

Sickle cell disease: What can nuclear medicine offer?

Artor Niccoli Asabella¹ MD, PhD, Corinna Altini¹ MD, Anna Giulia Nappi¹ MD, Valentina Lavelli¹ MD, Cristina Ferrari¹ MD, Andrea Marzullo² MD, PhD, Alessandra Loiodice³ MD, Giuseppe Rubini¹ MD, Prof

1. Nuclear Medicine Unit, Interdisciplinary Department of Medicine, University of Bari "Aldo Moro", Bari, Italy, 2. Section of Pathology, Department of Emergency and Organ Transplantation, University of Bari "Aldo Moro", Bari, Italy, 3. Section of Gastroenterology, Department of Emergency and Organ Transplantation, University of Bari "Aldo Moro", Bari, Italy

Corresponding author: Artor Niccoli Asabella, MD, PhD, Piazza G. Cesare 11, 70124 Bari, Italy, Phone number: +39 080 5592913, Fax number: +39 080 5593250, Email: artor.niccoliasabella@uniba.it

Hell J Nucl Med 2019;22(1):2-3

Epub ahead of print: 7 March 2019

Published online: 5 April 2019

Sickle cell disease (SCD) is the best known haemoglobinopathy, caused by a mutation substituting valine for glutamic acid at position 6 of the beta-globin chain of adult hemoglobin A [1], resulting in hemoglobin S (HbS). The homozygous HbS disease (HbSS), an autosomal recessive disorder, is the most common form and the Mediterranean area, along with sub-Saharan African and India, have the highest prevalence (1%-15%). In particular, Sicily with a prevalence of 2%-5%, is among the most interested regions. However, migratory flows have led to a wider diffusion of the disease no longer confined to endemic areas.

In Europe, the yearly estimate of affected births are 1,300 but more than 90% of children with SCD survive into adulthood thanks to screening programs and early available care; however, their lifespan remains shortened by two or three decades compared to general population [2]. In Greece, the number of affected births surpassing 100,000 yearly and the total number of newborns carrying two deleterious genes, if no prevention measures are taken, is estimated to be about 120-130/year.

Diagnosis of SCD is based on analysis of haemoglobin through protein electrophoresis or chromatography, that are cheap and widely available techniques, even if haemoglobin mass spectrometry and DNA analysis are techniques with high-throughput testing. Prenatal diagnosis is used in many European countries, so the number of affected newborns has significantly decreased during the last 3 years [3].

Over the course of SCD, sickling process may cause acute and chronic abdominal pain due to vaso-occlusive crisis, bone pain often in long bones due to bone marrow infarction, chronic hemolytic anemia, splenic sequestration with rapid enlargement of the spleen, delayed sexual maturation and cholelithiasis, with important inter-individual variability [4].

Sickle hepatopathy reflects liver sickling process within hepatic sinusoids and includes gallstone disease, hepatic sequestration, hepatic siderosis, acute sickle cell hepatic crises (ASHC) and sickle cell intrahepatic cholestasis (SCIC). Clinically, it appears with fever, right upper quadrant pain, jaundice and increased serum liver function tests. These patients are repeatedly exposed to transfused red cells that contributes to iron overload and may contribute to hepatic hemosiderosis [5].

Increased bone turnover and resorption by osteoclasts and by marrow expansion due to activation of hematopoiesis. The hematopoietic system may expand physiologically [6, 7].

Computed tomography (CT) is an easily reproducible imaging method that allows the morphologic whole-body evaluation although with a high dose of radiation exposure and possible side effects from intravenous contrast media. Magnetic resonance cholangiopancreatography (MRCP) is a noninvasive technique without radiation chosen to image cholangiopathy and may be followed by the execution of endoscopic retrograde cholangiopancreatography (ERCP) in case of gallstone disease. Otherwise it can be helpful in identifying extramedullary hematopoiesis sites [8-10].

Dual-energy X-rays absorptiometry (DEXA) is performed to evaluate deficit of bone mineral density (BMD), in which reduction of osteoblastic activity, high risk for necrosis may induce to fragility fractures [6].

We recently had the experience of a typical case of a 56 years old Albanian woman with SCD, with jaundice after a long history of recurrent vaso-occlusive crisis. She was submitted to splenectomy and cholecystectomy 5 years before and since then she was treated with hydroxyurea. Hemochromatosis was excluded by genetic analysis. Hepatic biopsy (Pearl's stain) showed sinusoidal dilatation and diffuse iron accumulation in hepatocytes and Kupffer cells. Endo-hepatic jaundice was observed in MRCP images.

It was interesting that DEXA examination was within normal range in both right proximal femur. This may probably be due to the presence of sclerotic lesions in the vertebrae, as was seen in the CT images.

Technetium-99m-methylene bisphosphonate (^{99m}Tc-MDP) skeletal scintigraphy is a highly sensitive whole-body diagnostic nuclear medicine technique able to evaluate early bone metabolic changes. Multimodality SPET/CT allows to correlate scintigraphic findings with anatomical images with higher sensitivity and specificity [11]. The higher uptake of ^{99m}Tc-MDP in SCD

patients is due to the activation of hematopoietic system and relies on the osteoblastic response to bone resorption as in our patient (Figure 1a) [12]. The ^{99m}Tc-MDP scan may be better than fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (¹⁸F-FDG PET/CT) to show sclerotic lesions [13].

Technetium-99m nanocolloids bone marrow scintigraphy (BMS) provides information about the assessment of the reticulum-endothelial system (RES), the whole-body distribution of functional red bone marrow and the presence and the extent of extramedullary hematopoiesis, especially in liver, spleen and bone marrow [14-16] (Figure 1 b, c, d).

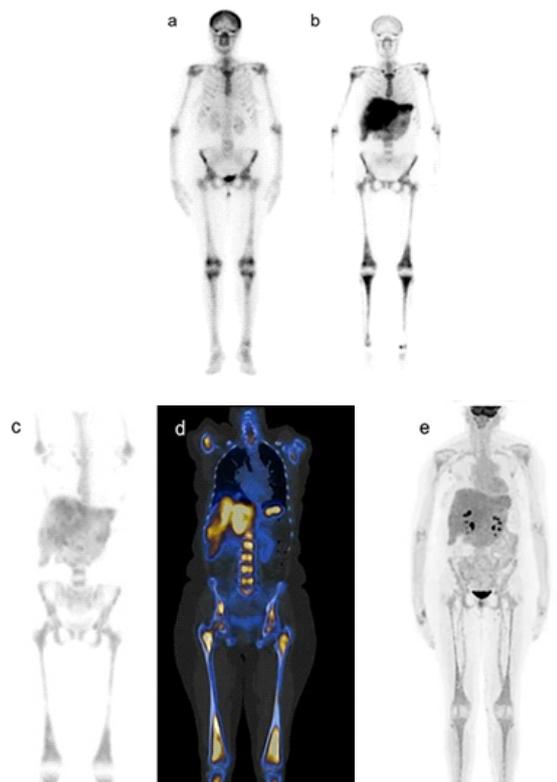


Figure 1. a-b) Technetium-99m-MDP skeletal scintigraphy in anterior whole-body image showed increased tracer uptake in the proximal half of the humeri and femora. **c-d)** Technetium-99m-nanocolloid BMS in anterior whole-body scan showed marrow expansion, throughout the skeleton, but above all in the skull, humeri, femora, elbows, wrists and ankles. **e)** Fluorine-18-FDG PET/CT MIP and coronal section showed an increased uptake of radioactive tracer not only in the liver but also in all the skeleton, especially in upper and lower limbs.

Fluorine-18-FDG PET/CT completes the whole-body assessment with an integrated multimodal approach with high spatial resolution that evaluates the metabolic activity and the standardized uptake value (SUV) in SCD patients [17-20].

Modern genetic diagnosis and gene treatment give promise for having fewer cases of SCD in the future.

Acknowledgement

We thank Gaetano Vito Difonzo and Giampaolo Sigrisi for

the technical support in Nuclear Medicine images acquisition.

Bibliography

1. De Franceschi L. Pathophysiology of sickle cell disease and new drugs for the treatment. *Medit J Hemat Infect Dis* 2009; 1(1):e2009024.
2. Modell B, Darlison M. Global epidemiology of haemoglobin disorders and derived service indicators. *Bull World Health Organ* 2008; 86(6):480-7.
3. Rees DC, Williams TN, Gladwin M. Sickle-cell disease. *Seminars* 2010; 376:2081-203.
4. Gardner CS, Boll DT, Bhosale P, Jaffe TA. CT abdominal imaging findings in patients with sickle cell disease: acute vaso-occlusive crisis, complications, and chronic sequelae. *Abdom Radiol (NY)* 2016; 41(12):2524-32.
5. Gardner K, Suddle A, Kane P et al. How we treat sickle hepatopathy and liver transplantation in adults. *Blood* 2014; 123:2302-7.
6. Buisson AM, Kawchak DA, Schall JI et al. Bone area and bone mineral content deficits in children with sickle cell disease. *Pediatrics* 2005; 116:943-9.
7. Karam LB, Disco D, Jackson SM et al. Liver biopsy results in patients with Sickle Cell Disease on Chronic transfusions: poor correlation with Ferritin Levels. *Pediatric Blood Cancer* 2008; 50(1):62-5.
8. Yang M, Roarke M. Diffuse pulmonary extramedullary hematopoiesis in myelofibrosis diagnosed with technetium-99m sulfur colloid bone marrow scintigraphy and single photon emission computerized tomography/CT. *Am J Hematol* 2017; 92:323-4.
9. Zhang HZ, Li Y, Liu X et al. Extramedullary hematopoiesis: A report of two cases. *Exp Ther Med* 2016; 12(6):3859-62.
10. Altini C, Niccoli Asabella A, Di Palo A et al. ¹⁸F-FDG PET/CT role in staging of gastric carcinomas: comparison with conventional contrast enhancement computed tomography. *Medicine (Baltimore)* 2015; 94(20):e864.
11. Van den Wyngaert T, Strobel K, Kampen WU et al. The EANM practice guidelines for bone scintigraphy. *Eur J Nucl Med Mol Imaging* 2016; 43(9):1723-38.
12. Niccoli-Asabella A, Cimmino A, Altini C et al. ¹⁸F-FDG positron emission tomography/computed tomography and ^{99m}Tc-MDP skeletal scintigraphy in a case of Erdheim-Chester disease. *Hell J Nucl Med* 2011; 14(3):311-2.
13. Caglar M, Kupik O, Karabulut E, Høiland-Carlson PF. Detection of bone metastases in breast cancer patients in the PET/CT era: Do we still need the bone scan? *Rev Esp Med Nucl Imagen Mol* 2016; 35:3-11.
14. Van der Bruggen W, Glaudemans AWJM, Vellenga E, Slart RHJA. PET in Benign Bone Marrow Disorders. *Semin Nucl Med* 2017; 47: 397-407.
15. Blebea JS, Houseni M, Torigan DA et al. Structural and functional imaging of normal bone marrow and evaluation of its age-related changes. *Semin Nucl Med* 2007; 37(3): 185-94.
16. Agool A, Glaudemans AW, Boersma HH et al. Radionuclide imaging of bone marrow disorders. *Eur J Nucl Med Mol Imaging* 2011; 38: 166-78.
17. Niccoli-Asabella A, Altini C, Notaristefano A et al. A retrospective study comparing contrast-enhanced computed tomography with ¹⁸F-FDG-PET/CT in the early follow-up of patients with retroperitoneal sarcomas. *Nucl Med Commun* 2013; 34(1): 32-9.
18. Cistaro A, Niccoli Asabella A, Coppolino P et al. Diagnostic and prognostic value of ¹⁸F-FDG PET/CT in comparison with morphological imaging in primary adrenal gland malignancies-a multicenter experience. *Hell J Nucl Med* 2015; 18(2):97-102.
19. Altini C, Niccoli Asabella A, Ferrari C et al. ¹⁸F-FDG PET/CT contribution to diagnosis and treatment response of rhino-orbital-cerebral mucormycosis. *Hell J Nucl Med* 2015; 18(1):68-70.
20. Niccoli Asabella A, Notaristefano A, Rubini D et al. ¹⁸F-FDG PET/CT in suspected recurrences of epithelial malignant pleural mesothelioma in asbestos-fibers-exposed patients (comparison to standard diagnostic follow-up). *Clin Imaging* 2013; 37(6):1098-103.