Extremely High Resolution, High Field Imaging of Brain Iron in an Iron-Storage Disease

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Introduction

The iron-dependent contrast first noted at 1.5 tesla[1] has become of great interest with the widespread availability of 3T and 7T MRI and the suspected relevance of iron deposition to neurodegenerative diseases.[2-4] Aceruloplasminemia (aCp) is a very rare, autosomal recessive disorder characterized by massive iron accumulation in brain, liver and other organs; and by early onset of diabetes, retinal changes and brain dysfunction. Mutations leading to aCp have been reported worldwide but most cases come from Japan where the incidence is estimated at one in two million.[5] We have followed for several years a case of aCp using 3T MRI along with periodic neurological and psychometric evaluations. Following the unfortunate death of this patient due to diabetic complications of the disorder we have conducted very high resolution MRI at 3T and 7T on the postmortem brain specimen. To our knowledge this is the first high resolution, high field postmortem brain imaging in this remarkable disease. This has shown striking details of brain iron deposition in the cerebral cortex, white matter tracts, and other regions where MRI evidence for iron deposition has been lacking or equivocal.

Methods

At autopsy the brain was divided in the midline, one hemisphere was frozen and the other hemisphere was formalin-fixed for 15 days. The fixed hemisphere was cut into coronal slices approximately one cm thick except for a coronal central section approximately 5.6 cm thick which extended from the anterior commissure to the mammillary bodies. Gradient echo, spin echo and phase contrast imaging of the postmortem brain was conducted at both 3T and 7T. Special coils were constructed for the 7T imaging. The gradient echo 7T imaging used isotropic voxels ranging from 202 to 312 μ on a side.

Results and Discussion

Our working hypothesis has been that the pattern of deposition in aCp is closely similar to that in normal human brain but of a much higher magnitude. Furthermore, because of the nature of aCp we regard the presence of regions of abnormal MRI hypointensity on T2-weighted images or enhanced transverse relaxation in this brain as prima facie evidence for iron deposition. Of course, only future investigations can conclusively validate these assumptions. High resolution MRI of the aCp brain reveals patterns of iron deposition that are likely to be present in normal brains but that are difficult to image in the normal cases because of the lower concentration. It is hoped that with the knowledge the location of these additional regions of iron deposition that they can now be demonstrated in normal or pathological brain MRI by “knowing where to look.” Striking and previously unrecognized iron deposition has now been seen in the aCp case in the thalamus, various white matter tracts, the hippocampus and other regions of this brain. Particularly striking has been the identification of iron-related contrast extending through a large section of the limbic system from the hippocampus, through the complete length of the fornix to the mammillary bodies and from there through the mammillothalamic tract to the anterior nuclei of the thalamus. This suggests a previously unrecognized role for iron in the functioning of the extremely important limbic system. Some of this pathway is indicated in Figure 1. Figures 2 and 3 show aspects of the 7-tesla results. Previous studies of brain iron deposition have emphasized the high concentrations of iron in the nuclei of the extrapyramidal motor system such as the putamen, globus pallidus, etc. These regions are extremely high in iron in this patient as well. However, the detailed fine structure of the hypointense regions in the cortex and in the white matter are the most striking aspect of the iron deposition in this patient. It may be that further study of the white matter iron deposits will shed light on the hypothesized axonal transport of iron[6] and iron deposits in white matter and cortex as well as in deep brain nuclei may prove useful in the MRI characterization of neurodegenerative diseases.

References

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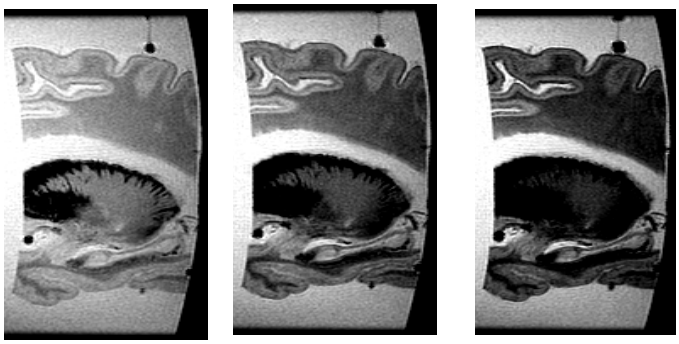

Figure 1. Multiple gradient echo sequence at 3-tesla. Note the structure within the hippocampus and the rapid loss of signal in the parahippocampal gyrus and in white matter structures generally. Slice thickness is 1 mm; TR 1000 ms; TE 4 ms.

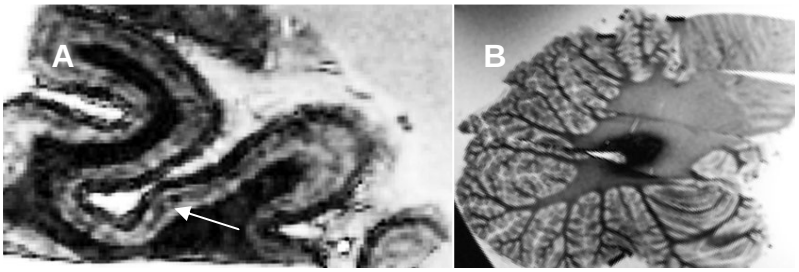

Figure 2. Seven-tesla imaging. A. Note the loss of signal, presumed secondary to iron accumulation in the outer molecular layer of the cortex and in the white matter beneath the cortex. The arrow demonstrates a faint layer of presumed iron deposition in the vicinity of cortical layer 3. This line is present in only limited regions of the cortex. B. Images of the cerebellum show evidence for iron deposition in the dentate nucleus and the white matter of the cerebellar folia.

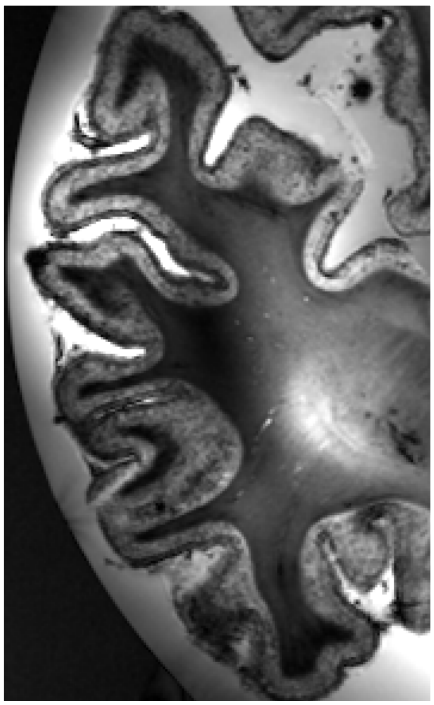

Figure 3. Seven-tesla gradient echo image of a coronal slice with evidence of iron deposition in the superficial cortical layer and in the subcortical white matter (U-fibers). At 7T the estimated T2* of iron-rich nuclei (e.g., putamen) is 1-2 ms; in the subcortical white matter it is about 3ms and about 6ms in deeper white matter.