[1]H Magnetic Resonance Spectroscopy Detection of Chromosomal Defects in Alzheimer's Dieases and Down Syndrome

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Synopsis: Down syndrome and Alzheimer's disease (AD) are thought to result from genetic defects that affect the formation of amyloid precursor protein (APP). In vivo short-echo single voxel 1H MRS was acquired in a population of patients with: genetically confirmed AD, post-mortem confirmed AD, genetically confirmed Downs with and without dementia, and age-matched controls. Results indicate that 1H MRS measurements of increased mI are identified in all patient groups that exhibit genetic defects in the APP pathway. This study also confirms the diagnosis of AD with MRS with genetic, histopathological, and neuropsychological confirmation.

Introduction: Genetic defects of the expression of chromosome 21 result in neurological disorders such as Down syndrome (DS) and has been linked to early onset of Alzheimer's disease (AD). DS is caused by trisomy of chromosome 21 [1]. Familial AD has been described as an autosomal dominant gene defect localized to chromosomes 14 [2] and 21 [3]. Adult DS patients exhibit the same dementia as that observed in AD patients. Post mortem results also demonstrate similar findings of increased beta-amyloid accumulation and neurofibrillary tangles in both diseases [4]. Although the origin of the two diseases share a similar genetic pathway, genetic testing has been proven to be effective only in diagnosing DS and not AD [5]. Current tests for AD rely only on neuropsychological evaluations based on DSM-IV criteria. Proton MR spectroscopy (MRS) however can quantitatively assess genetic disease by measuring the products of gene expression: neuronal metabolites. Several studies [6-8] have demonstrated that MRS can accurately distinguish between AD and non-AD by measuring the metabolic concentrations of N-acetyl aspartate (NAA), a putative neuronal marker, and myo-inositol (mI), a marker of gliosis or possibly of amyloid plaques [9]. These studies were conducted with neuropsychological evaluation as the gold standard for diagnosis of AD. No MRS studies have examined confirmed genetic defects in familial AD.

Methods: Image-guided proton MRS was performed in population of 12 elderly adults exhibiting symptoms of dementia and ten adults with chromosomally confirmed Down syndrome without evidence of dementia. Neurologically normal elderly (n=12) and middle-aged adults (n=10) were also examined as controls. MRS was acquired using stimulated echo acquisition mode (STEAM) using short echo (TE=30ms, TR=1500ms, TM=13.7ms) parameters using a voxel in the posterior cingulated gyrus (PCG). Metabolite concentrations of NAA, mI, choline (Cho), and creatine (Cr) were measured in all 34 subjects. Within the elderly patient cohort, one patient (age=61) was genetically confirmed to have Down's syndrome with dementia. Another patient (age=54) was directly descended from a family with fully penetrant AD due to a mutation in the presenilin-1 (PS-1) gene on chromosome 14. The additional ten patients in that cohort were confirmed to be AD based on post-mortem histopathology. Student t-tests were used for statistical analysis.

Results: MRS results are detailed in Table 1. Patients with both genetically and histopathologically confirmed Alzheimer's disease demonstrated significant ($p<0.05$-0.001) reductions of NAA/Cr and increases in mI/Cr when compared with elderly controls . Figure 1 demonstrates results of the MRS from the PCG in the patient with genetic defect in the PS-1 gene. Genetically confirmed Down syndrome with dementia also showed a similar metabolic pattern. Adults with Down syndrome but without signs of dementia show a significant ($p<0.01$) increase in mI only when compared to middle-aged controls, NAA/Cr is normal as indicated in Figure 2.

Conclusions: This study demonstrates for the first time confirmation of reduced NAA and increased mI in patients with Alzheimer's disease confirmed by all methods of AD diagnosis: genetic analysis, histopathology, and/or neuropsychological evaluation. Down syndrome is thought to result from triplication and overexpression of the gene for amyloid precursor protein (APP) [10]. The genetic defect of presenilin-1 acts on the same APP pathway causing the formation of amyloid plaques [11] observed in post-mortem studies in both AD and DS patients. The similarity in metabolic patterns in AD patients and the patient with DS and dementia indicates that MRS is sensitive to these genetic changes. Furthermore, the observation of increased mI in patients with DS only indicates that mI may be specific to amyloid accumulation.

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References:

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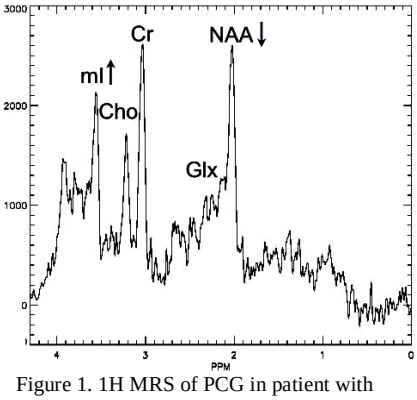

Figure 1. 1H MRS of PCG in patient with defect in presenilin-1 gene.

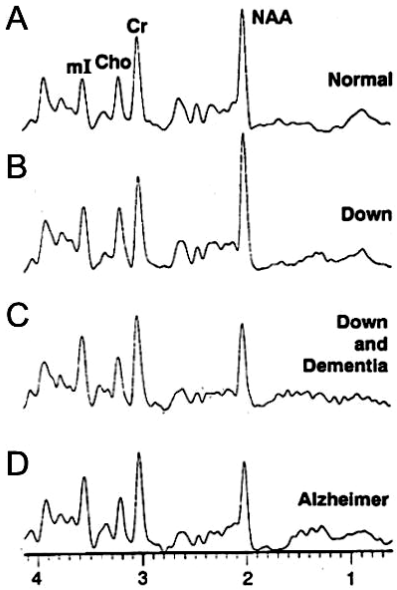

Figure 2. Representative spectra of patient groups compared to control.

	Age	N	NAA/Cr	Cho/Cr	mI/Cr
Familial Alzheimer's disease	54	1	0.98*	0.51	0.77*
Alzheimer's Disease (confirmed pm)	59-84	10	1.13±0.12*	0.69±0.10	0.69±0.07*
Adult down syndrome w/ dementia	61	1	0.91*	0.55	0.79*
Adult down syndrome w/o dementia	26-44	10	1.38±0.03	0.67±0.04	0.71±0.06*
Controls	26-37	10	1.36±0.08	0.61±0.08	0.60±0.04
	50-78	12	1.26±0.09	0.60±0.05	0.59±0.06

Table 1. Demographics and MRS results in patient and control groups.
* indicates significant difference ($p<0.05$-0.001) when compared to age-matched controls in student t-tests.