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T_2 relaxation rate of basal ganglia and cortex in patients with β-thalassaemia major

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Abstract. In thalassaemic patients, neurophysiological disturbances have been associated with high serum ferritin levels and desferrioxamine therapy. In the presence of a magnetic field, ferritin, the main iron storage protein, induces a preferential decrease of the T_2 relaxation time. The purpose of this study was to evaluate thalassaemic patients for brain iron deposition by assessing the T_2 relaxation rate ($1/T_2$) of the grey matter. 41 thalassaemic patients (age range 8.5–44 years, mean 24 years) and 58 age- and sex-matched controls were included in the study. Current serum ferritin levels were obtained. The $1/T_2$ values of the cortex (motor and temporal) (mean 0.0122 ms^{-1}, SD 0.0004), putamen (mean 0.0137 ms^{-1}, SD 0.0004) and caudate nucleus (mean 0.0132 ms^{-1}, SD 0.0003) were higher in patients compared with the controls (mean 0.0110 ms^{-1}, SD 0.0004; mean 0.0120 ms^{-1}, SD 0.0005; mean 0.0117 ms^{-1}, SD 0.0003, respectively) ($p<0.001$ for all parameters). No statistically significant differences were found in the globus pallidus. No correlation was found between $1/T_2$ and serum ferritin. The higher values of $1/T_2$ in the cortex, putamen and caudate nucleus of thalassaemic patients probably reflect a higher iron deposition. The lack of differences in $1/T_2$ of the globus pallidus might suggest that even in thalassaemic patients iron cannot exceed a saturation level.

β-thalassaemia major is an inherited, severe haemolytic anaemia with an inefficient erythropoiesis necessitating lifelong blood transfusions [1–3]. Frequent transfusions and desferrioxamine therapy have improved the long-term prognosis, but problems related to secondary haemochromatosis are still common [1, 4–6]. Although iron is essential in many metabolic processes, iron overload has a cytotoxic effect that leads to organ dysfunction. The most commonly affected organs are the liver, heart and endocrine glands [1, 7, 8]. Iron is stored within tissues in the form of ferritin [1, 9]. This protein is a superparamagnetic substance that, in the presence of a strong magnetic field, induces a decrease of the T_2 relaxation time [10, 11]. In previous studies of patients with β-thalassaemia major, a decrease of signal intensity within tissues has been attributed to a T_2 effect due to iron overload [6–8, 12]. Neurophysiological evaluation of thalassaemic patients has demonstrated subclinical involvement of neural pathways, attributed to desferrioxamine therapy and high serum ferritin levels [2, 3]. Iron enters the central nervous system (CNS) through a receptor-mediated process before being stored as ferritin [9, 10]. In normal subjects, age-related changes of the brain iron are well correlated with a decrease of the T_2 relaxation time in the cortex and the deep grey matter [10, 13–15]. To our knowledge, the brain of thalassaemic patients has never been studied by MRI for iron overload. The purpose of this study was to evaluate iron changes in patients with β-thalassaemia major by assessing the T_2 relaxation rate of the grey matter.

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Subjects and methods

41 patients (23 males, 18 females) with transfusion-dependent β-thalassaemia major, aged 8.5–44 years (mean 24 years), were included in this study. None of the included patients had any symptoms or history of neurological or mental disorder. Subcutaneous desferrioxamine (Ciba-Geigy, Basel, Switzerland) (50 mg kg^{-1} day^{-1}) was given for iron overload in all patients. Desferrioxamine was administered overnight, 5 nights per week.

MRI was performed on a 1.5 T unit (Philips Gyroscan ACS NT power track 1000; Philips Medical Systems, Best, The Netherlands) using a head coil and a 23 cm field of view. In all patients, as well as in 58 age- and sex-matched controls, the

T_2 relaxation rate of the cortical grey matter (motor and temporal cortex), the caudate nucleus, the putamen and the globus pallidus was evaluated using a coronal single slice spin echo (SE) sequence with TR 2000 ms, eight echos with TE 20, 40, 60, 80, 100, 120, 140 and 160 ms, slice thickness 4 mm and matrix 256×256. T_2 values were calculated by the MRI unit and displayed on the grey scale as an image. The T_2 relaxation rate was evaluated by one author (MIA) using the region of interest (ROI) function (Figure 1). Because a better definition of the anatomical structures studied was provided in the earliest echos (1st to 3rd), each ROI was initially positioned in one of these and was then copied to parametric images of T_2. The T_2 relaxation rate of the cortex was studied in areas known in the elderly to have the highest (motor cortex) and the lowest (temporal cortex) iron concentration [14]. All T_2 relaxation rate measurements were performed symmetrically in both hemispheres.

The medical records of the controls were reviewed to exclude any patient with systemic or CNS disorder. The entry criteria for healthy controls was a normal MR scan on all pulse sequences including post-contrast scans. The brain MR protocol was as follows: (a) sagittal SE T_1 weighted, 500/20 (repetition time/echo time), 6 mm thick sections with 0.6 intersection spacing; (b) axial turbo SE T_2 weighted, 3500/90, 6 mm thick sections with 0.6 intersection gap; and (c) sagittal, coronal and axial SE T_1 weighted post-contrast scans, if necessary.

Serum ferritin levels of all thalassaemic patients were measured on the day of the MRI study.

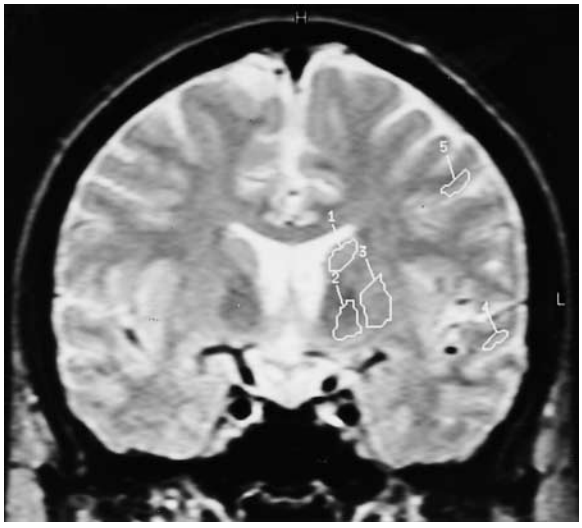

Figure 1. Coronal scan of the 4th echo (TR 80 ms) demonstrating the regions of interest (ROIs) adjusted to cover the entire area of the visualized caudate nucleus (1), globus pallidus (2) and putamen (3) of the left hemisphere. ROIs are also demonstrated in the temporal (4) and motor (5) cortex of the same hemisphere.

All adult subjects and the parents of children included in the study signed a written informed consent form allowing performance of the MRI examination. The study was performed with the approval of the Institutional Review Board.

Statistical analysis

Statistical analysis was performed with SPSS base 7.5 for windows. The normality of distribution of the parameters was assessed using the Kolmogorov–Smirnov test. The relationship between T_2 relaxation rate and serum ferritin was studied using the Pearson correlation coefficient. Differences in T_2 relaxation rate between patients and controls were evaluated using unpaired two-tailed Student's t-test. A p-value less than 0.05 was considered statistically significant.

Results

There was no significant variation in the measurements between the left and right hemispheres. Moreover, there were no statistically significant differences in T_2 relaxation rate values between the motor and temporal cortex in either patients or controls.

The T_2 relaxation rate of the putamen (mean 0.0137 ms^{-1}, SD 0.0004) and caudate nucleus (mean 0.0132 ms^{-1}, SD 0.0003) was higher in patients compared with the controls (mean 0.0120 ms^{-1}, SD 0.0005; mean 0.0117 ms^{-1}, SD 0.0003, respectively) ($p<0.001$ for all values). The T_2 relaxation rate of the motor cortex (mean 0.0122 ms^{-1}, SD 0.0004) and temporal cortex (mean 0.0122 ms^{-1}, SD 0.0004) was higher in patients compared with the controls (mean 0.011 ms^{-1}, SD 0.0004 for both cortexes) ($p<0.001$). No statistically significant differences were found in the globus pallidus, with a mean of 0.0141 ms^{-1} (SD 0.0008) and 0.0141 ms^{-1} (SD 0.0010) in patients and controls, respectively.

The serum ferritin ranged from 580–5066 ng ml^{-1} (mean 2358.2 ng ml^{-1}), with normal values less than 230 ng ml^{-1}. No correlation was found between T_2 relaxation rate of the studied brain structures and serum ferritin levels.

Discussion

β-thalassaemia major is a hereditary haemolytic anaemia treated with multiple blood transfusions. The main complication of this treatment is iron overload, which has been associated with cell death and organ dysfunction [1, 4–8]. Excess non-haem iron is stored in the form of ferritin. This protein contains iron in crystalloid form and, in the presence of a magnetic field, displays

superparamagnetic properties that are responsible for the preferential decrease of the T_2 relaxation time in tissues overloaded with iron [6–8, 10–12]. In β-thalassaemia major, the pituitary gland is the only intracranial structure that has been studied for iron overload by MRI [8, 12]. Although high serum ferritin levels and desferrioxamine therapy have been implicated in the development of neurophysiological disturbances, to our knowledge the brain of thalassaemic patients has never been studied by MRI for iron overload [2, 3]. Although ferritin does not cross the blood–brain barrier, it can be synthesized in CNS cells, because iron bound to transferrin gains access to neurons through a receptor-mediated process [9, 10, 16]. The highest concentration of transferrin receptors is found in the grey matter [9].

A decrease of basal ganglia signal on T_2 weighted images has been previously reported in patients with hereditary haemochromatosis [17, 18]. In the present study, the T_2 relaxation rate of the putamen, caudate nucleus, and motor and temporal cortex of thalassaemic patients was significantly higher compared with the controls. Previous studies in normal subjects have demonstrated an exponential decrease of the T_2 relaxation time of the basal ganglia with age [10, 15]. The plotted curves of T_2 relaxation time were congruent with curves of iron concentration found in autopsy studies. The age-related T_2 relaxation time changes have therefore been attributed to increased iron deposition in the basal ganglia [10]. Moreover, in subjects over 60 years of age a decrease of the T_2 relaxation time of the cortex has also been demonstrated by MRI [13, 14]. This was considered secondary to increased iron deposition found histologically in the cortex of elderly subjects [14]. Iron overload might also be responsible for the increased T_2 relaxation rate in the periphery as well as in certain areas of the deep grey matter within thalassaemic patients observed in the present study. A previous study has demonstrated that elevated serum iron levels induce ferritin synthesis in the CNS, with a consequential decrease of transferrin receptors [9]. Such mechanisms might protect the brain from iron deposition exceeding a certain saturation level, which for both putamen and caudate nucleus is normally reached at the age of 50–60 years [10]. However, this saturation level was apparently reached at a much younger age in the group of thalassaemic patients in this study.

No statistically significant difference in the T_2 relaxation rate of the globus pallidus was found between thalassaemic patients and controls. This is probably because the T_2 relaxation rate of the globus pallidus in normal subjects is reduced by 90% at the age of 20 years [10]. The mean age of the study population was 24 years. The lack of difference may possibly be because even in thalassaemic patients iron deposition in the globus pallidus cannot exceed a saturation level for iron overload, which would have caused a significant change in T_2 relaxation rate.

Serum ferritin levels in the thalassaemic patients showed no correlation with the T_2 relaxation rate of the studied brain structures. This is probably because ferritin does not cross the blood–brain barrier and its serum levels are therefore not a good index of brain iron burden.

Several studies have demonstrated increased iron deposition in the basal ganglia of patients with mainly basal ganglia disorders, such as Parkinson's disease, and also in the cortex of patients with degenerative disorders such as Alzheimer's disease and amyotrophic lateral sclerosis [9, 19, 20]. Although all patients included in this study had no symptoms or history of neurological disorders, the clinical implications of brain iron overload remain speculative, especially since treatment with multiple blood transfusions and therapy with chelating agents have increased the life expectancy of thalassaemic patients [1, 2].

In conclusion, the T_2 relaxation rate of the putamen, caudate nucleus, and motor and temporal cortex were higher in thalassaemic patients compared with controls. This suggests a higher iron deposition in these areas of brain. The lack of differences between patients and controls in T_2 relaxation rate of the globus pallidus indicates that even in iron overload states, iron cannot exceed a saturation level in certain CNS areas.

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