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PICTORIAL REVIEW

Imaging features of thalassaemia

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ABSTRACT

This article highlights the range of osseous findings that can be encountered as well as the imaging features of extramedullary haematopoiesis. As iron overload remains a major cause of morbidity and mortality in these disorders, we also discuss the MRI evaluation of hepatic and cardiac hemosiderosis, to aid in the optimization of iron chelation therapy. Future imaging use will be dictated by evolving clinical needs, such as in screening for emerging morbidities, including hepatic fibrosis and hepatocellular carcinoma.

INTRODUCTION

In thalassaemia, a heterogeneous group of inherited blood disorders, there is ineffective erythropoiesis resulting from decreased or absent globin chain synthesis. Based on clinical severity, thalassaemia can be divided into transfusion dependent thalassaemia (TDT) and non-transfusion dependent thalassaemia (NTDT), with an associated range of radiologic features.¹ NTDT presents at a later age with a similar but milder spectrum of clinical findings.²

Osseous manifestation

The severity of osseous changes is dependent on the thalassaemia subtype, duration of disease as well as transfusion–chelation treatment. Changes overall are most pronounced in undertreated TDT. Marrow hyperplasia secondary to chronic anaemia results in medullary expansion, cortical bone thinning, cancellous bone resorption as well as osteopaenia, which may result in pathological fractures.³ Osteopaenia remains a prominent cause of morbidity, even in optimally treated patients.^{1,4}

Vertebra and pelvis

Vertebral osteopaenia may produce a striated appearance, resulting from preserved primary trabeculae with resorbed secondary trabeculae⁵ (Figure 1a). Superior and inferior endplate compression fractures may occur. The pelvic bones may demonstrate marrow expansion and trabecular

destruction, with subsequent trabecular coarsening, resulting in a “cobweb” appearance⁴ (Figure 1b).

Ribs

Generalised osteopaenia may be present with osseous expansion, particularly affecting posterior segments (Figure 1c). Permeative erosions of the inner cortex secondary to subperiosteal proliferation may give rise to para-osseous extramedullary haematopoiesis (EMH) (Figure 1c).⁶

Craniofacial bones

Widened diploic spaces with cortical thinning may occur, with outer table resorption, new bone formation and resultant classic “hair on end” appearance (Figure 2).⁶ The occipital bone is spared due to absent haematopoietic marrow (Figure 2b).⁷

Facial bone marrow overgrowth reduces pneumatization of the sinuses, with sparing of the ethmoid sinuses due to absent haematopoietic marrow (Figure 2b).⁷ The classic “rodent facies” of TDT is infrequently seen in modern practice, but results from prominent malar eminences, lateral displacement of orbits, and ventral displacement of incisors.^{1,4} (sorry, we made a reference error. Please remove reference 6 here)

Peripheral skeleton

Loss of the normal concave outline secondary to marrow expansion may be noted, mostly affecting the humerus and

Figure 1. (a) Coronal CT (bone window) in a 29-year-old female with TDT shows diffuse osteopaenia with cortical thinning and striated vertebral appearances. (b) Coronal CT (bone window) in the same patient as (a) shows medullary expansion and “cobwebbing” of the pelvic bones. (c) CT chest in a 45-year-old male with TDT demonstrating bulbous expansion of the osteopaenic posterior ribs, cortical erosions, and para-osseous soft-tissue masses (arrows), representing extramedullary haematopoiesis. TDT, transfusion dependent thalassaemia.

Figure 2. (a) Axial CT of the calvarium in a 17-year-old girl with TDT and a history of delayed onset transfusion therapy shows marked diploic space widening and “hair-on-end” appearance of the frontal and parietal bones. (b) CT topogram of the same patient as in (a) shows sparing of the occipital bone (arrow) as well as sparing of the ethmoid sinuses (arrowhead). TDT, transfusion dependent thalassaemia.

femur and the tubular bones in hands and feet of children.^{4,6} Vascular impressions may result from nutrient foramina enlargement. Premature epiphyseal fusion occurs infrequently.³

Figure 3. 25-year-old female with hypertransfused, suboptimally chelated TDT demonstrating severe vertebral marrow hypointensity on sagittal lumbar spine MRI (a) T_1 and (b) T_2 weighted sequences. This patient was also found to have severe hepatic and cardiac iron overload (not shown). TDT, transfusion dependent thalassaemia.

Marrow changes according to treatment status

In untransfused thalassaemia, there is lack of normal centripetal red marrow regression hence red marrow persists throughout the central/peripheral skeleton, beyond the first few years of life.⁴ In hypertransfused but unchelated thalassaemia, there is iron deposition in the central/peripheral skeleton with minimal marrow expansion, manifesting as marrow hypointensity compared with muscle on all sequences⁴ (Figure 3). In hypertransfused but chelated thalassaemia some iron deposition may be seen within the central skeleton however the peripheral skeleton is composed of predominantly fatty marrow.⁴

NTDT

The medullary expansion encountered in NTDT is less severe compared with TDT.² However, growth retardation and skeletal deformity may occur. Osteoporosis is common, especially with advancing age.²

Treatment complications

Chelation regimes must be adjusted periodically to account for underchelation with increased iron toxicity or overchelation with increased chelator toxicity.¹ Desferrioxamine toxicity can result in rickets-like bony lesions, genu valgum, and vertebral body flattening.¹ Deferiprone toxicity can result in subchondral bone flattening and thickened articular synovium/cartilage.

Extraosseous manifestations

Extramedullary haematopoiesis (EMH)

EMH may be classified as paraosseous or extraosseous and is more common in NTDT than in regularly transfused TDT.² Paraosseous EMH typically occurs in the thoracic region, followed by the lumbar region. This appears as lobulated posterior mediastinum soft-tissue masses involving the posterior rib segments, or less often the anterior ends of ribs or presacral region.⁸

Extraosseous EMH is thought to arise from pluripotential stem cells, most commonly affecting the liver and spleen, resulting in hepatosplenomegaly or pseudotumours when mass-like.⁶ EMH can also occur in lymph nodes or less commonly in the kidneys, CNS, adrenals, mesentery, middle ear, paratracheal region, thymus, heart, breasts, prostate, and broad ligaments.²

Figure 4. (a) Frontal chest radiograph and (b) coronal T_2 weighted MR image of the thorax of a 55-year-old female with thalassaemia intermedia demonstrating extensive posterior mediastinal EMH (arrowheads). These masses demonstrated high T_1 and T_2 signal intensity, consistent with fat-infiltrated EMH. Note partially imaged splenomegaly (arrow). EMH, extra medullary haematopoiesis.

Figure 5. Coronal non-contrast CT image of the abdomen in a 16-year-old girl with TDT shows uncomplicated cholelithiasis and massive splenomegaly. Note also diffusely hyperattenuated mildly enlarged siderotic liver with an average HU of 85 secondary to transfusional siderosis (normal liver attenuation should be approximately 54–60 HU). Also note decreased attenuation of the imaged heart and visualized vessels correlating with anaemia. HU, Hounsfield unit; TDT, transfusion dependent thalassaemia.

MR is the modality of choice for evaluation. Active masses demonstrate intermediate T_1/T_2 signal, while inactive lesions with iron deposition are T_1/T_2 hypointense, or T_1/T_2 hyperintense due to fatty infiltration⁹ (Figure 4). Gadolinium IV enhancement may be minimal or absent. Biopsy may still be necessary for definitive diagnosis, particularly in atypical locations.

Spleen

Massive splenomegaly (Figure 5) carries risks of splenic rupture or hypersplenism. Splenomegaly due to undertransfusion may

Figure 6. Axial MR abdominal images in a 23-year-old man with thalassaemia major shows large right suprarenal mass (arrows), similar in appearance to the native spleen on (a) T_1 (b) T_2 and (c) post-gadolinium portal venous phase image. Although unusual in location, this proved to be an accessory spleen on pathology, post-surgical resection, with areas of necrosis. Note globally decreased liver signal intensity due to iron overload. Mild splenomegaly was also present.

be reversible. Although there is potential reduction in transfusional iron loading after splenectomy, this must be weighed against long-term asplenia consequences.¹ Accessory spleens occur in greater frequency in haematologic disorders. They are commonly located at the splenic hilum, but can occur throughout the abdomen, occasionally mimicking tumours. On cross-sectional imaging, they appear similar to normal splenic tissue on all phases. (Figure 6). Tc-99m heat-damaged RBCs or sulphur colloid scans can aid in diagnosis.

Gallbladder

The incidence of gallstones has declined in TDT, since the routine use of transfusion therapy. If a thalassaemia patient is proceeding to splenectomy, concomitant cholecystectomy can be considered if cholelithiasis is present.¹

Iron overload (hemosiderosis)

Iron overload secondary to repeated transfusions (such as in beta-thalassaemia major) and increased intestinal absorption (such as in beta-thalassaemia intermedia), is a major cause of morbidity and mortality.¹ Signal loss associated with siderosis is particularly apparent on T_2^* MRI sequences. Although multiorgan siderosis occurs, the liver is the main storage organ (Figure 7). Sequential liver iron quantification provides the best estimate of total body iron stores, hence can be used to tailor chelation therapy.^{10–12}

Figure 7. Same patient as in Figure 6 showing diffuse hepatic siderosis on T_1 WI as evidenced by decreased signal on (a) in-phase compared with (b) out-of-phase images: opposite finding to steatosis. Subtle siderotic splenic nodules also noted (arrows). T_1 WI, T_1 weighted imaging

Figure 8. Selected axial MR images of the abdomen, T_2^* sequences, in a 27-year-old male with TDT demonstrating hepatic signal loss over increasing TEs from (a) to (d), consistent with moderate to severe hepatic siderosis; estimated LIC of 14.21 mg g^{-1} . In an unaffected patient, there would be no substantial change in SI across TEs. LIC, liver iron concentration; SI, signal intensity; TDT, transfusion dependent thalassaemia; TE, echo time.

Hepatic siderosis and liver iron concentration (LIC)

The two main methods for LIC determination are the signal intensity ratio (SIR) and the T_2 relaxometry method. The semi-quantitative SIR method requires no specialized software.¹³ The SIR Protocol uses a body coil and gradient recalled echo (GRE) sequences with a fixed repetition time (TR) and multiple echo times (TEs).^{13,14} The SIR is calculated after sampling regions of interest (ROI), comparing the signal intensity (SI) in the liver with that of the paraspinal muscles.¹³ This method, has limited accuracy in severe iron overload, with a tendency to overestimate mild and moderate iron overload.¹¹

The T_2 relaxometry method usually requires commercial post-processing software, hence is limited in availability.¹² The paramagnetic effects of iron decrease T_2 relaxation times on multi echo GRE sequences, proportional to iron content (Figure 8). A parametric map is generated with SI as a function of TE, with estimation of the LIC value. A variety of techniques are used, namely T_2 or T_2^* , which can be expressed as relaxivity rates: R_2 ($1/T_2$) or R_2^* ($1/T_2^*$).¹¹

T_2 or R_2 relaxometry generates more accurate results compared with SIR methods.¹² It, however, has a non-linear relationship with biopsy LIC.¹¹ T_2^* or R_2^* relaxometry is more sensitive than T_2/R_2 methods, as it reflects true T_2 as well as magnetic field inhomogeneities. Additional advantages of R_2^* relaxometry

Figure 9. Selected cardiac MR T_2^* sequences in a 28-year-old female with TDT demonstrating cardiac signal loss over increasing TEs from (a) to (d), consistent with moderate to severe cardiac siderosis; T_2^* of 10.6ms corresponding to estimated MIC of 2.53 mg/g. Again, in an unaffected patient, there would be no substantial change in SI across TEs. This patient's LIC examination (not shown) demonstrated severe hepatic siderosis estimated at 21.21 mg g^{-1} . MIC, myocardial iron concentration; LIC, liver iron concentration; SI, signal intensity; TDT, transfusion dependent thalassaemia; TE, echo time.

includes faster acquisition times, steatosis quantification and reduced motion artefacts due to single breath-hold technique.¹¹

The development of hepatic fibrosis and cirrhosis, along with the associated risk of HCC, has been reported in high hepatic iron overload, even in the absence of transfusion-related viral hepatitis infection.¹ As extended life expectancy for thalassaemia patients has become evident in the industrialised world, the above complications are being seen with increasing incidence. Transient elastography in conjunction with ultrasound can prove useful for screening and surveillance of these complications.¹

Myocardial siderosis and myocardial iron concentration (MIC)

Myocardial siderosis can result in cardiac failure and myocardial infarction, and is the leading cause of mortality in TDT, but is not a critical factor in NTDT.^{1,2} Ferritin and LIC values are not very useful in predicting extrahepatic iron overload. Cardiac iron deposition and unloading following chelation occurs at a slower rate compared with that in the liver. The relationship between biochemically measured MIC and myocardial T_2^* on MRI, however, has been confirmed post-mortem.¹

The MR protocol used by Fahmy *et al*¹⁵ includes GRE T_2^* images acquired with multiple TEs and end-diastolic ECG triggering. SI is measured in the full-thickness region of the ventricular septum. There is high risk for myocardial dysfunction when T_2^* values are below 10 ms.¹⁰ (Figure 9).

Endocrine organ hemosiderosis

There is a correlation between cardiac siderosis and deposition in endocrine tissues such as the pituitary and the pancreas.¹

Figure 10. Unenhanced abdominal CT in a 30-year-old diabetic man with TDT shows extensive pancreatic fatty replacement changes. He had no concurrent diagnosis of cystic fibrosis. Prior splenectomy also noted. TDT, transfusion dependent thalassaemia.

Following splenectomy, preferential iron accumulation has been noted in both of these organs.

Pancreatic siderosis can result in fat replacement and pancreatic dysfunction. Pancreatic R_2^* measurements can be used for iron quantification,¹⁰ however, accuracy may be limited in pancreatic fat infiltration (Figure 10). Pituitary siderosis may result in pituitary volume loss, diffuse low T_2 signal, and clinical signs of pituitary dysfunction. R_2 is preferred over R_2^* methods due to the magnetically inhomogeneous sella turcica.¹⁰

CONCLUSION

Radiologists must be aware of the spectrum of multimodality imaging findings in both treated and undertreated thalassaemia disorders. The mainstay of imaging in modern practice is the MRI evaluation of hepatic and cardiac hemosiderosis, to aid in iron chelation optimisation. Studies are ongoing for the clinical utility of siderosis evaluation of other organs. Imaging in the thalassaemia syndromes is likely to remain dynamic in accordance with evolving clinical needs as well as further technological advancements.

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