childhood stroke and is associated with conditions such as Down syndrome, neurofibromatosis, and sickle cell disease.



# Different causes of Hemorrhagic Stroke



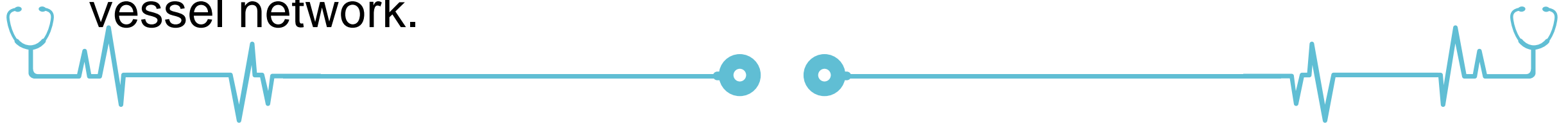
Jordan LC, et al 2009





# Moya Moya Disease (MMD)

- MMD is a non-inflammatory vasculopathy that is associated with the stenosis of intracranial arteries, notably the distal internal carotid artery (ICA) and its branches.
- Patients with MMD are likely to have a stroke due to the occlusion and stenosis of the blood vessels.
- Compensatory mechanisms allow for the formation of collateral vessels at the base of the brain.
- MMD has a variable presentation broadly categorized into two groups; symptoms due to ischemia or symptoms due to intracranial hemorrhage which occurs as a complication of the collateral blood vessel network.





# **Diagnosis and Management of Acute Ischemic Stroke in Children**

## Spotting a Stroke

# BEFAST

Balance  
Loss



Eyesight  
Changes



Face  
Drooping



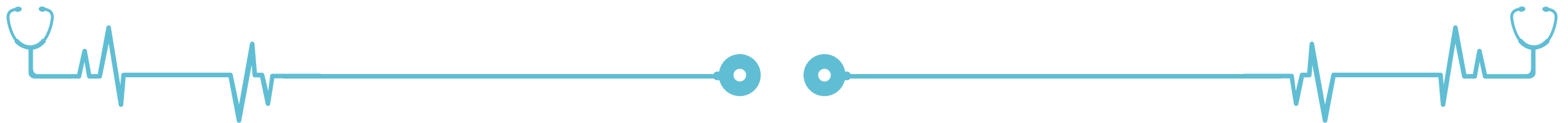
Arm  
Weakness



Speech  
Difficulty

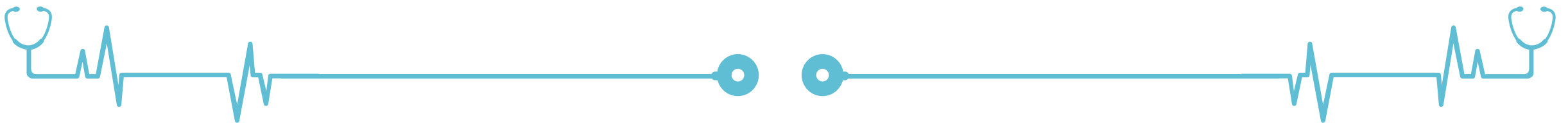


Time to  
call 911



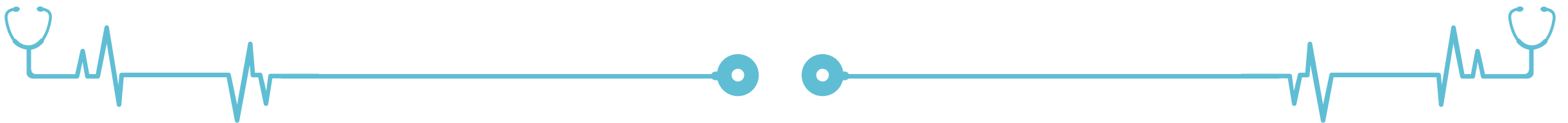
# Presentation of AIS

- Pediatric stroke requires the same urgency but lacks similar protocols for universal recognition.
- Focal weakness and limb and face weakness can be presentations of pediatric AIS .
- However, the hallmark sign of stroke, acute hemiparesis, is common only in older pediatric patients.
- Seizures are the primary presenting symptom for younger children.



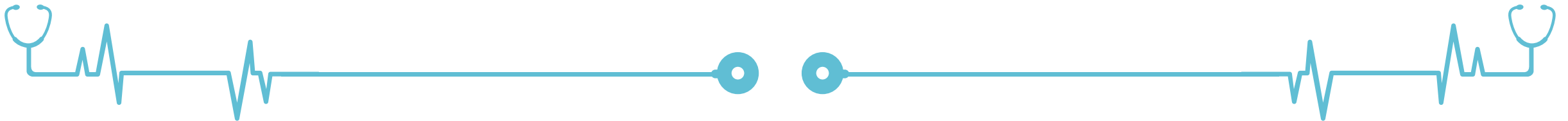
# Difficulties in Diagnosis

- Nonspecific symptoms such as fever, nausea/vomiting, headache and cardio-pulmonary dysfunction permeate all pediatric patients.
- Lack of specific symptoms makes recognition more difficult.
- Broad differential diagnosis for hemiparesis adds to the complexity of diagnosis in pediatric stroke, as there are many stroke-mimicking disorders.



# Differential Diagnosis

- Nearly 21–76% of children with acute-onset focal neurological deficits are found to have
  - Migraines,
  - Focal seizures,
  - Demyelinating diseases,
  - Conversion disorders and
  - Central nervous system tumors, among other possible diagnoses.
- The rarity of pediatric AIS and subsequent lack of clinical suspicion can delay diagnosis



# Investigations in AIS

Magnetic resonance imaging (MRI) is the preferential imaging modality; however, there are challenges to obtaining them in the pediatric population.

High-quality scans can be difficult to achieve in children without sedation because of movement artifacts from restlessness in MRI scanners.





# Other Investigations

## Laboratory studies.

- Blood count PT and PTT.
- Special studies, in selected cases.
- Hemoglobin electrophoresis.
- Protein C/S.
- Antithrombin III.
- Antiphospholipid antibodies.
- Lupus anticoagulant.
- Lactate pyruvate (for mitochondrial dysfunction).
- HIV, VDRL.

## Cardiac studies.

- EKG.
- Transesophageal echocardiogram in cases of congenital cardiac defects or to demonstrate an intracardiac thrombus or valvular vegetations.



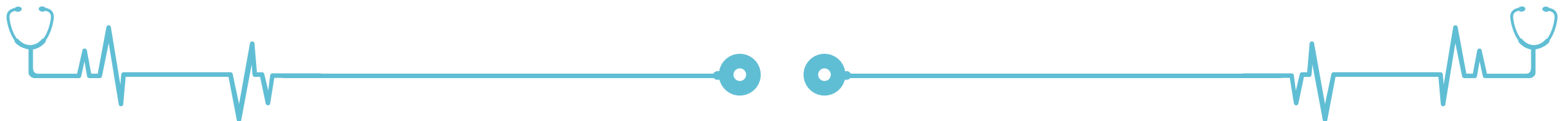
# Perinatal AIS management

- Perinatal AIS in the neonatal period is managed with supportive measures, including oxygenation and managing dehydration and anemia.
- Aspirin and anticoagulation are often not pursued due to the low risk of recurrence of neonatal AIS, though these treatments are considered when AIS is due to cardiac disease.
- Additionally, thrombolytics and mechanical thrombectomy are often not considered in neonates following AIS due to the lack of evidence and small size of neonatal arteries.



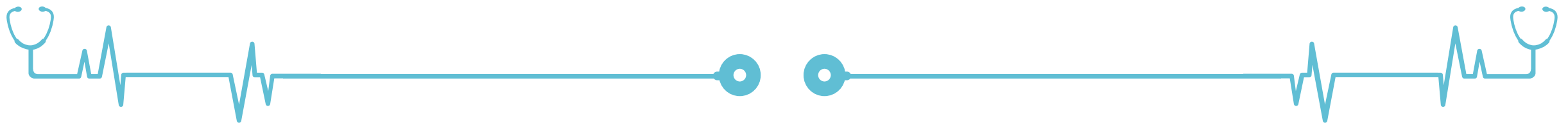
# Childhood AIS management

- The hallmarks of both acute and chronic therapies include anticoagulation and antiplatelet medications.
- Controversy exists in the literature, however, regarding the optimal treatment.
- Partly due to the low risk of bleeding in pediatric AIS, while monitoring the risk of acute hemorrhagic conversion and acknowledging the prominent risk of pediatric AIS recurrence.
- In cases of pediatric AIS with a specific disease etiology, management specific to each disease should be considered, i.e., chronic transfusions in SCD.



# Presentation of MMD

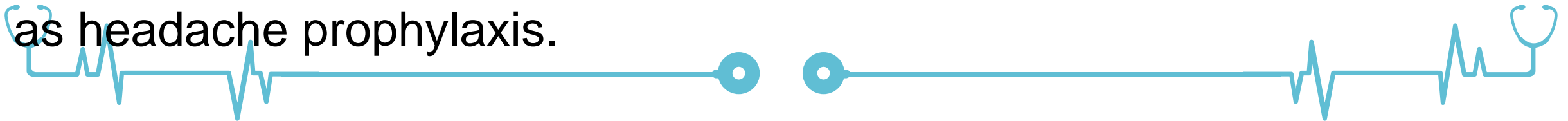
- Most patients present with ischemia, adults are more likely to present with hemorrhagic strokes than children.
- Moyamoya has been linked to both genetic and environmental factors and should be a consideration for any patient displaying neurological deficits or cerebral ischemia.
- Moyamoya can be confirmed via various radiographic studies including CTs, MRIs, and angiography



# Management of MMD (1)

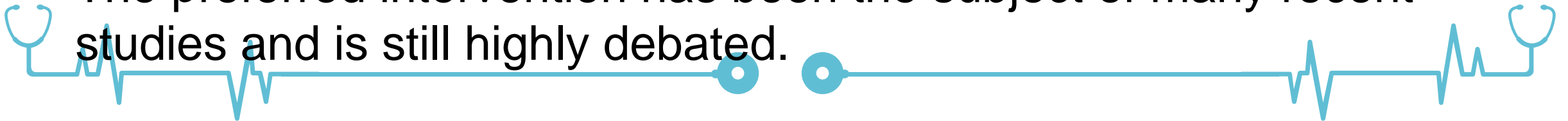
- Currently, there is no known treatment to reverse the progression of Moyamoya.
- Therapies do exist to prevent further strokes in symptomatic patients.
- The current treatment options for MMD are divided into conservative or surgical interventions.

Conservative treatment includes medical interventions with anti-platelets, and symptomatic management such as anti-epileptics, as well as headache prophylaxis.



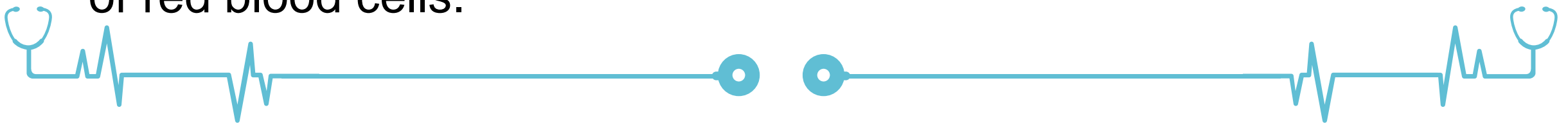
# Management of MMD (2)

- Surgical treatments are divided into direct revascularization and indirect revascularizations.
- **Direct revascularization** involves a superficial temporal artery (STA) to middle cerebral artery (MCA) bypass.
- **Indirect revascularization** involves placing tissue that is supplied by the external carotid artery onto the brain surface in order to promote angiogenesis.
- The preferred intervention has been the subject of many recent studies and is still highly debated.



# Management of Sickle Cell Stroke

- The hallmark of stroke prevention and treatment in SCD is chronic red blood cell (RBC) transfusion with a target of maintaining total hemoglobin at 10-12.5 g/dL and sickle hemoglobin (HbS) at less than 30%.
- Hydroxyurea, an oral medication, recommended as an add on therapy to red blood cell transfusion/chelation therapy.
- Hydroxyurea induces the expression of fetal hemoglobin, which prevents the formation of polymers that ultimately cause the sickling of red blood cells.



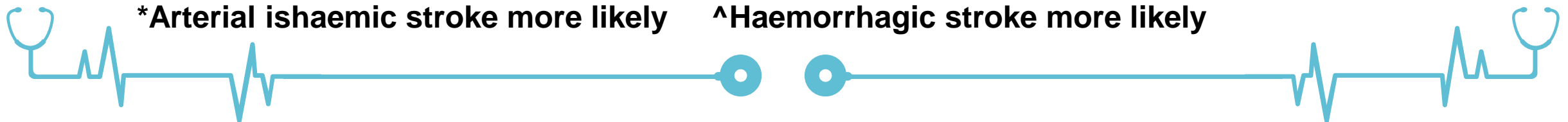




# **Diagnosis and Management of Hemorrhagic Stroke in Children**

# Presentation of Hemorrhagic Stroke

- Presentation of does not differ greatly from AIS, and it requires a similar workup.
- ✓ Focal limb or facial weakness\*
- ✓ Visual or speech disturbance\*
- ✓ Limb incoordination or ataxia\*
- ✓ Headache with other neurological signs or symptoms^
- ✓ Altered mental state^
- ✓ Signs of raised intracranial pressure^
- ✓ New onset seizures associated with persistent neurological signs or symptoms



# Investigations in Hemorrhagic Stroke

- A computed tomography (CT) head scan may be very useful as a diagnostic tool.
- Given that almost half of hemorrhagic strokes are due to vascular issues, a complete MRI study, including magnetic resonance angiography and venography (MRA, MRV), can be obtained, when possible, in order to look for additional abnormalities or other causes.



# Hemorrhagic Stroke management (1)

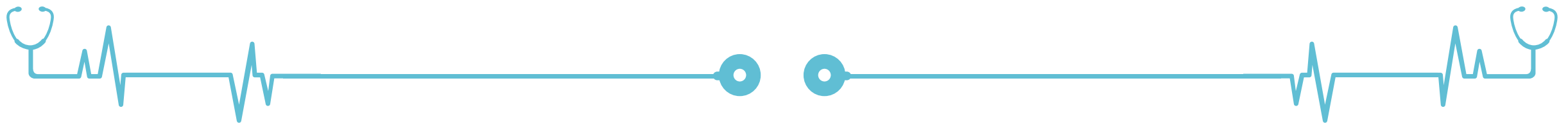
- Management of hemorrhagic stroke varies and depends on the type and severity of the hemorrhage.
- Some may receive medications, surgical intervention, or both medications and surgical interventions.
- Patients with altered mental status should be monitored in the ICU with an intracranial device, while alert patients can be monitored in a less invasive fashion.
- Neurological exams should be performed often to evaluate the patient for signs of increased intracranial pressure or herniation of the brain.

■ Vital signs should be kept within appropriate limits for the patient's age

A decorative graphic at the bottom of the slide features a blue ECG (heart rate) line. The line starts on the left with a stethoscope icon, passes through the text 'Vital signs should be kept within appropriate limits for the patient's age', and ends on the right with another stethoscope icon. There are two blue circular markers on the line, one before and one after the word 'age'.

# Hemorrhagic Stroke management (2)

- Surgical intervention for hemorrhagic stroke may include decompressive craniectomy.
- Resection of an arteriovenous malformation with or without placement of an extracranial drain, and endovascular procedures to treat intracranial aneurysms.
- Medications used to treat hemorrhagic stroke revolve around symptom management, such as antiepileptics and NSAIDs.



# Conclusions

Favorable long-term outcomes and minimizes significant neurologic deficits



Overall, stroke in the pediatric population has a lower incidence than in adults.

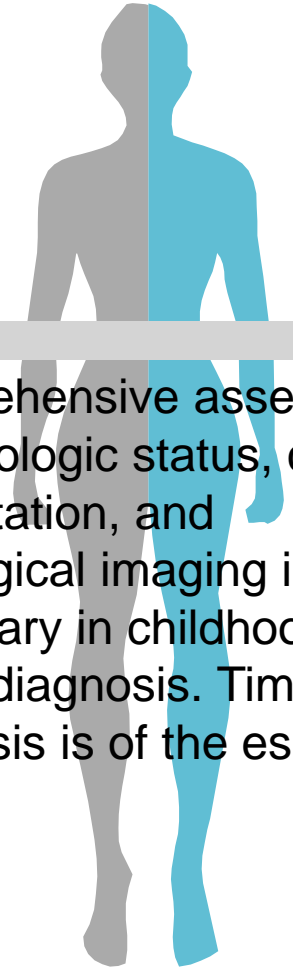


Neurologic impairments following AIS and hemorrhagic stroke can be devastating in children due to the effects on the quality of life across the increased lifespan in this population compared to adults..



Pediatric strokes are often challenging to identify due to the subtleness of signs and symptoms, therefore, are frequently undiagnosed or misdiagnosed .

Comprehensive assessment of neurologic status, clinical presentation, and radiological imaging is necessary in childhood stroke diagnosis. Timely diagnosis is of the essence.





# Thank You for Listening!

