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The Current State of Imaging Pediatric Hemoglobinopathies

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The hemoglobinopathies are a group of genetic disorders with a broad spectrum of clinical manifestations and radiologic findings. The imaging of pediatric hemoglobinopathies, which is influenced by concomitant hemosiderosis and the sequela of chelation therapy, has evolved over the years along with ever-improving technology. This article reviews and illustrates the most common radiographic and cross-sectional imaging findings of the 2 best known and clinically relevant hemoglobinopathies in pediatric patients, sickle cell disease and β-thalassemia.

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Hemoglobinopathies

The hemoglobinopathies are a group of genetic disorders in which there is an abnormality of the hemoglobin molecule. Sickle cell disease (SCD) and β-thalassemia are the 2 most clinically relevant hemoglobinopathies in the pediatric population. Both diseases have variable courses, ranging from benign to severe depending mainly on genetic factors and giving rise to a broad spectrum of clinical manifestations. As a result, the imaging findings can vary greatly even among patients with the same disease and depending upon therapeutic interventions.

This article reviews and illustrates the common imaging findings, in conventional radiography and cross-sectional imaging, of the 2 best known hemoglobinopathies in pediatric patients, SCD and β-thalassemia.

Sickle Cell Disease

Introduction

The normal hemoglobin molecule, hemoglobin A (Hb A), is composed of 2 α and 2 β globin chains. SCD and its variants result from a single point mutation causing the substitution of a valine for glutamic acid in the β chain of the hemoglobin molecule. These point mutations cause the hemoglobin molecules to become "sticky" with abnormal polymerization. These polymeric chains cause rigidity, which deforms the red blood cells into the classic sickle shape. Individuals with SCD have at least 1 abnormal sickle gene giving rise to hemoglobin S (Hb S) instead of the normal Hb A. The carrier, which comprises the heterozygous form of the disease and is known as the sickle cell trait, Hb SA, is characterized by one abnormal sickle gene designated S and one normal hemoglobin gene designated A; it is generally a benign condition. Sickle cell anemia (SCA) refers to the most severe, homozygous form of the disease, which is due to the presence of 2 genes encoding for sickle cell hemoglobin (Hb SS) and accounts for 60%-70% of cases in the United States. Other less severe genotypes of SCD include at least one Hb S chain and another abnormal β globin chain, such as hemoglobin C or β thalassemia, resulting in sickle C disease (Hb SC), hemoglobin sickle beta plus thalassemia (Hb Sβ+ thalassemia), or sickle beta null thalassemia (Hb Sβ0 thalassemia).[1-3]

There are an estimated 89,000 people with SCD in the United States, of which an estimated 80,000 are of African descent and 9000 are Hispanic, according to Brousseau et al.[4] Worldwide, it is estimated that 200 million or more people carry the sickle cell trait, and up to 300,000 people may live with a clinically significant hemoglobinopathy.[5] In the United States, approximately 1 in 400 infants born of African descent or 1 in 2400 infants in the general population tests positive for SCD or the sickle cell trait at screening.[6]

In SCD, almost every tissue in the body can be affected by the sickling of red cells and the resultant microvascular

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occlusion. In addition, the associated anemia has global effects. Ischemic events are presumed to result from a cascade of events related to sickled red cells, abnormally increased red blood cell-endothelial adherence, intimal damage and proliferation, and vascular stenosis. Increased blood flow and turbulence results in a vicious cycle of additional endothelial damage and narrowing.[1] The sickling is reducible or reversible depending on the combination of factors, including oxygenation, degree of cellular dehydration, decreasing pH, and circulating levels of Hb S. Sickled cells may not be able to traverse capillary beds due to both their abnormal shape and relative rigidity.[1,7] Increased binding of red cells to the vascular endothelium, inhibited vasorelaxation, and intimal hyperplasia with irregular endoluminal narrowing also contribute to tissue ischemia and infarction.[1,7-10]

Imaging of Sickle Cell Disease

Brain

Complications from SCD occur relatively commonly in the head and neck.[11] Decreased cognition, stroke, and atrophy are common in patients with SCD, although intraparenchymal or subarachnoid hemorrhage and aneurysm are encountered less frequently.[1] There is also an increased incidence of posterior reversible encephalopathy syndrome in the setting of hypertension and intracranial hypertension.[11-14] Sickle cell is one of the most common causes of stroke in children and may or may not be clinically apparent.[15] Wong et al.[16] estimated the incidence of first overt brain infarct in SCA (Hg SS) patients to be 11% by 20 years of age and 24% by 45 years of age. The peak is bimodal, with the first peak occurring between the ages of 2 and 9 years (most commonly before age 5) and a second peak occurring in adults after their second decade.

MRI/MRA. Abnormalities in magnetic resonance imaging (MRI) or MR angiography (MRA) are seen in nearly 50% of patients[17] (Fig. 1). Ever-advancing imaging techniques promise to increase that percentage even further. Imaging findings at conventional MRI in patients with SCD include the following: acute cortical or deep white matter infarct, hemorrhagic infarct, multifocal white matter fluid-attenuated inversion recovery hyperintensities secondary to prior infarct, multiple flow voids in the basal ganglia representing lenticulostriate collateral vessels (moyamoya vasculopathy), increased leptomeningeal fluid-attenuated inversion recovery signal, enhancement due to vascular stasis, and leptomeningeal collaterals (the "ivy sign"). The infarcts, not surprisingly, are most commonly located in the white matter and the watershed zones between the anterior cerebral artery (ACA) and middle cerebral artery (MCA).[1] Diffusion-weighted imaging) is currently the most sensitive imaging technique to detect infarcts and can demonstrate areas of restricted diffusion heralding ischemia or infarction that may be missed by conventional MR sequences. Mullins et al.[18] demonstrated that diffusion-weighted imaging demonstrated ischemic lesions that were less than 6 hours old, while only 18% of the infarcts had been detected upon conventional MRI.

MRA is also important in screening for arterial abnormalities, including arterial stenosis, aneurysms, and moyamoya vasculopathy.[16] Arterial stenosis occurs more often in the distal internal carotid arteries (dICAs), MCAs, and ACAs and rarely affects the vertebrobasilar circulation.[13] Lenticulostriate collateral vessels can be seen in the setting of moyamoya with bilateral ICA narrowing. Turbulent intracranial blood flow secondary to anemia may mimic stenosis on MRA. The use of shorter echo times (TE), higher matrix, and possibly a gadolinium injection may decrease this artifact and reduce false-positive rates.[16,19]

Perfusion imaging, dynamic contrast-enhanced MRI, or arterial spin labeling can demonstrate decreased regional cerebral blood flow and regional cerebral blood volume with increased time to peak and mean transit time in ischemic areas.[20] However, an overall increase in the baseline regional

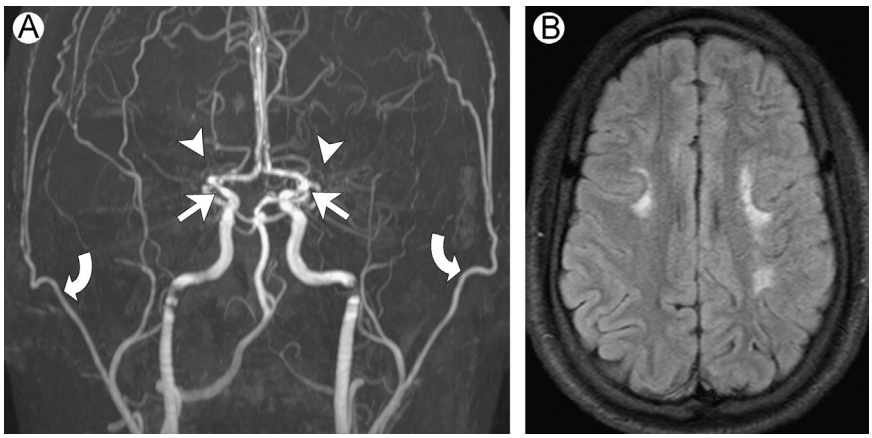

Figure 1 An 18-year-old boy with sickle cell anemia and vaso-occlusive disease. (A) Frontal maximum intensity projection image of an intracranial MR angiogram with a selection of the carotid circulation demonstrates the narrowing of both distal internal carotid arteries (arrows). Nonvisualization of the middle cerebral arteries with consequent enlargement and tortuosity of the lenticulostriate arteries (arrowheads). Prominent external carotid arterial branches (curved arrows) are seen. (B) Axial FLAIR MR image of the brain demonstrates white matter signal abnormalities, the sequelae of prior infarcts. FLAIR, fluid-attenuated inversion recovery.