An Interactive Review of Sickle Cell Anemia

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Disclosure

The authors of this electronic exhibit do not have a financial relationship with any commercial organizations that may have a direct or indirect interest in the subject matter being presented.
Goals and Objectives

- Explain the pathophysiology of sickle cell anemia (SCA)
- Display the distinguishing radiographic findings of SCA and contrast with those of mimics
- Discuss the pathophysiology underlying organ-specific radiographic findings in SCA patients
- This exhibit is aimed at residents, fellows, and general radiologists, as well as anyone with a particular educational focus on the pediatric population
Sickle-Cell Anemia

Sickle-cell anemia is a hereditary blood disorder characterized by the predisposition of red blood cells to assume an abnormal sickle-like shape (see left figure).

**Genetics and Prevalence:**
- Autosomal recessive inheritance pattern
- Mutation in the hemoglobin-Beta gene found on chromosome 11 which encodes hemoglobin S (rather than the normal hemoglobin A)
- Higher incidence of this mutated allele in malaria stricken countries (African countries, Mediterranean countries, India and the Middle East)
- Current prevalence in the US is 1:400 African-Americans births

**Pathophysiology:**
- Hemoglobin S is less water soluble than hemoglobin A due to the presence of a hydrophobic patch which is present on the molecule surface when it is in the deoxygenated state.
- These hydrophobic patches interact with one another leading to the formation of insoluble fibers.
- The insoluble fibers increase in number and accumulate during oxygen delivery (due to precipitation during the deoxygenated state) leading to distortion of the normal red blood cell into a sickle/crescent shape or to cell rupture.
- The abnormally shaped red blood cells obstruct small capillaries and precipitate pathologic changes in all organ systems within the human body.
Select the vascular pathology associated with sickle cell anemia.
Moyamoya

- **Pathophysiology:**
  - Progressive stenosis and eventual occlusion of the distal internal carotid artery and proximal vessels of the anterior circulation of the circle of Willis with lenticulostriate, thalamostriate, leptomeningeal, and dural collaterals
  - 1° moyamoya has an AD inheritance pattern with incomplete penetrance
  - 2° moyamoya is associated with sickle cell anemia, neurofibromatosis type 1, connective tissue diseases, among other disorders
  - In SCA, stasis and ischemia in the vasa vasorum results in intimal and medial hyperplasia with eventual stenosis or occlusion of the involved vessels

- **Imaging findings:**
  - T1WI demonstrates curvilinear hypodensities representing collateral vessels coursing through the basal ganglia as confirmed on this enhanced MRI (yellow arrows)
  - T2WI MRI demonstrates absence of the normal flow voids with CTA and MRA demonstrating stenosis or occlusion of the involved vasculature
  - Increased sulcal FLAIR signal abnormality is due to slow-flow through engorged pial vessels suggesting decreased cerebral vascular reserve

- **Clinical Pearls:**
  - Moyamoya loosely translates as “puff of smoke” in Japanese due to the cloud-like appearance of the proliferation of lenticulostriate and thalamostriate collaterals on angiography (red arrow)
  - Children more often present with transient ischemic attacks and a more progressive course while adults present more commonly with hemorrhages and a slower course
  - Sickle cell related moyamoya is treated with hypertransfusion therapy
Meningitis

**Pathophysiology:**
- Inflammatory infiltration of the leptomeninges (arachnoid and pia mater) and CSF
- May be infectious: bacterial, viral, fungal, mycobacterial or noninfectious: leptomeningeal carcinomatosis, sarcoid
- Usually spread hematogenously most commonly as well as via direct extension

**Imaging findings:**
- Imaging may be normal early in the course of the infection
- Increased FLAIR signal abnormality involving sulci and cisterns on MRI
- Leptomeningeal enhancement on postcontrast imaging
- Basilar meningitis with extensive leptomeningeal enhancement involving the basal cisterns is often seen with TB, bacterial infections, cryptococcosis, and sarcoid
- Imaging is helpful to detect complications: empyema, abscess, cerebritis, ventriculitis, ischemia, hydrocephalus

**Clinical Pearls:**
- Clinical diagnosis
- CSF sampling often indicated

- *Get FLAIR images*
Arteriovenous Malformation (AVM)

- **Pathophysiology:**
  - Congenital vascular malformation
  - Consists of $\geq 1$ enlarged feeding artery, a nidus of tightly packed vessels, and enlarged early draining veins, no intervening capillary network or normal brain
  - Predominately supratentorial in location (85%)

- **Imaging findings:**
  - Unenhanced CT can demonstrate the dilated vessels which may be isodense or hyperdense with or without calcification
  - T2WI demonstrates serpiginous flow voids
  - Avid enhancement of AVM after contrast administration
  - Minimal to no mass effect
  - Increased T2 signal changes in the adjacent brain parenchyma may represent gliotic changes from prior infarct or hemorrhage
  - Catheter angiogram demonstrates the nidus with feeding arteries and early draining veins

- **Clinical Pearls:**
  - Steal phenomenon: Preferential flow of blood to the AVM rather than the brain parenchyma. Can result in neurologic deficits and seizures
  - Hemorrhage rate of 2-3% annually
  - Spetzler-Martin classification scale is based on size, location, and venous drainage of the AVM with a higher score equating to a worse surgical outcome
Case 2

Select the parenchymal pathology associated with sickle cell anemia.
**Pathophysiology:**
- Contributed to intimal damage and hyperplasia, endoluminal narrowing, and stasis resulting from aggregation of sickled cells along the walls of the blood vessels.
- Decreased blood flow to the brain results in ischemia and infarction.
- Embolic/thrombotic strokes are rare in SCA.

**Imaging findings:**
- CT demonstrates areas of hypodensity with loss of gray-white differentiation.
- Acute infarct is diagnosed on MRI with high signal on DWI and corresponding low signal on ADC.
- Increased FLAIR signal intensity is often seen approximately after 6 hours of the infarct.

**Clinical Pearls:**
- Approximately 11% of SCA patients develop infarcts before the age of 20, which can lead to lifelong cognitive and functional impairments.
- Silent infarcts are more common than clinical infarcts.
- Elevated velocities detected with transcranial Doppler ultrasonography (TCD) are correlated with increased risk of strokes (≥200 cm/sec).
- Screening recommended starting after age 2.
- Patients with 2 consecutive elevated velocities are offered chronic transfusion therapy to attempt to decrease HB S concentration to ≤30% of the total hemoglobin concentration.
Acute Disseminated Encephalomyelitis (ADEM)

- **Pathophysiology:**
  - Autoimmune mediated brain and spinal cord demyelinating disease
  - May be idiopathic, but often associated with recent history of viral or respiratory infections, vaccination, or childhood diseases associated with rashes (measles, chicken pox)
  - Classically monophasic, which classically differentiates ADEM from multiple sclerosis, but rarely may be multiphasic or relapsing

- **Imaging findings:**
  - Imaging findings tend to lag behind symptom onset and resolution
  - Multifocal or confluent white matter and deep gray matter lesions which appear hyperintense on T2WI/FLAIR MRI
  - Callososeptal interface usually spared
  - May demonstrate peripheral, ring or incomplete ring enhancement
  - Mass effect is usually mild in relation to the size of the lesions

- **Clinical Pearls:**
  - Affects all ages, with mean age of 5-8 years
  - Male predominance
  - Usually self-limited, treated with steroids
  - Acute hemorrhagic leukoencephalitis (Hurst disease) is a rapidly fulminant form associated with demyelination and hemorrhage that can lead to death within days
Cavernous Malformation

**Pathophysiology:**
- AKA cavernous angiomas, cavernoma
- Benign vascular hamartoma
- Mass of interwoven blood vessels without intervening normal brain tissue
- Often associated with a developmental venous anomaly

**Imaging findings:**
- On unenhanced CT usually appears as a hyperdense lesion with or without calcifications
- Lack associated edema and mass effect in the absence of recent hemorrhage
- T1 hyperintensity suggests subacute hemorrhage
- Hypointense rim on T2WI MRI
- Dephasing on GRE or SWI
- Mild enhancement may be present
- Characteristic popcorn appearance is seen with heterogeneous T1 and T2 signal related to intralesional hemorrhage of varying ages
- Angiographically occult

**Clinical Pearls:**
- May be congenital, familial (if multiple) or acquired (for example after radiation therapy)
- Usually asymptomatic
- May present with recurrent hemorrhages resulting in focal neurologic deficits and seizures
Case 3

Select the pulmonary pathology associated with sickle cell anemia.
Acute Chest Syndrome

- **Pathophysiology:**
  - Multifactorial severe acute pulmonary illness
  - Most common cause in children is pneumonia with other etiologies including fat embolism, rib infarction, and pulmonary vascular occlusion

- **Imaging findings:**
  - Initial CXR may be normal
  - CXR and CT may demonstrate lower lobe predominant airspace and interstitial disease, cardiomegaly, pleural effusions, rib expansion,
  - Consolidations are nonspecific may represent atelectasis, pneumonia, or infarction

- **Clinical Pearls:**
  - Occurs in 50% of SCA children
  - SCA children are 100x more susceptible to developing pneumonia than the average child
  - Leading cause of death and 2nd leading cause of hospitalization in SCA patients
  - Clinical presentation includes fevers, chest or bone pain, cough, tachypnea, dyspnea
  - Late complications include pulmonary hypertension, high-output cardiac failure, and chronic lung disease with pulmonary fibrosis
Bronchopulmonary Sequestration

- **Pathophysiology:**
  - Congenitally abnormal lung tissue with anomalous systemic blood supply and no connection with the pulmonary arteries or tracheobronchial tree
  - Anomalous blood supply is usually from the aorta (yellow arrow)
  - Intralobar type is more common, lacks a separate pleura from adjacent normal lung tissue, usually has venous drainage into the pulmonary vein
  - Extralobar type has a separate pleura from adjacent normal lung tissue, usually has venous drainage into systemic venous system

- **Imaging findings:**
  - Most common location is posterior basal segment of left lower lobe
  - Extralobar type may occur below the diaphragm
  - Most commonly appears as a recurrent or persistent opacity/consolidation
  - CTA confirms the systemic arterial supply

- **Clinical Pearls:**
  - Extralobar type is usually detected in prenatal/postnatal period and is often associated with other congenital anomalies such as congenital diaphragmatic hernia
  - Intralobar type may not be congenital and is often identified in older children
  - Intralobar type often presents as recurrent pneumonia
Bronchial Atresia

- **Pathophysiology:**
  - Congenital atresia of typically the proximal portion of a segmental bronchus thought to be due to in utero disconnection of bronchial cells from bronchial bud or vascular insult
  - Distal lung is aerated via collaterals

- **Imaging findings:**
  - Most commonly in LUL > LLL > RML
  - Airway mucoid impaction is seen as a tubular, branching, or round filling defect distal to the obliterated airway
  - Mucocele does not demonstrate enhancement
  - On MRI the mucocele is hyperintense on both T1WI and T2WI
  - Surrounding lung is hyperlucent and hyperinflated with decreased vascular markings

- **Clinical Pearls:**
  - Bronchoscopy recommended to exclude an endobronchial neoplasm
  - Air-fluid level within mucocele suggests superimposed infection
Select the splenic pathology associated with sickle cell anemia.
**Pathophysiology:**
- Impaired immunity due to functional asplenia

**Imaging findings:**

**Clinical Pearls:**
- Risk of encapsulated bacteria pneumonia (staphlococcus, haemophilus)
Splenic Granulomata

- Pathophysiology:
- Imaging findings:
- Clinical Pearls:
Splenic Lymphoma

- **Pathophysiology:**

- **Imaging findings:**

- **Clinical Pearls:**
Select the IVP pathology associated with sickle cell anemia.
Papillary Necrosis

Correct!
Calyceal Diverticulum
Medullary Sponge Kidney (MSK)

- **Pathophysiology:**
  - Congenital malformation of the kidneys thought to result from disruption of the ureteric bud-mesenchyme interphase which results in the formation of dilated collecting tubules within the renal papilla and pyramids.

- **Imaging findings:**
  - On IVP, the dilated ducts will form clusters of rounded opacities within the papilla which may have a paintbrush appearance.
  - On US will demonstrate medullary cavities with or without nephrocalcinosis (hyperechoic foci with acoustic shadowing within renal pyramids)
  - On CT will show contrast accumulation within the papillae. Nephrocalcinosis may also be present on CT.

- **Clinical Pearls:**
  - Thiazide diuretics may be used to prevent the formation of nephrolithiasis in those patients with nephrocalcinosis
  - MSK has been associated with other congenital abnormalities (Marfan syndrome, Caroli syndrome and horseshoe kidney)
Select the renal pathology associated with “sickle cell disease.”
Medullary Renal Cell Carcinoma
Pathophysiology:
- AMLs are benign mesenchymal tumors composed of vascular, adipose and immature smooth muscle cells.
- The most widely accepted theory on their origin suggests that these benign tumors originate from metaplastic change of the reticuloendothelial cells of capillaries in response to stimuli.

Imaging findings:
- On ultrasound, AMLs appear as hyperechoic masses relative to surrounding renal parenchyma.
- On CT, AMLs be identified by the presence of macroscopic fat within these lesions which will demonstrate Hounsfield units measuring less than -20.
- On MRI, the fatty portion of these lesions will follow the signal characteristics of fat on all sequences. This is best seen on pre and post fat saturation sequence which will show a drop in signal within the lesion after fat saturation.
- In and out-of-phase MR sequences may also be employed for the diagnosis of AML as the interface between normal renal parenchyma and the intralesional fat will demonstrate India ink artifact.

Clinical Pearls:
- AMLs greater than 4 cm in size should be excised due to increased risk of hemorrhage.
- The presence of calcification raises the possibility of renal cell carcinoma over AML as AMLs should not contain calcification.
Transitional Cell Carcinoma

Incorrect
Case 7

Select the calvarial pathology associated with sickle cell anemia.
Marrow expansion of the skull
Wormian bone
Langerhans Cell Histiocytosis
Select the vertebral pathology associated with sickle cell anemia.
Correct!

Lincoln Log Vertebra
Mucopolysaccharidosis
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- **Pathophysiology:**
- **Imaging findings:**
- **Clinical Pearls:**