To the Editor:

We read with interest the editorial ‘Genetic testing for hemochromatosis: Diagnostic or confirmatory test for iron overload?’ in the January/February 2015 issue of the Journal. Coming from a radiology department in a tertiary referral institution for liver diseases, we would like to offer a perspective on the suitability of magnetic resonance imaging (MRI) for the investigation of iron overload.

MRI is a widely available, reliable and rapid noninvasive diagnostic test. Due to its paramagnetic properties, iron causes local magnetic field distortion on MRI, leading to shortening of longitudinal (T1) and transverse (T2) relaxation times, and especially the transverse relaxation time influenced by magnetic field inhomogeneity (T2*) (1). This results in signal loss on MRI in organs affected by iron overload, with the magnitude of signal loss proportional to the extent of iron deposition. By determining the pattern of organ involvement, MRI can differentiate primary hemochromatosis (which may involve the liver, pancreas, heart, pituitary and thyroid) from secondary hemosiderosis (which may involve the liver, spleen and bone marrow) (1). This distinction is important because prognosis, management and treatment strategies vary for these two categories. In primary hemochromatosis, MRI has an additional role in liver surveillance to assess for the development of complications such as cirrhosis and hepatocellular carcinoma.

Liver iron concentration (LIC) is an important estimate of total body iron stores. The current gold standard for determining LIC is a liver biopsy with spectrophotometry. A liver biopsy samples 1/50,000 of the liver and, as such, is limited by sampling variability, which is accentuated by conditions, such as cirrhosis, that involve the liver nonuniformly. Moreover, the procedure is invasive, uncomfortable and is associated with potential complications such as hemorrhage and death. Biopsy is also poorly suited for longitudinal patient monitoring. Serum tests, such as ferritin and transferrin saturation, are nonspecific and may be elevated in inflammation and malignancy, while liver iron overload may occur without hyperferritinemia – this limits the usefulness of these tests in evaluating iron overload (2,3).

Two principal MRI techniques have been developed for the noninvasive quantification of liver iron. These are the signal intensity ratio (SIR) method and relaxometry. The SIR method, popularized by Gandon et al (4) from the University of Rennes (France) uses the ratio of the signal intensity of the liver to the paraspinal muscle (which does not accumulate iron) to calculate LIC. The SIR method is widely used in clinical practice (including at our institution) given its simplicity and applicability at various magnet strengths (5-7). Using Gandon’s protocol, five gradient echo sequences are acquired of the liver using a TR of 120 ms, flip angle of 20 and 90°, and varying TE (4 ms to 30 ms) depending on the magnet strength (0.5 T, 1 T or 1.5 T). Regions of interest (ROIs) of at least 1 cm² are drawn on the same slice for all five sequences. Three ROIs are placed over the right lobe of the liver, and an ROI each over the right and left paraspinal muscles. Entering these data into a free online calculator designed by the University of Rennes (http://www.radio.univ-rennes1.fr/Sources/EN/HemoResult.html) generates an MRI-derived LIC, which is expressed in μmol Fe/g. In a study involving 174 patients, Gandon et al (4) found this protocol to be highly accurate over an LIC range of 3 μmol/g to 375 μmol/g, with the mean difference and CIs between biopsy-derived LICS and MRI derived LICS being 0.8 μmol/g (CI −6.3 to 7.9 μmol/g) for the study group (139 patients) and −2.1 μmol/g (CI −12.9 to 8.9 μmol/g) for the validation group (35 patients) (4). However, the protocol is limited in severe iron overload because the technique saturates above 375 μmol/g; therefore, such cases are classified as having an LIC > 375 μmol/g. A study involving 171 patients by Castiella et al (8) compared MRI-derived LICS (according to Gandon et al’s protocol) with biopsy derived LICs. For the detection of hemochromatosis, the study found that MRI values >170 μmol/g had a 100% positive predictive value while values <60 μmol/g had a 100% negative predictive value. The authors concluded that Gandon et al’s protocol was useful for ruling out or detecting high iron overload in 74.3% of patients but had a tendency to overestimate iron overload.

Relaxometry methods involve acquiring a series of MRI images at increasing echo times and fitting a decay model to the signal intensity time curve to measure specific relaxation parameters, either T2 or R2 (1/T2) on spin-echo sequences or T2* or R2* (1/T2*) on gradient-echo sequences. Iron shortens T2 and T2* relaxation times and increases R2 and R2* relaxation rates. For this reason, as the LIC increases, T2 and T2* signal decreases, and R2 and R2* signal increases. Reports have confirmed a strong correlation between T2/R2 and T2*/R2* values with biopsy derived LIC values (9,10). In addition to liver iron quantification, T2*/R2* methods may also be used to estimate myocardial iron concentration – this helps to identify individuals at risk for iron-induced cardiotoxicity and can inform patient management. T2*/R2* techniques are short breath-hold acquisitions (20 s) that offer whole liver coverage but are susceptible to confounding factors such as fat, noise and background field variations (11,12). T2/R2 techniques have relatively long acquisition times (15 min to 20 min), restricted anatomical coverage and are prone to motion artifacts (11,12). However, T2/R2 relaxometry methods (which use spin echo sequences) are more accurate than T2*/R2* and SIR methods (which use gradient echo sequences) for quantifying severe iron overload (5). Currently, relaxometry methods are not widely utilized because they require dedicated software and specialized expertise, and lack standardization (5). Offsite post-processing analysis of T2 relaxometry data is offered commercially by Resonance Health (www.ferriscan.com) – which has received regulatory approval by the United States Food and Drug Administration.

Taking into consideration all of the above, we believe that MRI is well suited as a modality for evaluating patients with suspected iron overload including a role as an alternative to biopsy for iron quantification.

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