High Field MRI Demonstrates Global Brain Iron Overload in Aceruloplasminemia

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Introduction. There are increasing reports suggesting that disorders of iron metabolism may be involved in the pathogenesis of several important neurodegenerative diseases.[1] Shortened T2 relaxation times caused by increases in regional of brain iron concentration are well recognized as potentially clinically useful markers of disease.[2,3] However issues, such as the specificity of iron concentration as a cause of T2 reduction, continue to limit this application of MRI. Here we present extensive MR imaging and clinical evaluations of a 56 year-old subject with long-standing diabetes and a six-year history of progressive mental decline who was referred as a research volunteer to an IRB-approved project for neuroimaging of dementia. 3T brain MRI disclosed remarkable T2 shortening as did 1.5 T liver imaging. Blood studies showed markedly elevated serum ferritin, reduced transferrin saturation and serum ceruloplasmin was below the limits of detection. These findings are diagnostic of the rare, recessive genetic disorder aceruloplasminemia (aCp). Such patients accumulate dramatic levels of iron in the brain and systemic organs.[4,5]

MR Imaging. Whole brain dual spin echo (SE) and gradient echo (GRE) MRI was performed at 0.5, 1.5 and 3.0 tesla. T2 and T2* values were calculated from these image sets. It is believed that this is the first case of aCp to be studied at 3T and also the first in which T2 values have been established at any field strength. The MR findings are striking in several ways: (i) although iron-dependent contrast is usually weak or absent at 0.5 T, it is prominent in this subject at that field strength (Fig. 1a); (ii) because of the very short T2 values in the basal ganglia and other regions, iron-dependent contrast is prominent on T1-weighted as well as on T2-weighted sequences (not shown); (iii) on gradient echo images at 1.5 and 3 T (Fig 1b, 1c), there is a nearly continuous dark line along the boundary between the cortex and the subjacent white matter[6] and (iv) iron-dependent contrast is prominent in many brain regions (e.g., in thalamic nuclei) in which it is normally absent (Fig. 1c). The T2 values in the aCp subject are markedly short when compared to normal values in all brain regions, including white matter. (Table 1). In addition, the mean T2 values in the caudate, putamen and hippocampus are more than three standard deviations below those of group of age-matched controls ($p<0.0001$).

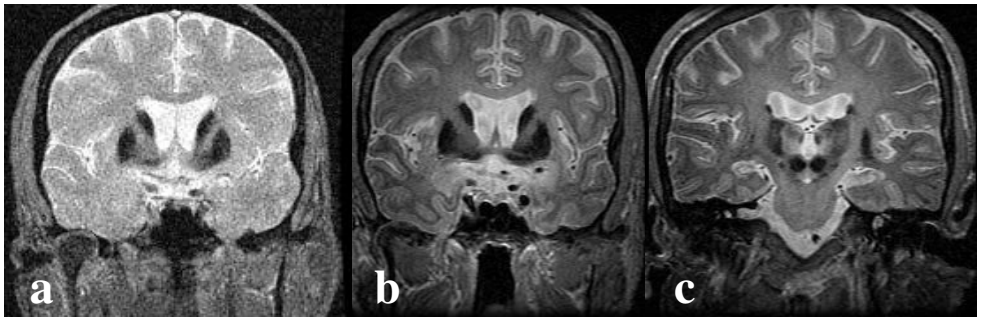

Figure 1. a) 0.5 T, GR, FOV 22 cm, slice thickness (ST) 5 mm, TR 667 ms, TE 25 ms. b) 3T, GRE, FOV 22 cm, ST 2 mm, TR 5000 ms, TE 30 ms. c) 3T, GRE, FOV 16 cm; ST 2 mm, TR 5000 ms, TE 30 ms.

Discussion. Ceruloplasmin is a ferroxidase, converting Fe^{++} to Fe^{+++}. The absence of ceruloplasmin is associated with impaired cellular iron efflux and intracellular iron accumulation. We suggest that the familiar pattern of regional brain iron deposition is approximately maintained in aCp but its magnitude is greatly increased throughout the brain. The finding of a global reduction of brain T2 in aCp implies that brain iron plays some role in T2 relaxation more or less throughout the brain, not just in the basal ganglia and related nuclei where it is normally studied. This suggests that it may be worthwhile to investigate in other diseases the possibility of iron-dependent T2 shortening in brain regions such as the hippocampus, thalamus and white matter that are not normally considered as containing sufficient iron to have a significant effect on T2 relaxation.

Table 1. Spin-echo T2 (in ms) at 3T

Region	aCp T2	Control T2
GCC[1]	28.6	48.7
FWM[2]	27.6	49.4
Caudate	15.8	44.6
Putamen	16.2	42.8

[1]GCC-Genu of Corpus Callosum

[2] FWM- Frontal White Matter

1. Zecca L, et al. Iron, brain ageing and neurodegenerative disorders. Nat Rev Neurosci 2004; 5:863-873
2. Schenck JF, Zimmerman EA. High-field magnetic resonance imaging of brain iron: birth of a biomarker? NMR Biomed 2004; 17:433-445
3. Haacke EM, et al. Imaging iron stores in the brain using magnetic resonance imaging. Magn Reson Imaging. 2005;23:1-25
4. Miyajima H, et al. Aceruloplasminemia, an inherited disorder of iron metabolism. Biometals. 2003;16:205-213
5. Harris ZL, et al.. Targeted gene disruption reveals an essential role for ceruloplasmin in cellular iron efflux. Proc Natl Acad Sci USA. 1999;96:10812-1081
6. Grisoli M, et al. MR Imaging of cerebral cortical involvement in aceruloplasminemia. AJNR 2005;26:657-661