Sickle Cell Disease: a pictorial review of well-known and less well-known imaging findings in children.

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Learning objectives

Sickle cell Disease (SCD) is characterized by a wide spectrum of clinical presentations, with various involvement of cerebral, thoracic and abdominal districts, as well as a large range of musculoskeletal manifestations; so, it could present some diagnostic pitfalls, not only for Clinicians but also for Radiologists, especially in those cases of children whose clinical history is difficult to reconstruct, due to a foreign origin.

The aim of this article was to illustrate both well-known and less well-known SCD imaging findings emerged from Literature's analysis; if present, best-known SCD imaging findings, as well as some more rare ones listed below, represent a good tool for general Radiologists to easily identify SCD and give more confidence when suspecting SCD in children whose disease has not been set yet.
Background

Sickle Cell Disease (SCD) is a hemolytic anemia due to reduced or abnormal production of hemoglobin, because of a single aminoacid substitution in the #-globine gene. This genetic mutation leads to the production of a defective form of hemoglobin, hemoglobin S (HbS), which aggregates with other abnormal hemoglobin molecules into long chains; then, red blood cells take a rigid "sickle" shape and are removed from the circulation by the reticuloendothelial system and destroyed at increased rates, leading to anemia. Moreover, the sickled red blood cells cause vascular occlusions due to obstruction of the microcirculation, with consequent ischemia and tissue infarctions [1].

SCD is transmitted as autosomal recessive disease; therefore, a condition of SCD results only in presence of two sickle cell hemoglobin genes (HbSS), while in presence of a normal and of a sickle cell hemoglobin gene, the outcome is heterozygosis (HbSA), which is a protective condition for falciparum malaria; this data explains some similarities in the geographic distribution of SCD and areas where malaria is endemic [1].

The most common and early clinical manifestations of SCD can vary from the typical signs of chronic anemia (such as delay in growth, gallstones, skin ulcers of the lower limbs and aplastic crises) to acute painful vaso-occlusive crises, predominantly in the form of dactylitis, involving both bones and soft tissues; osteonecrosis, osteomyelitis, acute chest pain, splenic infarcts and sequestrations, kidney failure and papillary necrosis, cognitive impairment, functional neurological deficits and priapism represent frequent conditions in SCD, as well [1].

As for the prognosis, average life expectancy of SCD-patients is growing in western countries [2], thanks to the improvement of therapeutic tools and prevention instruments of acute complications. However, SCD still causes significant mortality and morbidity, with a decrease of 25-30 years in the average life expectancy [2], determined by a progressive multiorgan failure caused by this disease.
Findings and procedure details

Imaging techniques

When suspecting SCD, as for instrumental diagnostics, abdominal ultrasound (US) represents a first-level exam, easy to repeat, safe and cheap, that allows evaluation of abdominal parenchymal organs and of retroperitoneum, also assessing the presence of fluid and/or intra-abdominal masses and the measurement of abdominal organs; however, it is technical operator-dependent and has a low specificity.

Radiological investigation (x-Ray) and Computed Tomography (CT) are non-invasive techniques, but require the patient's exposure to ionizing radiation. The protocols used in pediatric patients provide low-dose techniques, modulated in relation to the patient's BMI. Magnetic Resonance Imaging (MRI) is a multiparametric exam with high contrast resolution, which does not use ionizing radiation; thus it is considered by many Authors the gold-standard in the identification and characterization of certain types of complications related to SCD. The acquisition protocols in our center include the execution of images acquired in the three spatial planes (axial, coronal, and sagittal), T1 and T2-weighted, with and without fat suppression, depending on the clinical question. Eventually, some additional sequences, as T1-weighted images after administration of paramagnetic contrast (gadolinium) bolus (0.2 ml/kg) through automatic injector are performed, with a speed of 2 ml/s, acquired in the arterial, venous and delayed phase during breath-holding.

Main clinical manifestations SCD-related

We reported well-known and less well-known imaging findings described for main clinical manifestations of SCD, considering both signs identifiable with first-level exams (US and xRay), and findings recognizable with in-depth techniques (CT and MRI), according to the district examined; in particular, we approached the following entinites linked to SCD:

Skeletal system

According to the analysis of the literature, skeletal complications of SCD mainly include bone infarcts and osteomyelitis [1].
On X-Ray examination, bone infarction shows various radiological appearances, depending on the time when the radiogram is acquired; in particular, it is firstly characterized by a pathological radiolucent area, which later develops intramedullary and subchondral arcuate areas of radiopacity, with associated contextual sclerotic areas and transparent patches (Fig. 1 a). In addition, a peripheral rhyme of sclerosis is often observed, especially in cases of medullary bone infarcts [3]. MRI is the most sensitive technique in the detection and characterization of bone infarction, because it can show changes in a few days after the infarct event; on MRI, infarction appears as a dishomogeneous area, hypointense on T1-weighted images and hyperintense on T2-weighted and STIR images (Fig. 1 b; Fig. 2 a - b). Using this exam it is also possible to observe the modifications of soft tissues and the associated abnormal signal intensity of periosteum [3].

In the spine, bone infarction may present as a central biconcave depression of the vertebral body surface, due to microvascular occlusion, with associated disproportionate growth of the surrounding portions of the metamer. The aspects described are pathognomonic of SCD, known as the "sign of Lincoln," "spinal H" or "fish mouth deformity" [1] (Fig. 3 a - b).

Osteomyelitis is another severe complication of SCD, which presents an incidence of 18% of the subjects, according to the study of Bahebeck J et al [4]. Radiographic findings, such as periostitis, osteopenia and sclerosis, become evident after about 8-10 days after the event but are non-specific signs, as they are observable both in infection and in bone infarction [5] (Fig. 4 a - b).

US can be used as an alternative to CT, especially in pediatric patients, since it allows detection of fluid collections, periosteal reactions and other pathological changes of soft tissues, without using ionizing radiation and with greater tolerability by young patients; it can also act as a guide to perform percutaneous drainage, as analyzed in the study of Baba PD Inusa et al [6].

Even in this case, MRI represents the gold standard for a correct diagnostic definition; osteomyelitis appears as an area of hyperintensity signal on T2-weighted and STIR sequences. On T1-weighted post-contrastographic sequences, with fat suppression, it can be observed a hypointense central area surrounded by a peripheral enhancement (Fig. 4 c - d) [5].

Other skeletal signs that may be found in SCD-patients are epiphyseal infarcts and dactylitis, pathological fractures and the so-called skull brush [1].

Finally, a "hemangioma-like" pattern, characterized by an hemangioma-like appearance involving vertebral bodies and to lesser extent ribs, sternum and shoulder
blades (Fig. 5), is a less-well known sign detected in children with SCD, probably as a consequence of marrow hyperplasia or vascular malformations.

**Lungs**

Pulmonary manifestations of SCD can range from acute processes, such as Pneumonia or Acute Chest Syndrome, to chronic forms, like pulmonary fibrosis.

The detection of a consolidation on chest radiograph greatly helps to support and confirm clinical suspicion of pneumonia (Fig. 6 a).

"Acute-chest-syndrome" (ACS) is an acute lung disease, characterized by the appearance of a pulmonary consolidation on chest X-Ray and, in combination, by one or more of the following symptoms: fever > 38.5 ° and/or chest pain, cough, dyspnea, tachypnea and arterial oxygen desaturation [7]. Radiological signs identified in ACS are: single or multiple areas of consolidation on chest X-Ray, mainly involving middle and lower lung fields (Fig. 6 b); however, this examination may also be negative in the early stages of ACS [7].

As concerns chronic lung disease, a reticular or reticulonodular interstitial pattern represents the spy of a development in fibrotic sense. On CT, typical findings of this condition include: thickening of the reticular septa, secondary pulmonary lobules dilatation and distortion, traction bronchiectasis and architectural macroscopic distortion (Fig. 7 a) [8].

**Pulmonary Hypertension** is another possible chronic complication of SCD and is linked to a high risk of mortality, according to the study of Gladwin MT et al [9]. Indicative radiological signs of this condition are represented by an increased size of the pulmonary arteries and cardiomegaly on chest X-Ray; chest CT shows growth of the pulmonary artery main trunk diameter and of its main branches, right ventricular hypertrophy, right atrial enlargement, tricuspid regurgitation and mosaic perfusion pattern.

**Air-trapping** areas on chest HRCT in these patients represents a possible indicator of obstructive alterations of small airways (Fig. 7 b); this finding is interesting in relation to the increased incidence of abnormalities on bronchial hyper-reactivity tests and of obstructive airway disease in patients with SCD, as depicted in the study of Koumbourlis AC et al [10].
Heart and mediastinal vessels

The remodeling of the left ventricle consequent to chronic anemia and the fluid overload due to hydration that follows sickle cell crises are responsible for an increase in the size of the cardiac silhouette on chest X-Ray (Fig. 8). In addition to cardiomegaly in these patients it is also possible to observe a smooth thickening of the interstitial septa, for the establishment of interstitial pulmonary edema, and, in the most severe cases, interstitial-alveolar pulmonary edema [11].

Finally it can be detected the hypodensity of blood within heart chambers and mediastinal vessels, related to the condition of anemia and consequent poverty of blood within the cardio-vascular district, with associated apparent parietal hyperdensity (Fig. 9 a - b).

Spleen

Splenic infarction results from entrapment of sickled red cells in splenic microcirculation, with following congestion and increase in volume and weight of the organ; sequestered sickled erythrocytes are continuously removed by mononuclear phagocytes in the course of "extravascular" hemolysis. Over time, as a result of this chronic process of eritrocateresis, splenic infarction and functional autosplenectomy occur. The spleen with multiple infarcts is then replaced by fibrosis, with associated deposition of calcium and hemosiderin [1].

On imaging exams, the spleen, firstly enlarged and inhomogeneous, due to the presence of contextual ischemic areas, becomes small and appears hyperechoic on US and hyperdense on CT scans (Fig. 10 a - c). On MRI, a spleen with multiple areas of infarction and fibrotic aspects presents a widespread and heterogeneous hypointensity signal (regardless of the sequences used) secondary to ferrocalcinosis (Fig. 10 d); infarctions appear as focal triangular areas of altered signal, mostly peripheral. The signal depends on the period when the process occurred; after administration of Gadolinium, infarction areas are not endowed with enhancement [12].

In addition, some portions of spleen tissue, preserved or regenerated, may occasionally be present in older children and in adults with SCD. These areas can be firstly documented performing a US examination with a convex probe, then completed using a linear probe for a more accurate evaluation of splenic parenchyma. They appear as circular hypoechoic masses in the context of a hyperechoic organ; on CT they show a similar density to normal spleen. On MRI, they have similar features to those of normal spleen, too (Fig. 11).
Another complication involving spleen in SCD is known as "sequestration syndrome." It is characterized by a rapid obstruction of venous vessels, causing depletion of intravascular volume and reduced hematocrit values (with loss greater than 2 g/dL) [1].

In the sequestration syndrome, spleen appears heterogeneous on US, with multiple hypoechoic areas that can be seen mostly along its edges. On CT, as well, hypodense peripheral areas can be observed. On MRI, focal hyperintense areas both on T1 and on T2-weighted images may be present and are compatible with haemorrhagic foci, as showed in the study of Levin TL et al [13].

Liver and biliary tract

SCD liver complications are secondary both to the sickling process and to the great number of transfusions that these patients require during their life [14].

Liver, on US and occasionally x-Ray exams, may appear as an enlarged organ (Fig. 12 a - b), homogeneous or inhomogeneous, depending on the presence of infarction areas; profiles can be irregular and size can be reduced in patients with chronic hepatitis or cirrhosis. A liver increased in size is detectable on CT, (Fig. 13) which in these patients is used for searching areas of infarction, abscesses and possible complications after cholecystectomy [14].

MRI can show an altered parenchymal signal intensity related to iron overload, with hypointensity both on T1 and on T2-weighted images; signal hypointensity can also involve both pancreas and spleen, due to iron deposition and prior parenchymal atrophy at these levels [15].

As for the gallbladder and the biliary tract, there is a higher incidence of gallstones because of an increased production of bilirubin following chronic hemolysis; therefore, cholecystectomy results to be the most frequently performed surgical procedure in these patients, as resulted from the study of Al-Salem AH et al [16].

Even as regards these sites, abdominal US is the examination routinely performed to check a possible involvement. Through abdominal US, it is possible to observe the presence of intrahepatic bile ducts stenosis and the eventual associated cholestasis, probably secondary to repeated episodes of infarction; it is also possible to provide and quantify gallstones. Gallstones, typically pigmented due to the increased excretion of bilirubin, are highlighted in 20% of children with SCD (Fig. 14 a - b), while "biliary sludge" is frequently detectable in patients of all ages [14].
Kidneys

According to the study of Sharpe CC et al [17], renal involvement in SCD includes a great number of glomerular and tubular disorders, associated with increased mortality. On US, kidneys may have increased echogenicity (Fig. 15 a), normal (89% of patients), or mild and widespread hypoechochogenicity (5%); in other cases a hyperechoic medulla with isoechoic cortex can be detected (3%). This last data can be found in nephrocalcinosis from other causes and in SCD it could reflect a sub-clinical phase of papillary necrosis [18], or an incidental finding with no certain clinical relevance. Other US alterations to be mentioned are represented by a reduced corticomedullary differentiation (Fig. 15 a), indicator of nephropathy, and the presence of kidneys small in size and with a poor echogenicity, these last features often in patients with a clear renal failure. Contrast enhanced CT is useful in studying infarction areas, papillary necrosis and in staging of renal medullary carcinoma, which resulted almost exclusively occurring in patients heterozygotes for HbS during the analysis of Davis CJ et al [19].

MRI can show the following findings: an altered T1 and T2 signal of renal cortex, probably due to anomalies of iron metabolism at this level, with increased iron-deposition in SCD patients; in renal medulla the signal can result higher on T2-weighted images, because of a reduced vascularity of pyramids, as a consequence of sickling; this event could protect from the deposition of calcium or iron, differently from what happens in the cortex (Fig. 15 b).

Brain

The main neurological complication is represented by ischemic injury, with secondary brain atrophy and cognitive deficits; less common problems include parenchymal and subarachnoid hemorrhages and aneurysms [1]. Doppler US screening, CT and MRI, performed in a specialized environment, play a major role in the diagnosis and characterization of cerebral-SCD findings[1].

On CT, infarct appears as a hypodense area localized mainly in the white matter and in peripheral areas irrorated by anterior cerebral and middle cerebral arteries, gradually becoming better defined and evolving into atrophic scar. On MRI acute infarct presents low signal intensity on T1-weighted images and hyperintensity on T2-weighted images. In a subacute phase, up to one month after onset, it becomes slightly hypointense on T1-weighted images, maintaining a T2 hyperintensity. Chronic infarct shows a well-defined hypointensity on T1 and hyperintensity on T2-weighted images, with better defined margins and associated signs of focal atrophy (Fig. 16 a - b) [1].
Patients with SCD have an increased incidence of **aneurysms**, especially in adulthood. These are mostly multiple, often originated from the arteries of the vertebrobasilar system (about 30%) and can occur with subarachnoid or parenchymal hemorrhage; CT-angiography and MRI-angiography are non invasive techniques indicated to identify these complications (Fig. 16 c - d) [1].
**Fig. 1:** 15-year-old patient with SCD and pain crisis occurred in right arm; x-Ray (a) shows an osteolytic lesion in the right humeral head, with finely irregular and thickened margins, compatible with bone infarction (arrowhead); other focal osteostructural alteration with a thickened labrum is appreciable at the mid diaphyseal third, possible outcome of a similar previous injury (arrow). The same patient performs an in-depth investigation with MRI (b) which confirms the presence of an area of altered signal, hyperintense on T2-weighted images (arrow), affecting the right proximal humeral epiphysis. After intravenous administration of paramagnetic contrast medium it is not documented a significant impregnation of this lesion.
**Fig. 2:** MRI of the spine performed in a 16-year-old patient after a painful crisis; it is possible to detect a subtle signal alteration (arrow) on T2-weighted sequences, involving the upper somatic limitant of D11 (a); after intravenous administration of paramagnetic contrast medium (b) it is possible to notice a tenuous contrast enhancement by the described area of altered signal that is compatible with bone infarction (arrow).

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**Fig. 3:** 6 year-old patient with SCD and history of bone painful crises. CT (a), sagittal view with bone window, reveals the presence of vertebral bodies with a "H-shape"; a similar
finding is detectable in a MR exam (b), performed in a 15 year-old patient of with SCD and history of pervasive painful crises, particularly in the spine.

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**Fig. 4:** 11 year-old patient with SCD and osteomyelitis of the left fibula; x-Ray exam (a) shows a widespread osteostructural alteration both of the distal third of the diaphysis and of epiphysis of fibula, with mixed features, mainly thickening, with small areas of contextual radiolucency; the bone segment involved appears stocky and swollen with signs of periosteal apposition in the proximal tract, while at the mid third of the bone, on the lateral side, it is possible to appreciate a focal continuous solution (arrow). Increase in volume of surrounding soft tissues is associated. Control X-Ray (b) shows regular repair
processes in the distal fibula. MRI reveals a widespread and extensive osteostructural alteration of bone medulla both in the diaphysis and in the distal epiphysis of left fibula, with associated cortical and periosteal areas of bone remodeling; simultaneously, extension of the inflammatory process at the level of muscle planes and surrounding soft tissues occurs (fat saturated T1-weighted images, sagittal view: c; see arrows). T1-weighted images after contrast agent administration, axial view (d): organization aspects can be seen in the context of both bone and muscle components interested by osteomyelitic process (arrow), some of them circumscribed by a peripheral labrum enhancing after contrast medium administration.

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**Fig. 5:** Axial CT scans of a 12-year-old patient with SCD; CT study, visualized with bone window, highlights an hemangioma-like appearance of vertebral bodies (arrowhead) and other bone segments, such as sternum (asterisk) and ribs (arrow).

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**Fig. 6:** (a): 7-year-old patient with fever and abdominal pain; chest radiograph (AP view) shows a parenchymal consolidation in the right upper lobe, compatible with pneumonia (arrows); as an accessory finding, cardiomegaly can be noticed. (b): 16 year-old patient with SCD, fever and desaturation; chest x-Ray shows bilateral parenchymal consolidations involving lower lobes, with associated pleural effusion.

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**Fig. 7:** (a): 16 year-old patient with SCD, fever and desaturation; high-resolution CT visualized with lung-parenchyma window shows fibrotic parenchymal striae in both lower lung fields, associated with irregular thickening of the interstitial septa and initial architectural distortion of lung parenchyma. (b): Chest HRCT performed in 8-year-old patient with SCD and obstructive syndrome on function tests; espirium scans highlight some areas of reduced attenuation due to air trapping caused by small airways disease (asterisks).

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Fig. 8: Enlargement of the whole heart due to SCD can be detected on chest x-Ray (arrow).

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**Fig. 9:** Axial chest CT images of 10-year-old subject, displayed with mediastinal window, reveal a hypodensity inside heart chambers (a) and mediastinal vessels (b), with consequent apparent parietal hyperdensity, due to chronic anemia (arrows).

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Fig. 10: On US investigation, spleen can appear enlarged with an inhomogeneous echostructure (a) for the presence of some contextual hypoechoic lesions, due to areas of infarction. (b): CT images acquired in a 7-year-old patient with SCD show an enlarged spleen (cranial-caudal extension of 16 cm) which determines malrotation and downward displacement of the left kidney (arrow). (c): hyperdense spleen is detectable on a CT executed in a SCD patient; on MRI (d) the corresponding finding is represented by a spleen with a diffusely hypointense signal, in relation to the involution of the organ (arrow).

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Fig. 11: the spleen of a 7 year-old-patient with SCD appears normal for size, but with an inhomogeneous signal intensity and morphology for the presence of multiple rounded formations (the biggest of about 3 centimeters; see arrow), more hyperintense compared to the remaining parenchyma both on T1 and on T2-weighted images, and isointense compared to liver parenchyma, compatible with areas of spared parenchyma.

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Fig. 12: Presence of hepatomegaly in spine x-Ray (a) performed for evaluation of scoliosis in a 15-year-old patient with SCD; US (b) carried out in a 3-year-old patient shows a liver with homogeneous echostructure, slightly enlarged;

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Fig. 13: CT images of a 14-year-old patient illustrate a liver increased in size at the expense of both lobes; density is homogeneous.

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**Fig. 14:** Abdominal US (a), performed with convex probe, shows the presence of choledolithiasis; ultrasonography (b) carried out in a patient with splenomegaly and history of splenic infarcts, highlights the presence of a gallbladder filled with biliary sludge.

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**Fig. 15:** US (a) performed with convex probe in a 12-year-old patient: diffuse hyperechoic renal cortex with initial loss of cortical-medullar differentiation in relation to the underlying disease; upper abdominal MRI (axial T2-weighted sequences; b) in a 7-year-old patient without particular clinical and laboratory nephrologic abnormalities: both renal cortex, markedly hypointense (arrow), and medulla, which presents increased intensity show an altered signal (arrowhead); these are incidental findings in patients with SCD and are related to the altered metabolism of iron and calcium in these districts, secondary to the underlying disease.

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Fig. 16: Brain MRI performed in a 5 year-old patient with SCD and a known ischemic lesion localized in the right frontal lobe; axial GRE T2* (a) and coronal T2-weighted sequences (b) show an area of hazy hyperintensity on T2-weighted images in the white matter (arrows) with associated thinning of the parasagittal cortex and consequent expansion of the subarachnoid spaces. Brain MRI performed in a 11-year-old patient detecting multiple aneurysms in angiographic acquisitions; here are shown 3D angiographic sequences (c) and VR reconstructions (d) that highlight some aneurysmal dilatation localized in both carotid siphons (arrows).

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Conclusion

In conclusion, SCD frequently shows hazy symptoms and non-specific clinical signs, as well as a series of events similar to those of other illnesses. The imaging findings described in this article, both the better-known ones, and others more uncommon, but possible indicators as well, highlight the diagnostic value of imaging studies in the identification of SCD and provide a useful guide for general Radiologists in the recognition of this disease and in the correct setting of pediatric patients, especially in the ones whose clinical history is not clear (foreign patients).

In similar cases, SCD-radiological indicators listed here are a valuable aid in orienting towards the right diagnosis, allowing a good patient's clinical placement.
Personal information

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