Brain Metabolite Changes Detected by MRS in Early Onset Type-1 Diabetes

R. M. Wellard[1], D. Rankin[2], D. Boyce[2], G. D. Jackson[1], G. Werther[3], E. Northam[2]

[1]Brain Research Isntitute, Melbourne, Victoria, Australia, [2]Psychology, Royal Children's Hospital, Melbourne, Victoria, Australia, [3]Endocrinology and Diabetes, Royal Children's Hospital, Melbourne, Victoria, Australia

Introduction

Despite the use of insulin and regular monitoring to maintain blood glucose concentration within the normal physiological range, abnormal fluctuations do occur, particularly in young patients. Reduced IQ and lowered performance on tasks such as attention, processing speed, long-term memory and executive skills, relative to matched controls, are evident on neuropsychological testing six years after disease onset[1]. The long-term effects on functional outcomes (academic achievement and vocational opportunity) have yet to be determined. Magnetic resonance spectroscopy (MRS) provides information about short-term changes in brain tissue viability and in the long-term, information about the relative distribution of neural and glial cell types. MRS has previously been used to demonstrate changes in cerebral metabolites (glucose, myoinositol (MI), acetone, trimethylamines (TMA) and total N-acetylaspartate (NAA))[2]. The availability of a large cohort of early-onset diabetic subjects and matched controls enabled us to assess the long-term tissue changes associated with type-1 diabetes. The aim of this study was to examine, at least 13 years after diagnosis, the metabolite profile in brain regions associated with performance deficits observed at 6-years after diagnosis.

Methods

MRS was performed 13-15 years after diagnosis on a group of young people with childhood onset type-1 diabetes (n = 63), 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 = 42) that had been assessed at similar times. All participants underwent an MR examination and completed a battery of neuropsychological measures.

Proton MRS was recorded from 2 cm isotropic 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 at 3T and a standard head coil (GE Healthcare). MRS data were analysed with LCModel[3] 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

Left and right metabolite concentrations were not different for either group, therefore, the mean of left and right hemisphere measurements is presented. Thirteen to fifteen years after disease onset, children with type-1 diabetes had higher levels of MI and TMA and reduced NAA in the frontal lobes, compared to controls. In basal ganglia, MI was increased and NAA was reduced. Temporal lobe MI was also increased.

Table showing differences in metabolite concentrations for diabetic and control subjects in the 3 regions examined.

		MI	TMA	NAA
Frontal lobe	Control (n = 42)	**3.5 ± 0.4**	**1.5 ± 0.2**	**8.7 ± 0.7**
	Diabetes (n = 63)	**4.2 ± 0.5**	**1.6 ± 0.2**	**8.4 ± 0.6**
Basal ganglia	Control (n = 42)	**3.2 ± 0.5**	1.6 ± 0.2	**8.7 ± 1.0**
	Diabetes (n = 63)	**3.4 ± 0.5**	1.6 ± 0.2	**8.1 ± 0.8**
Temporal lobe	Control (n = 42)	**3.9 ± 0.8**	1.7 ± 0.3	7.7 ± 0.9
	Diabetes (n = 63)	**4.4 ± 0.7**	1.6 ± 0.2	8.0 + 1.3

Results (expressed in institutional units approximating mM concentration) are mean and standard deviations, with metabolites showing a significant difference between groups shown in bold: $p < 0.01$ compared to controls. Abbreviations: MI, myoinositol; NAA, 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 in a group of childhood onset type-1 diabetics. It is of interest that the regions showing metabolite change are affected differently. In the frontal lobe, an increase in the metabolite MI is consistent with a previous report of MRS in diabetics[2]. MI is a putative osmolyte and an increase may be a marker of fluid imbalance resulting from regular disruption of glucose homeostasis. Hypoglycaemia may also stimulate MI production, which is also associated with increased gliosis. A change in the relative distribution of cell type would also be consistent with reduced NAA. Elevated TMA suggests altered membrane turnover. The reduced NAA in basal ganglia suggests reduced neuronal population or function.The altered frontal lobe metabolite profile is consistent with the neuropsychological changes observed in children with early onset type-1 diabetes, who show subtle functional changes in executive function (eg mental flexibility, planning, processing speed). The results of this study are consistent with increased gliosis, osmotic regulation and cell membrane turnover in the frontal lobe, neuronal loss in basal ganglia and osmotic regulation or gliosis in the temporal lobe of patients with childhood onset type-1 diabetes.

1. Northam, E. A. et al. Diabetes Care 24, 1541-6 (2001).
2. Kreis, R. & Ross, B. D. Radiology 184, 123-30 (1992).
3. Provencher, S. W. Magn Reson Med 30, 672-9 (1993).