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The utility of susceptibility-weighted imaging to evaluate the extent of iron accumulation in the choroid plexus of patients with β-thalassaemia major

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AIM: To assess iron accumulation in the choroid plexus of β-thalassaemia patients using fast spin echo (FSE) T2-weighted, gradient echo (GRE) T2*-weighted, susceptibility-weighted imaging (SWI) and compare the results.

MATERIALS AND METHODS: Eighteen patients with transfusion-dependent β-thalassaemia and the control group underwent magnetic resonance imaging (MRI) examinations. Signal intensities were separately evaluated using a "number of hypointensity in the choroid plexus" (NHICP) grading system on axial FSE T2-weighted, GRE T2*-weighted, and SWI images. The NHICP grading system scores were compared using the chi-squared test. Spearman's correlation analysis was used to explore relationships between the variables and NHICP grading system scores.

RESULTS: The sensitivity of each technique was calculated: FSE T2-weighted imaging=0.17, GRE T2*-weighted imaging=0.48, and SWI=0.81. Three-sample test for equality of proportions showed that chi-squared=74.85, df=2, $p<0.0001$. All of the FSE T2-weighted, GRE T2*-weighted, and SWI images differed significantly in terms of their capacity to reveal iron accumulation in the choroid plexus. Of the three methods, SWI was the most sensitive.

CONCLUSIONS: SWI is useful for revealing iron deposition in the brains of β-thalassaemia patients, especially those in the early stages of disease, and it can be used to predict disease prognosis. The present study contributes to an understanding of the important role played by the choroid plexus in brain iron metabolism.

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Introduction

B-thalassaemia major is a common genetic haemoglobinopathy characterised by defective production of the haemoglobin β-chain, resulting in ineffective erythropoiesis, haemolysis, and severe anaemia.[1,2] Conventional management involves regular blood transfusions, triggering iron overload.[1] During the natural course of the disorder, intestinal iron absorption increases, as does red blood cell haemolysis (caused by ineffective erythropoiesis). Iron accumulation (caused by peripheral haemolysis) is a major problem in patients dependent on lifelong blood transfusions, and is the major cause of morbidity and mortality in such patients.[1,3,4] Iron accumulates to excessive levels in different parts of the body, principally the reticuloendothelial system, liver, heart, pituitary gland, and pancreas.[5] As iron overload is cytotoxic, the organs in which iron accumulates may become dysfunctional, causing heart failure, liver siderosis, hypogonadotropic hypogonadism, and diabetes mellitus.[6,7] To minimise such complications, patients require treatment with iron-chelating agents.[6]

As the tissues in which iron accumulates may differ in terms of the rates of iron deposition and clearance, and also in their response to chelating agents, effective management requires painstaking monitoring of the extent of iron overload. Such data are used to choose optimal treatment regimens.[8,9] The liver iron concentration measured in biopsy material is the reference standard indicator of bodily iron load.[10] In routine practice, the serum ferritin level is the preferred marker of the total iron burden; such data can be obtained non-invasively; however, the serum ferritin level may not always be a reliable indicator of iron load; the level can be affected by inflammation and liver damage.[10] Moreover, iron overload may be organ or tissue specific. In other words, the serum ferritin level is not an adequate surrogate for evaluation of (for example) tissue siderosis; other non-invasive techniques to reliably evaluate such siderosis are required. Magnetic resonance imaging (MRI) can be used to non-invasively and repeatedly evaluate tissue-specific iron overload.[5,11–19]

In the present study, two hypotheses were tested: first, it was hypothesised that as serum ferritin *per se* does not directly cross the blood–brain barrier, the extent of cerebral iron overload in structures lacking a blood–brain barrier (for example, the choroid plexus) would correlate to a greater extent with the serum ferritin level (a marker of iron stores) than with the iron overload evident in other structures that do have a blood–brain barrier. Second, it was hypothesised that the use of SWI to evaluate the extent of cerebral iron overload in structures such as the choroid plexus would improve the accuracy of data obtained from patients with β-thalassaemia major, due to the sensitivity of the technique. These hypotheses were tested by assessing iron accumulation in the choroid plexus using fast spin-echo (FSE) T2-weighted, gradient echo (GRE) T2*-weighted, and susceptibility-weighted imaging (SWI) techniques, and the associations between the low signal intensities and the serum ferritin level (a marker of the iron burden) were determined in β-thalassaemia patients and controls.

Materials and methods

Patients

Eighteen patients (17 males and one female; aged 7–39 years; median age, 19 years) with transfusion-dependent β-thalassaemia (17 patients with β-thalassaemia major and one patient with β-thalassaemia intermedia) underwent MRI examinations. The age at diagnosis ranged from 1–6 years. The total duration of disease ranged from 7–39 years. All patients were on transfusion regimens that maintained the pre-transfusion haemoglobin level between 7.4 and 9.9 g/dl. Blood haemoglobin levels were measured 22 days before and 3 days after MRI examination. Each patient was transfused with 1–2 units of blood every 2–4 weeks. All were on iron-chelation therapy with deferasirox (Exjade; Novartis Pharmaceuticals, Basel, Switzerland). All patients exhibited increased serum ferritin levels (280–2,000 ng/ml; mean, 1,064.5 ng/ml; normal value, 30–300 ng/ml), reflecting the severity of iron overload. Serum ferritin levels were measured 1 month before and 1 month after MRI examination (thus, at 2 months apart on average). Eighteen healthy volunteers were also imaged (the control group). All data were acquired between February 2013 and June 2015. The study protocol was approved by the institutional review board and written informed consent was obtained from each participant. The principal demographic and clinical characteristics of the β-thalassaemia patients and controls are shown in Table 1.

Data acquisition

MRI images were acquired using a 1.5-T unit (Magnetom Avanto; Siemens, Erlangen, Germany) fitted with an eight-channel head coil. The MRI protocols included transverse T2 FSE imaging (3,830 ms repetition time [TR]/93 ms echo time [TE]; 5 mm section thickness, 150° flip angle, 218×320 acquisition matrix and 230 mm field of view [FOV]); transverse T1-weighted spin-echo (SE) imaging (580 ms TR/17 ms TE, 5 mm section thickness, 90° flip angle, 202×256 ms acquisition matrix, and 230 mm FOV); coronal T2 FSE imaging (4,180 ms TR/79 ms TE, 5 mm section thickness, 150° flip angle, 269×384 ms acquisition matrix,

Table 1
Patients characteristics.

Parameter	Value
Mean age ± SD, years (range)	19 ± 9.35 SD, (7–39)
Male : female	17:1
Mean duration of disease, years (range)	18.80 ± 9.84 SD, (7–39)
Spenectomy, *n* (%)	12 (67)
Mean Hb ± SD, g/dl (range)	8.73 ± 0.78 SD, (7.4–9.9)
Mean ferritin ± SD, ng/ml (range)	1064.5 ± 500.83 SD, (280–2000)

SD, standard deviation; Hb, haemoglobin.