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Proton MR Spectroscopic Imaging in NF-1

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14. ABSTRACT
Neurofibromatosis Type 1 (NF-1) is the most common autosomal dominant genetic disorder, affecting the skin, central (CNS) and peripheral nervous systems. Children with NF-1 have an increased risk of developing significant learning disability (LD), cognitive impairment, and optic or brain stem gliomas. Cerebral magnetic resonance imaging (MRI) in NF-1 reveals regions of high signal intensity (often called "unidentified bright objects", or UBOs). The pathophysiology of UBOs is poorly understood, and it is controversial to what extent they are involved in cognitive impairment. The aims of this proposal are to characterize the underlying metabolic abnormalities in NF-1 with proton MR spectroscopic imaging (MRSI). We have developed a rapid, quantitative MR spectroscopic imaging (MRSI) protocol for the evaluation of cerebral metabolite levels in NF-1. Metabolite levels will be determined both in UBOs and other brain regions, both in order to improve understanding of the etiology of UBOs, and to understand the relationship between regional brain metabolism and LD. 60 subjects with NF1 and 60 control subjects will be evaluated with proton MRSI and detailed neuropsychological testing. Ultimately, proton MRSI may be a useful test for identifying children with NF-1 at risk of developing LD, and also help in distinguishing UBOs from other, malignant lesions which require therapeutic intervention.

15. SUBJECT TERMS
Neurofibromatosis Type 1, Magnetic Resonance Spectroscopy, Magnetic Resonance Imaging, Diagnosis

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Introduction

Neurofibromatosis Type 1 (NF-1) is the most common autosomal dominant genetic disorder, affecting the skin, central (CNS) and peripheral nervous systems. Children with NF-1 have an increased risk of developing significant learning disability (LD), cognitive impairment, and optic or brain stem gliomas. Cerebral T2-weighted magnetic resonance imaging (MRI) in NF-1 reveals regions of high signal intensity (often called “unidentified bright objects”, or UBOs) in the basal ganglia, brain stem and cerebellum. The pathophysiology of UBOs is poorly understood, and it is controversial to what extent they are involved in cognitive impairment. Proton magnetic resonance spectroscopic imaging (MRSI) is a relatively new non-invasive metabolic imaging technique that can provide information about the cellular composition and metabolism of brain tissue. Our pilot data of proton MRSI in NF-1 indicate highly significant perturbations in thalamic metabolism in NF-1, regardless of presence or absence of UBOs (Wang et al, 2000). UBOs themselves were metabolically more similar to normal brain tissue. These data indicate dissociation between imaging and metabolic findings, and may indicate more widespread cerebral involvement in NF-1 than that indicated by MRI.

In this proposal, we are extending these preliminary findings to investigate the hypotheses that: (1) thalamic metabolism is abnormal in NF-1 and evolves with age, (2) proton MRSI measures of thalamic metabolism will correlate with neuropsychological performance, and (3) metabolic abnormalities in NF-1 are more diffuse and widespread than abnormalities visualized by MRI. The study design to test these hypotheses involves the performance of proton MRSI, MRI and neuropsychological testing in 60 subjects with NF-1 and 60 age-matched control subjects. To test hypothesis (1), thalamic metabolite levels will be compared between NF-1 subjects and controls in 3 different age ranges, and regression analysis performed with respect to age. To test hypothesis (2) thalamic metabolite levels in NF-1 patients will be correlated with results of a battery of neuropsychological tests. To test hypothesis (3), multiple regions of interest in the basal ganglia and cerebellum will be evaluated both by MRI and MRSI, and compared between NF-1 and control subjects.

In addition to improving the understanding of the pathophysiology of NF-1 brain lesions, this proposal will establish the relationship between regional cerebral metabolism and cognitive impairment in NF-1. If successful, MRSI may serve as a screening tool for young children with NF-1; the observation of normal MRSI may be reassuring prognostic information for normal subsequent development, while children with abnormal MRSI may be identified for early intervention for possible learning or developmental problems.
Body

Data collection has continued over the last year according to the protocol described in the original proposal. As previously noted, progress on this project was considerably delayed in the first 2 years because of IRB and HIPAA issues, however these problems were overcome and subject recruitment has proceeded steadily since then. Because of the delay in data collection, last year we requested (and received) a one-year no cost extension, in order to fully perform the study as described in the statement of work contained in the original proposal. Subject recruitment and data analysis have been performed steadily over the last year, and we have made good progress in this area. However, additional subjects are still required to finish the study, so we have requested an additional one year no cost extension to both complete data collection, and also perform final statistical analysis and publication of results. Interim analyses (see below) are encouraging, showing differences in thalamic metabolism and Boston naming tests between NF1 patients and controls, and some trends for correlations between imaging and neuropsychological test scores.

Typical MRI and MRSI of a 9 year old female with NF1 are shown in the figure on the right using the pulse sequence we developed (Golay et al 2002).

Metabolite ratios, for left and right thalamus, Boston naming test (BNT) and judgment of line orientation (JLO) scores for NF1 and controls to date are indicated in the graphs below.

NF1 subjects and controls were age-matched (NF1 10.5 ± 2.2 years, controls 10.2 ± 1.6 years, p = 0.97). NF1 subjects scored lower on both BNT and JLO than controls subjects.
Thalamic NAA/Cho ratios were lower in patients with NF1 than controls (consistent with our prior preliminary data) while ratios of NAA/Cr and Cho/Cr were not significantly different between groups. NAA/Cho: NF1 1.39±0.23, Control 1.74±0.59, p < 0.029, NAA/Cr: NF1 2.06±0.45, Control 2.21±0.64, p = 0.48, Cho/Cr: NF1 1.57±0.52, Control 1.39±0.50, p = 0.28. Larger changes in the NAA/Cho ratio were seen in the right thalamus than in the left. Regression analysis in patients between thalamic NAA/Cho and BNT and JLO did not exhibit any significant correlations with the current sample size and age range.

The plans for the last (upcoming) year of funding are therefore:

1. To complete data collection of NF1 subjects and controls as indicated in statement of work.
2. To add the WISC test scores to the analysis (currently interim post-hoc analysis has only looked at BNT and JLO, although WISC scores are available for all cases evaluated so far),
3. To analyze metabolite ratios and concentrations in multiple brain regions, including other structures in the basal ganglia, mid-brain, brain stem and cerebellum, and to evaluate sub-thalamic regions in more detail,
4. To analyze metabolite ratios in UBOs, and compare to metabolite ratios in normal MRI appearing brain regions,
5. To evaluate UBOs on MRI in terms of number, volume and location, and investigate the relationship to BNT, JLO and WISC-3 scores,
6. To perform all post-hoc statistical analyses as described in the original proposal, including stratification into different age ranges,
7. Manuscript preparation, presentation of results, and publication.
Key Research Accomplishments

- Established MRSI and neuropsychological test methodology and collected data in NF1 and control subjects in the 6 to 16 year old age range
- Interim statistical analysis shows significant differences between groups, and trends for correlation.
Reportable Outcomes

Since we are still in the data collection phase of the project, there have been no publications this year regarding results in NF1.
Conclusions

The collection of data for the evaluation of the relationship between neurometabolism, in particular thalamic NAA and choline levels (and the ratio of NAA/Cho), and LD in NF-1 as described in the proposal is continuing. This work is important for the clinical evaluation of patients with NF-1 in two respects. Firstly, proton MRSI may allow for a quantitative biochemical determination of the degree of brain involvement in children with NF-1, the observation of normal MRSI may be reassuring prognostic information for normal subsequent development, while children with abnormal MRSI may be identified for early intervention for possible learning or developmental problems. Secondly, the characterization of UBO metabolism is important for the diagnostic reasons; since patients with NF-1 are at increased risk for development of brain and optic gliomas, it can sometimes be difficult to distinguish these very different pathologies using conventional magnetic resonance imaging. Early, non-invasive diagnosis of a malignant glioma (and distinguishing it from a benign UBO) is extremely important in improving therapeutic outcome in these patients.
References
Appendices
None