Two Iron Forms in the Globus Pallidus in PKAN Patients

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Introduction

Non-haemic iron begins to deposit in the human brain, especially in the globus pallidus, shortly after birth and its concentration increases with age [1]. It is generally accepted that iron is deposited especially in a form of a water soluble intracellular protein ferritin. High concentrations of iron deposits are visible on MR images and are a sign of several diseases. Among others the Panthotenate-Kinase Associated Neurodegeneration (PKAN) disease is characterized by genetically contingent irreversible accumulation of iron in the brain.
In this study, based on data published previously [2], we estimated iron concentration in the brain of PKAN patients in the form of ferritin and superparamagnetic iron nanoparticles using quantitative T2 relaxometry at different field strengths and comparison with iron containing phantoms.

Subjects and Methods

Three patients (18, 30, and 32 y/o) from different families with genetically proved PKAN and five healthy controls (23, 39, 41, 43, and 62 y/o) were studied using T2 MR relaxometry (CPMG sequence, 32 echoes, echo-spacing TE=6.9 ms, TR≥3000 ms, slice thickness 5 mm through the basal ganglia) on 1.5T, 3T and 7T Siemens whole-body systems. All controls and PKAN patients were informed about the examination protocol and their written consent was obtained according to the local Ethical Committee rules.
Phantoms containing different concentrations of antiferromagnetic iron (ferritin with loading factor 1062), and superparamagnetic iron oxide (SPIO) nanoparticles (Endorem®) were prepared and measured at five different magnetic fields. Measurements at 1.5T, 3T and 7T were supplemented by measurements at 0.5T (Bruker Minispec 20 relaxometer, CPMG sequence, TR/TE=5000/2 ms, 500 echoes), and at 4.7T (Bruker Biospec 4.7/20, CPMG sequence, TR/TE=5000/7.2 ms, 256 echoes).
T2 maps were calculated by a home-made software described in [3] using a three-parameter fit. T2 values in subjects were then obtained from the hypointense regions in the globus pallidus (GP) in both hemispheres and their mean values were used. Concentration of iron in samples was checked by atomic emission spectrometry and was used for the relaxivities calculation.

Results/Discussion

Significantly higher relaxation rates 1/T2 were found in the GP in all PKAN patients compared to controls independently on magnetic field used showing non-linear increase with the field (see Figure). We obtained field dependences of relaxation rates for ferritin and SPIO phantoms and we compared these dependences with in vivo results obtained in healthy and PKAN brain. Relaxation rates of ferritin solutions almost linearly increased with static magnetic field B_0 contrary to SPIO nanoparticles whose relaxivity is almost field independent.
We calculated the iron concentration in the normal GP to be 178 μg/ml based on 1.5T data of controls and method described in [4] provided that all iron is in the form of ferritin. Estimation of iron in the brain of the patients is complicated by the fact, that both antiferromagnetic and superparamagnetic iron might be present. Assuming that the contribution of additional iron to the relaxation rate can be described as a difference of relaxation rates of PKAN patients and healthy controls, we estimated the proportional content of both iron components (antiferromagnetic and superparamagnetic iron) as their linear combination using a least-squares analysis. The best approximation to patient surplus iron content was 213 μg/ml of iron in an antiferromagnetic form and 1.1 μg/ml of iron in a superparamagnetic form. Thus, the total iron amount in GP in our PKAN patients is around 391 μg/ml of iron in the form of ferritin and 1.1 μg/ml superparamagnetic iron form.
The field dependence of observed relaxation rates supports the hypothesis that at least two different forms of iron are present in the GP in PKAN patients. The hypothesis is also supported by post-mortem Prussian blue staining [5].
Our results indicate that significant changes on MR images may not be caused by substantial increase of the total iron amount only, but the form of iron deposits may be crucial.
The calculation of iron content strongly depends on loading factor (LF) of the ferritin. As LF of ferritin in the brain in vivo remains unknown, our calculation should be considered as estimation only.

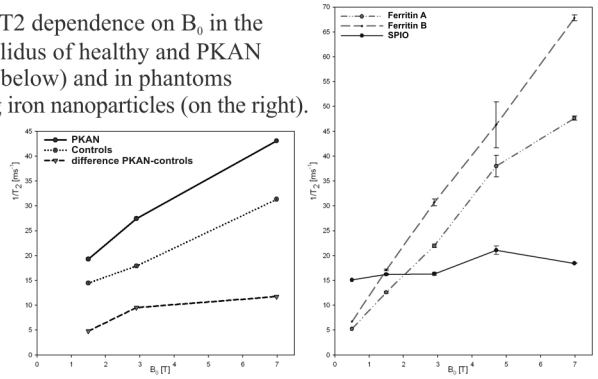

Figure. 1/T2 dependence on B_0 in the globus pallidus of healthy and PKAN brain (see below) and in phantoms containing iron nanoparticles (on the right).

Conclusion

Our data suggest that the MRI hypointensive lesions observable in the brain of PKAN patients are not simply proportional to increasing iron concentration but can be explained by rather small amount of iron (e.g. about 2 orders lower than in ferritin) in other superparamagnetic forms of deposits.

References

1. Hallgren B, Sourander P (1958) J Neurochem 3:41-51
2. Dezortova M, et al. (2011) ISMRM Proceedings, No. 608
3. Herynek V, et al. (2001) Magn Reson Mater Phy 12(1):10-15
4. Hajek M, et al (2005) Eur Radiol 15(5):1060-1068
5. Hallervorden J, Spatz H (1922) Zeitschrift fur die gesamte Neurologie und Psychiatrie 79:254-302

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