Evaluation of iron accumulation in choroid plexus in patients with beta-thalassaemia major by using susceptibility weighted imaging (SWI)

Poster No.: C-2254
Congress: ECR 2016
Type: Scientific Exhibit
Authors: Z. Is#k Hasiloglu, M. A##k, E. Üre, F. Ertem, H. Apak, S. Albayram; Istanbul/TR
Keywords: Neuroradiology brain, Hematologic, MR, Imaging sequences, Hematologic diseases
DOI: 10.1594/ecr2016/C-2254

Any information contained in this pdf file is automatically generated from digital material submitted to EPOS by third parties in the form of scientific presentations. References to any names, marks, products, or services of third parties or hypertext links to third-party sites or information are provided solely as a convenience to you and do not in any way constitute or imply ECR's endorsement, sponsorship or recommendation of the third party, information, product or service. ECR is not responsible for the content of these pages and does not make any representations regarding the content or accuracy of material in this file.

As per copyright regulations, any unauthorised use of the material or parts thereof as well as commercial reproduction or multiple distribution by any traditional or electronically based reproduction/publication method is strictly prohibited.

You agree to defend, indemnify, and hold ECR harmless from and against any and all claims, damages, costs, and expenses, including attorneys' fees, arising from or related to your use of these pages.

Please note: Links to movies, ppt slideshows and any other multimedia files are not available in the pdf version of presentations.

www.myESR.org
### Aims and objectives

- Thalassemia major is a common genetic hemoglobinopathy characterized by defective production of -chains of hemoglobin, resulting in ineffective erythropoiesis, hemolysis, and severe anemia [1,2]. Conventional management of the patients with -Thalassemia major requires regular blood transfusions, causing iron overload [1]. However, apart from increased intestinal absorption of the iron and hemolysis of the red blood cells due to ineffective erythropoiesis during the natural course of the disorder, life-long blood transfusion dependency predominantly leads to excess iron accumulation owing to peripheral hemolysis, being the major cause of morbidity and mortality in these patients [1,3,4]. The excess iron accumulation occurs in different parts of the body mainly including reticuloendothelial system, liver, heart, pituitary gland, and pancreas [5]. On account of the fact that iron overload has a cytotoxic effect, it may cause dysfunction of the organs in which iron accumulates, e.g., heart failure, liver siderosis, hypogonadotropic hypogonadism, and diabetes mellitus [6,7]. To minimize these complications, treatment with iron chelating agents is necessary [6].

Given that the tissues in which iron accumulated may not have similar rates of iron deposition or clearance and might not have similar response to the chelating agents, the effective management of these individuals requires painstaking monitoring of the iron overload to decide the optimal treatment regime [8,9]. Despite the fact that liver iron concentration obtained with liver biopsy is the gold standard method for evaluation of body iron load [10], in routine practice, serum ferritin level has been preferred to be used as a marker of total iron burden with the advantage of being a non-invasive method. Serum ferritin level, however, is not always considered to be a reliable method owing to the fact that it can be altered due to inflammation and liver damage [10].

In this study, there were two hypotheses to be studied on. Considering that serum ferritin itself is not allowed to pass through the blood-brain barrier directly, we firstly hypothesized that the assessment of the cerebral iron overload in the particular structures lacking of blood-brain barrier like choroid plexus would be more correlated with the serum ferritin level as a marker of iron stores than in the other structures that have blood-brain barrier. Secondly, it was hypothesized that evaluation of the cerebral iron overload in above-mentioned structures like choroid plexus using a much more sensitive method such as Susceptibility Weighted Imaging (SWI) could improve the accuracy of the measurements in patients with excess iron overload like -Thalassemia major. To support our hypotheses, we assessed the iron content in choroid plexus using SWI, FSE T2-weighted and GRE T2*-weighted MR imaging techniques and evaluated the associations between the signal intensities that were measured and the serum ferritin level as a marker of the iron burden in -Thalassemia major patients and control group.
Methods and materials

Patients

Eighteen patients (17 males and 1 females; ages 7 to 39 years; median age, 19 years) with transfusion-dependent thalassemia patients (17 patients with #-Thalassemia Major and one patient with #-Thalassemia Intermedia) underwent MR examination. The diagnosis age ranged from year of birth to 6 years old. The total duration of disease ranged from 7 years to 39 years. All patients were being treated with a transfusion regimen that maintained the pretransfusion hemoglobin level between 7.4 and 9.9 g/dL. The blood hemoglobin levels of patients were measured 22 days before and 3 days after than MR examination. The transfusion frequency was 1-2 units every 2-4 weeks. They received iron chelation therapy with deferasirox (Exjade, Novartis Pharmaceuticals, UK). All patients had increased serum ferritin levels (between 280 and 2000; mean value, 1064.5 ng/mL, normal value of, 30-300 ng/mL), a parameter that reflects the severity of iron overload. Serum ferritin levels were measured one month before and one month after than MR examination (the average two months period in). Except for two patients with hypothyroidism, one patient with growth retardation and one patient with growth hormone deficiency, there were no signs of other organ hemosiderosis. Neurological examinations were normal in cases. Splenectomy had been performed on 12 patients. Eighteen healthy volunteers were imaged as a control group. The data from patients and control subjects were acquired between February 2013 and June 2015. The study protocol was approved by our institutional review board, and informed consent was obtained from each subject. The main demographic and clinical characteristics of the #-Thalassemia Major and control groups are shown in Table 1.

Table 1: Patients characteristics (References: Department of Radiology, Istanbul University Cerrahpasa Medical Faculty- Istanbul/TR)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age ± SD, years (range)</td>
<td>19 ± 9.35 SD, (7-39)</td>
</tr>
<tr>
<td>Male: Female</td>
<td>17:1</td>
</tr>
<tr>
<td>Mean duration of disease, years (range)</td>
<td>18.80 ± 9.84 SD, (7-39)</td>
</tr>
<tr>
<td>Splenectomy, n (%)</td>
<td>12 (67)</td>
</tr>
<tr>
<td>Mean Hb ± SD, g dL (range)</td>
<td>8.73 ± 0.78 SD, (7.4 - 9.9)</td>
</tr>
</tbody>
</table>
Data acquisition

MR images were acquired by using a 1.5T unit (Magnetom Avanto; Siemens, Erlangen, Germany) with an 8-channel head coil. The MR imaging protocols included transverse T2 FSE imaging (TR/TE, 3830/93 ms; section thickness, 5 mm; flip angle, 150°; acquisition matrix, 218x320 ms; and FOV, 230 mm); transverse T1-weighted SE imaging (TR/TE, 580/17 ms; section thickness, 5 mm; flip angle, 90°; acquisition matrix, 202x256 ms; and FOV, 230 mm); coronal T2 FSE imaging (TR/TE, 4180/79 ms; section thickness, 5 mm; flip angle, 150°; acquisition matrix, 269x384 ms; and FOV, 230 mm); sagittal T2-weighted FSE imaging (TR/TE, 3500/97 ms; section thickness, 5 mm; flip angle, 150°; acquisition matrix, 218x320 ms; and FOV, 230 mm); transverse T2*GRE imaging (TR/TE, 628/22 ms; section thickness, 5 mm; flip angle, 20°; acquisition matrix, 218x256 ms; and FOV, 230 mm); and a transverse SWI sequence (TR/TE, 49/40 ms; section thickness, 2 mm; flip angle, 15°; bandwidth, 80 Hz/pixel; acquisition matrix, 196x320 ms; and FOV, 230 mm).

Imaging analysis

Two neuroradiologists (M.A. and Z.I.H, with 10 and 15 years of experience, respectively) independently reviewed the MR images. We established a system to describe mineralization in the regions of the choroid plexus. Signal intensities of the choroid plexus was evaluated with the use of scale of hypointensity in the choroid plexus (SHICP) on FSE T2-weighted, GRE T2*-weighted, and SWI axial images. The construction of SHICP was shown in Table 2. SHICP was scored as Grade 0 (no signal loss), Grade 1 (signal loss on one location), Grade 2 (signal loss on two locations), Grade 3 (signal loss on three locations), Grade 4 (signal loss on four locations) and Grade 5 (signal loss on five locations). The locations were evaluated in the study included the corpus of the lateral ventricle, the temporal horns of the lateral ventricle and the fourth ventricle. Respectively, right and left corpus of the lateral ventricle, right and left temporal horns of the lateral ventricle and the fourth ventricle were named as number one, two, three, four and five location. Due to the more frequent occurrence of calcification in the occipital horn of lateral ventricle and the difficulties in assessment of the choroid plexus in the third ventricle, the signal loss of the choroid plexus in these locations were excluded during the scoring stage. Datas acquired from the control group were used as reference. Signal intensities of the choroid plexus on per methods are shown in Fig. 1, 2 and 3.

Table 2: Scale of hypointensity in the chorid plexus (SHICP) (References: Department of Radiology, Istanbul University Cerrahpasa Medical Faculty - Istanbul/TR)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
0: no signal loss
1: signal loss on one location
2: signal loss on two locations
3: signal loss on three locations
4: signal loss on four locations
5: signal loss on five locations

**Statistical analysis**

We compared the performance of the detection by using SHICP of iron accumulation in choroid plexus with FSE T2-weighted, GRE T2*-weighted and SWI images by using the chi-squared test. The iron accumulation in choroid plexus that we detected with the use of SHICP between patients and controls was evaluated using the chi-squared test. A p-value less than 0.05 was considered statistically significant.

**Images for this section:**
Fig. 1: Fig. 1: a) Axial FSE T2-weighted and b) Axial SWI sequence of the supratentorial space reveal no signal loss on the choroid plexus of the lateral ventricle. This sample was one of controls and it was scored as Grade 0 by using SHICP.

© Radiology, Istanbul University, Cerrahpasa Medical School - Istanbul/TR
Fig. 2: Fig. 2: a) Axial FSE T2-weighted, b) Axial T2*-GRE and c) Axial SWI for a patient with #-Thalassemia Major. Although, overloading of iron accumulation in the choroid plexus can be observed as low signal intensity on SWI sequence, no signal changes are observed on FSE T2-weighted and T2*-GRE sequence. Due to the detection of signal loss on two locations, this patient was scored as Grade 2 by using SHICP on SWI.

© Radiology, Istanbul University, Cerrahpasa Medical School - Istanbul/TR
Fig. 3: a) Axial FSE T2-weighted, b) Axial T2*-GRE and c) Axial SWI sequence reveal marked low signal intensity on the choroid plexus of the lateral ventricle. Due to the detection of signal loss on five locations, this patient was scored as Grade 5 by using SHICP on SWI. Here, we showed only two locations (choroid plexus of right and left corpus of the lateral ventricle), the others were not shown in this section.

© Radiology, Istanbul University, Cerrahpasa Medical School - Istanbul/TR
Results

There are 5 locations for each imaging method, and 18 patients in the thalassemia group. Hence in total there are 90 locations to check for iron accumulation. We test the proportions of the sequencing methods (i.e. location methods FSE T2-weighted=0.17, GRE T2*-weighted=0.48, SWI=0.81) with the 3-sample test for equality of proportions without continuity correction (Chi-squared = 74.8509, df = 2, p-value < .0001). Hence, the proportions are significantly different, i.e., at least two of proportions are significantly different from each other. To determine which pair(s) exhibit significant differences, we compare the proportions pairwise and obtain the p-values (adjusted by Holm’s correction method for multiple testing) as <.0001 for each of (FSE T2-weighted, GRE T2*-weighted), (FSE T2-weighted, SWI) and (GRE T2*-weighted, SWI) pairs, respectively. Therefore, proportions of locations for each pair are significantly different from each other.

We evaluated comparisons of the number of locations between #-Thalassemia patients and controls. Since the number of locations are zero (0) for all control subjects, this comparison boils down to comparing the number or proportion of locations for each method with 0. The total number of locations to be checked is 90 for each method, and in none of these locations iron is detected in controls. In particular, smaller proportions occur with FSE T2-weighted methods. And so we start testing the proportions of FSE T2-weighted method for patients (i.e., 15/90=.17) with controls (i.e., with proportion 0/90=0) with a 2-sample test for equality of proportions with continuity correction (Chi-squared = 14.2545, df = 1, p-value < .0001). Hence the proportion of locations with FSE T2-weighted method is significantly larger than those of the controls. This also generalizes to GRE T2*-weighted and SWI methods, as their proportions are even larger than the FSE T2-weighted method.

Conclusion

In terms of noninvasive method to assess iron accumulation in different organs, MR imaging has long been utilized. Iron is a paramagnetic substance which can shorten the T2 relaxation time measurements [11]. Many studies have shown that hepatic MR parameters including T2 relaxation time in MR images have significant correlation with liver iron concentration determined by biopsy [12]. Another common location for using MR to assess iron accumulation is pituitary and deposition of iron in the pituitary or hypothalamus may cause hypogonadotropic hypogonadism and growth hormone deficiency [13].
As an imaging finding on MR, the adenohypophysis of patients with iron overload shows low signal intensity [13]. In several studies it has been shown that there is significant correlation between pituitary signal intensity reduction on MR imaging and serum ferritin or clinical manifestation of hypogonadotropic hypogonadism [14]. Cardiac iron accumulation is also important complication of iron accumulation due to several blood transfusions. There has been also studies using MR imaging in heart to detect iron accumulation [5]. In lipid rich tissues like vertebral bone marrow and pancreas along with fat suppression technique in MR iron accumulation can be detected and followed as well [15].

There are various MR imaging methods to evaluate in vivo tissue iron, e.g., direct saturation imaging, relaxation time mapping, magnetic field correlation, and SWI in that SWI is a relatively new MR imaging sequence, utilizing susceptibility differences between adjacent structures to provide an innovative tissue contrast [11,16]. What distinguishes the SWI from the other methods is that it uses the phase information, which is ignored by the conventional techniques, in addition to the magnitude data, making it extremely sensitive to the magnetic susceptibility differences of diamagnetic and paramagnetic substances such as iron, calcium, deoxygenated-hemoglobin, etc [17,18]. It can, therefore, be proposed as a useful imaging method to reveal normal iron distribution in tissues or to identify iron accumulation as a marker of progression of the various diseases that are associated with iron overload [19]. Although normal distribution and quantification of the brain iron in SWI is not well-known yet, from practical point of view, it is obvious that the increased sensitivity of SWI for the susceptibility effect of iron enables the brain structures such as basal ganglia, pituitary gland, and choroid plexus much more conspicuous than other available techniques.

There are several studies that evaluating iron content in the brains of patients with \#-Thalassemia major and in most T2-weighted MR imaging modalities have been applied for assessment. In previous studies; pituitary gland, basal ganglia, cortex, caudat nucleus, red nucleus, substantia nigra and dentate nucleus were investigated for iron accumulation. Duprez et al. has reported involvement of the choroid plexus with iron deposition in a case of \#-Thalassemia major by using GRE T2*-weighted imaging [20]. Also, Qui et al. quantified iron overload in the brains, including the choroid plexus, of patients with \#-Thalassemia major by using MR quantitative susceptibility imaging [19]. But to our knowledge, isolated choroid plexus of \#-Thalassemia patients for iron loading has never been studied by using SWI sequence with the new grading system such as SHICP. Also, no study comparing the efficacy of FSE T2-weighted, GRE T2*-weighted and SWI in detection of iron overload has been reported in \#-Thalassemia major. In this study, we have established that the choroid plexus due to lacking of blood-brain barrier is more correlated with the serum ferritin level as a marker of iron overload in \#-Thalassemia patients. Also we have shown that SWI with the use of a SHICP is a useful noninvasive method for detecting iron loading in patients with \#-Thalassemia major.
There are some limitations in our study. First of all, number of patients in our study is small and to get better data and confirm our findings further research with larger number of the patients is required. The other limitation of current study is that we did not acquire neurocognitive assessments. However, we compared datas with serum ferritin levels and the other variables. Future controlled studies with a larger cohort including neurocognitive assessments are warranted.

In conclusion, serum ferritin level has been preferred to be used as a marker of total iron burden, but it may not be good indicators of brain iron deposition in patients with #-thalassemia major indeed. MR imaging represents a reliable, noninvasive method for assessing iron overload in various tissues. Therein, a special technique SWI is the most useful method to show iron deposition in the brain of #-Thalassemia patients, especially in the early stages of disease. So SWI can be used as a reliable and valuable modality to investigate iron overload in #-Thalassemia major and to establish the prognosis of disease. Additionally, our study contributed to understand how an important role of the choroid plexus in brain iron metabolism.

Personal information

References


