[1]H-MRS Detects Brain Metabolite Changes Associated with Early Onset Type-1 Diabetes

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Introduction

The treatment of type-1 diabetes requires the administration of insulin for the maintenance of blood glucose within physiological concentrations. Despite regular blood glucose monitoring, fluctuations beyond the normal physiological range do occur, particularly in young patients. The consequences of poor glycemic control have been implicated in reduced performance on neuropsychological testing. Six years after disease onset, significant differences in IQ, attention, processing speed, long-term memory and executive skills were observed, relative to controls[1]. Deficits in executive function and long-term memory suggest involvement of the frontal and temporal lobes of the brain, respectively. The neuropathological correlates of these illness-related neuropsychological deficits and the impact of deficits on functional outcomes (academic achievement, vocational opportunity) over time are still unclear. Magnetic resonance spectroscopy can provide information relating to short-term changes in the viability of brain tissue and in the long-term, the relative distribution of neural and glial cell types. Using MRS, changes in cerebral metabolites (glucose, myoinositol, acetone, choline and NAA) in diabetes have been demonstrated[2], although another study was unable to demonstrate MRS changes in type-1 diabetes[3]. The availability of a large cohort of early-onset diabetic subjects and matched controls enabled the use of MRS to examine long-term metabolite differences associated with type-1 diabetes. The aim of this study was to examine in the same group of early-onset type-1 diabetes patients, 12 years after diagnosis, the metabolite profile of brain regions associated with performance deficits observed at six years after diagnosis.

Method

MRS was performed 12 years after diagnosis on a group of children with early onset type-1 diabetes (n = 12), who had previously undergone neuropsychological assessment soon after diagnosis and again two and six years later. Results were compared to a community control group (n = 10) that had been assessed at similar times. All participants underwent an MRS study and completed a battery of neuropsychological measures.

Proton MRS was recorded from 2x2x2 cm single voxels placed bilaterally in the temporal lobe (including the hippocampus and mesial structures), frontal lobe (dorsolateral prefrontal cortex) and the basal ganglia (centred on the lentiform nucleus). Spectra were recorded with a TE/TR of 30/3000 ms using a 3T LX Horizon scanner (GE medical Systems) and a standard head coil. Data were analysed with LCModel[4] using a 15 metabolite basis set acquired on-site and the unsaturated water signal was used as a reference for determination of metabolite concentrations. Metabolite data were rejected if the Cramer-Rao lower bounds were greater than 30%.

Results

There were no differences between left and right metabolite concentrations for any group. Therefore, the mean of left and right hemisphere measurements is presented. Twelve years after disease onset, children with type-1 diabetes had higher levels of myoinositol, trimethylamines and glutamate/glutamine in the frontal lobes, compared to controls. In basal ganglia, total NA was reduced. Diabetic children showed no differences from controls in the temporal lobes.

		MI	TMA	Glx	NA
Frontal lobe	Control (n = 10)	**3.39 ± 0.56**	**1.43 ± 0.20**	**9.27 ± 0.95**	8.74 ± 0.72
	Diabetes (n = 12)	**4.29 ± 0.62**	**1.65 ± 0.15**	**10.46 ± 0.82**	8.54 ± 0.68
Basal ganglia	Control (n = 10)	3.17 ± 0.72	1.55 ± 0.20	11.38 ± 1.90	**9.21 ± 0.70**
	Diabetes (n = 12)	3.39 ± 0.62	1.59 ± 0.22	11.24 ± 1.55	**8.21 ± 0.77**

Results are mean and standard deviations, with metabolites showing a significant difference between groups shown in bold: $p < 0.01$compared to controls. Abbreviations: Cr, creatine + phosphocreatine; Glx. Glutamine + glutamate; GSH, glutathione; MI, myoinositol; NA, total N-acetylaspartyl groups (NAA + NAAG); TMA, trimethylamines (choline + phosphocholine + glycerophophocholine).

Discussion

While metabolite abnormalities have been described previously in diabetes[2], this study demonstrates region-specific long-term abnormalities. It is of interest that the two regions showing metabolite change are affected differently. In the frontal lobe, an increase in the metabolite myoinositol is consistent with a previous report of MRS in diabetics[2]. Both myoinositol and glutamine are putative osmolytes and their presence may be a marker of fluid imbalance resulting from regular disruption of glucose homeostasis. Hypoglycaemia may also stimulate glutamate release, leading to elevated glutamine levels. Myoinositol is also associated with increased gliosis. Elevated TMA suggests altered membrane turnover.

The reduced NA in basal ganglia suggests reduced neuronal population or function, consistent with altered executive function in type-1 diabetes. The regions showing altered metabolite profiles are consistent with the neuropsychological changes observed in children with early onset type-1 diabetes, who show subtle functional changes in anterior and medial temporal brain regions.

The results of this study are consistent with increased gliosis, osmotic regulation and cell membrane turnover in the frontal lobe and neuronal loss in basal ganglia of patients with early onset type-1 diabetes.

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