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Hypoglycaemia-induced changes in regional brain volume and memory function

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Abstract

Background—Hypoglycaemic events can be a serious complication of insulin therapy in Type 1 diabetes mellitus. Severe hypoglycaemic exposure can lead to episodic memory impairments, including anterograde amnesia. However, relatively little is known regarding the long-term impact of severe hypoglycaemia on brain structure in Type 1 diabetes mellitus. The goals of the present study were to gain a greater understanding of the long-term effects of severe hypoglycaemia exposure on brain structure and the neural correlates of memory impairments in Type 1 diabetes mellitus.

Case report—Regional grey and white matter volume and total white matter lesion volume were quantified in an individual with long-standing hypoglycaemia-induced anterograde amnesia and compared with age- and gender-matched healthy control subjects. Our patient has significant reductions in grey matter volume in the hippocampus, thalamus and pallidum, and significant reductions in white matter volume in the splenium, isthmus of the cingulate and cerebellum. He also has a significantly larger total white matter lesion volume than control subjects.

Conclusion—This case study highlights the potential of hypoglycaemia for permanent deleterious effects on brain structure and memory function. Our results suggest that subcortical grey matter, periventricular white matter and posterior white matter may be most susceptible to injury from hypoglycaemia exposure, and that structural damage to the hippocampus and isthmus of the cingulate may play a central role in hypoglycaemia-induced memory impairments.

Introduction

Hypoglycaemic events can be a serious complication of insulin therapy in Type 1 diabetes mellitus [1]. Severe hypoglycaemia can lead to acute and chronic decrements in cognition, with memory function being particularly vulnerable [2,3]. For example, anterograde amnesia, the inability to form new memories of events, has been reported following severe hypoglycaemia in Type 1 diabetes [4–6]. However, relatively little is known regarding the long-term impact of severe hypoglycaemia on brain structure in Type 1 diabetes. In cross-sectional research in adolescents and adults, some studies have not found significant

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Competing interests

None declared.

alterations in brain structure associated with severe hypoglycaemia exposure [7,8]. Others have reported reductions in grey matter volume in the left posterior cerebellum [9], and the thalamus [10] and uncus [9] bilaterally. Clinical magnetic resonance imaging (MRI) scans administered within hours of severe hypoglycaemia have revealed abnormal signals in the hippocampus [4–6], thalamus [11], basal ganglia [12], cortical grey matter [4,5,11–13], splenium [14,15], internal capsule [13,15], centrum semiovale [11] and corona radiata [13]. Short-term clinical follow-up suggests that some of these signal abnormalities may lessen or even resolve over time [4,6,13,14], but longitudinal MRI and cognitive data are scarce. No quantitative structural analyses have compared these cases with age- and gender-matched control subjects, potentially missing important effects.

The present study quantified regional brain structure abnormalities in an individual with a history of multiple severe hypoglycaemic events, including one that resulted in permanent anterograde amnesia. Our goals were to examine the long-term effects of hypoglycaemia exposure on brain structure and the neural correlates of memory impairments in Type 1 diabetes.

Clinical history

Our patient was diagnosed with Type 1 diabetes at age 2 years. He experienced multiple episodes of severe hypoglycaemia (defined by American Diabetes Association criteria [16]) before he was 10 years of age, including one that resulted in transient right-sided upper extremity paralysis and confusion. In 1991, at 24 years of age, he was taken to the emergency department after having been found to be drowsy and disorientated. He was given an infusion of 50% dextrose in the ambulance. His blood glucose had recovered to 17.1 mmol/l at arrival in the emergency department. A neurological examination administered in the emergency department was normal except for disorientation, retrograde amnesia for recent events and profound anterograde amnesia. No structural abnormalities were noted on neuroradiological readings of a clinical computed tomography (CT) scan administered in the emergency department nor a clinical MRI exam that included proton density, T2-weighted and T1-weighted (with and without contrast) sequences administered the day after his hospital admission. His electroencephalogram (EEG) was also normal during his hospitalization. From an extensive medical diagnostic examination and neuropsychological testing, he was diagnosed with amnesia resulting from a hypoglycaemic episode. Between 1991 and 2010, he had at least four additional episodes of severe hypoglycaemia. However, his exposure to hyperglycaemia has been relatively minimal, as documented by his average HbA_{1c} from 2000 to 2010 of 56 mmol/mol (7.3%) [range 46 mmol/mol (6.4%) to 70 mmol/mol (8.6%)] and the absence of episodes of diabetic ketoacidosis. In 2010, at age 43 years, no signs or symptoms of retinopathy, nephropathy or peripheral neuropathy were detected in the history or physical examination, and his vitamin B12 levels were within the normal range. However, an electrocardiogram revealed a borderline R-R variability ratio of 1.18, suggesting that he may have been in the beginning stages of cardiovascular autonomic neuropathy. He also had a score of 21 on the Beck Depression Inventory II, suggesting that he had a moderate level of depressive symptoms.

Neuropsychological assessments

Our patient's intelligence quotient (IQ) and memory performance were assessed in 1991 and 2010, and were compared with a normative database. He was given the Wechsler Adult Intelligence Scale—Revised (WAIS-R), Wechsler Memory Scale—Revised (WMS-R), California Verbal Learning Test (CVLT) and Rey Complex Figure Test (RCFT; 2010 only).

Control subjects

Archival MRI data from 20 men (mean age 43 years, range 30–54 years) were used in volumetric analyses. They were screened for traumatic brain injuries and neurological and psychiatric conditions.

MRI data acquisition

The MRI examination included T1-weighted magnetization-prepared rapid acquisition with gradient echo (MP-RAGE) (1×1×1-mm sagittal slices, TR = 2400, TE = 3.16, TI = 1000, flip angle = 8, frames = 176; patient and control subjects), T2-weighted (1×1×1-mm sagittal slices, TR = 3200, TE = 455, flip angle = 120, frames = 176; patient only) and fluid attenuated inversion recovery (FLAIR) (0.86×0.86×3-mm transverse slices, TR = 9190, TE = 94, TI = 2500, flip angle = 150, frames = 42; patient only) scans acquired on a 3-Tesla Siemens Trio scanner (XXXX, XXXX).

Automated calculation of grey and white matter volume

FreeSurfer (v5.0; <http://surfer.nmr.mgh.harvard.edu/>) was used to calculate raw regional subcortical grey, gyral grey, subcortical white and gyral white matter volumes from high-resolution T1-weighted images of control subjects and our patient from 2010. Raw regional volumes were totalled across hemispheres and divided by intracranial volume to account for variability in head size. Total white matter lesion burden was calculated with FreeSurfer by dividing the raw total volume of hypointense regions within white matter on the T1-weighted images by intracranial volume.

Statistical analyses

Crawford and Howell's [17] modified *t*-test was used to compare our patient's brain measurements with those of the control subjects. For *a priori* region of interest (grey matter: hippocampus, thalamus, caudate, putamen and pallidum; white matter: splenium) and total white matter lesion volume analyses, we set statistical significance at $P < 0.05$, one-tailed. We hypothesized that our patient's grey and white matter volumes in these regions of interest would be smaller and that his total white matter lesion volume would be greater than those of the control subjects. For exploratory regions, significance was set at $P < 0.05$, two-tailed. Research procedures were approved by the Human Studies Committees of University of Missouri – St Louis and Washington University.

Results

Neuropsychological findings (Table 1)

Our patient's full-scale IQ score in 2010 was within the high average range. At his initial assessment, his memory scores were below the 5th percentile, indicating severe deficits in immediate recall, delayed recall and recognition. He performed better on memory tests in 2010, particularly within the recognition memory domain, suggesting some recovery over time. However, his general memory and delayed recall scores on the Wechsler Memory Scale—Revised were still more than 20 standard scale points below his full-scale IQ, consistent with anterograde amnesia [18].

Neuroradiological assessment of our patient's MRI scans (Fig. 1)

Clinical readings of our patient's 2010 MRI scans by a board-certified neuroradiologist (JSS) revealed a thin rim of hyperintense signal in the periventricular white matter on the FLAIR. There was also hyperintense signal on the FLAIR and T2, and hypointense signal on the T1, in the splenium of the corpus callosum, which extended into adjacent white matter.

Quantitative comparisons of grey and white matter volumes (Tables 2 and 3)

A priori region of interest analyses revealed that our patient has significantly reduced grey matter volume in the hippocampus, thalamus and pallidum compared with control subjects. He also has significantly reduced white matter volume in the splenium. Exploratory analyses revealed no significant differences between cortical or cerebellar grey matter volumes of our patient and the control subjects. However, his white matter volume in the isthmus of the cingulate and cerebellum is more than three standard deviations lower than that of the control subjects. In addition, his total white matter lesion volume is significantly larger than that of the control subjects (control subjects' mean = 0.09%, SD = 0.03%; patient = 0.25%; $t = 5.17$, $P = 0.000$, $z = 5.29$), likely driven by periventricular white matter lesions.

Discussion

This study investigated the long-term effects of hypoglycaemia exposure on brain structure and the neural correlates of hypoglycaemia-induced memory impairments in a rare case of hypoglycaemia-induced anterograde amnesia. Given the limitations of case studies, and the lack of a control group with Type 1 diabetes with matched hyperglycaemia exposure but no hypoglycaemia exposure, we cannot make strong conclusions about the causal relationships among our patient's hypoglycaemia exposure, volumetric changes and memory deficits. For example, we cannot rule out the possibility that hyperglycaemia exposure or glycaemic variability may have contributed to some of the effects noted. However, our patient's lack of retinopathy, nephropathy or peripheral neuropathy symptoms, and his available HbA_{1c} records, suggest that the alterations in brain structure observed in our patient likely resulted from his significant hypoglycaemia exposure.

Overall, our results suggest that hypoglycaemia can be associated with permanent reductions in subcortical grey matter volume, and that the hippocampus, thalamus and globus pallidus are among the brain regions most susceptible. The hippocampus plays a critical role in episodic (event) memory [19] and therefore alterations in hippocampal function are likely a major contributor to episodic memory impairments following hypoglycaemia. White matter surrounding the ventricles and in posterior brain regions, such as the splenium, isthmus of the cingulate and cerebellum, may also be susceptible to permanent injury from severe hypoglycaemia. Interestingly, anterograde amnesia has been reported following lesions to the isthmus of the cingulate (i.e. the retrosplenial region) [20], suggesting that this region could also play a role in hypoglycaemia-induced memory impairments. Overall, these results suggest that quantitative statistical analyses of high-resolution MRI scans in case studies are more sensitive than neuroradiological reads in identifying regional anomalies. This quantitative approach allows the detection of relatively subtle volumetric changes associated with critical case characteristics, which has heuristic value for planning future prospective group studies.

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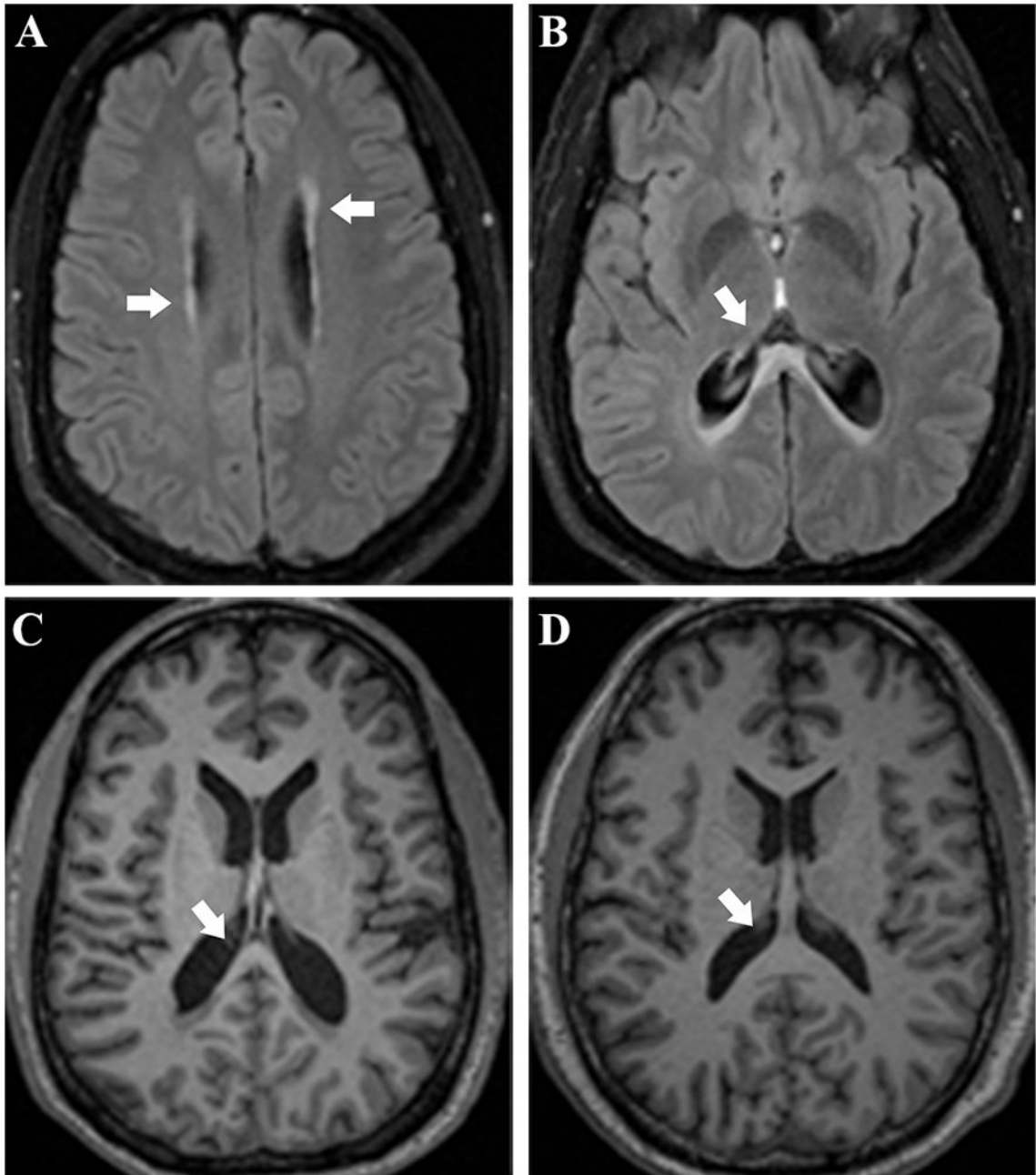


Figure 1.

(a) Axial fluid attenuated inversion recovery (FLAIR) image of our patient demonstrates hyperintense signal in the periventricular white matter. (b) Axial FLAIR image of our patient demonstrates hyperintense signal in the splenium. (c) Magnetization-prepared rapid acquisition with gradient echo (MP-RAGE) image showing marked atrophy in our patient's splenium. (d) MP-RAGE image showing the splenium of a 42-year-old healthy control subject.

Table 1

Neuropsychological assessments of our patient's cognitive function

	Testing session			
	Autumn 1991		Spring 2010	
	Score	Percentile	Score	Percentile
Wechsler Adult Intelligence Scale— Revised (WAIS-R)				
Verbal IQ	116	86	119	90
Performance IQ	83	13	109	73
Full-scale IQ	101	53	117	87
Wechsler Memory Scale—Revised (WMS-R)				
General memory	< 50	< 0.1	96	39
Verbal memory	< 50	< 0.1	96	39
Visual memory	< 50	< 0.1	103	58
Attention/concentration	93	32	123	94
Delayed recall	< 50	< 0.1	65	1
California Verbal Learning Test (CVLT)				
Trial 1	5	2	6	16
Trial 5	7	< 0.1	11	16
List B	4	2	8	85
Short delayed recall	0	< 0.1	7	2
Short cued recall	0	< 0.1	9	2
Long delayed recall	0	< 0.1	11	50
Long cued recall	0	< 0.1	12	50
Recognition	1	< 0.1	16	85
Rey Complex Figure Test (RCFT) *				
Copy	—	—	36/36	> 16
Short delayed recall	—	—	17.5/36	21
Long delayed recall	—	—	15/36	7

* Not administered during autumn of 1991.

Table 2

Regional grey matter volume of our patient and our control subjects

Region	Control subjects (%)		Patient (%)	t	P	z [†]
	Mean	SD				
<i>A priori</i> regions of interest						
Hippocampus*	0.56	0.05	0.42	-2.55	0.010	-2.61
Thalamus*	0.91	0.06	0.76	-2.55	0.010	-2.61
Caudate	0.47	0.06	0.38	-1.50	0.075	-1.54
Putamen	0.73	0.06	0.63	-1.68	0.055	-1.72
Pallidum*	0.22	0.02	0.18	-2.36	0.014	-2.42
Exploratory regions of interest						
Superior frontal	2.93	0.40	3.09	0.40	0.696	0.41
Precentral	1.76	0.24	1.96	0.84	0.410	0.86
Caudal middle frontal	0.81	0.12	0.94	1.02	0.320	1.05
Rostral middle frontal	2.06	0.30	2.04	-0.07	0.943	-0.07
Pars opercularis	0.58	0.09	0.47	-1.13	0.274	-1.15
Pars triangularis	0.50	0.09	0.49	-0.08	0.941	-0.08
Pars orbitalis	0.29	0.04	0.27	-0.37	0.719	-0.37
Lateral orbital frontal	0.94	0.11	0.96	0.17	0.868	0.17
Medial orbital frontal	0.67	0.10	0.62	-0.47	0.645	-0.48
Insula	0.93	0.14	0.85	-0.50	0.620	-0.52
Rostral anterior cingulate	0.32	0.07	0.36	0.47	0.642	0.48
Caudal anterior cingulate	0.26	0.07	0.23	-0.41	0.683	-0.43
Posterior cingulate	0.43	0.08	0.38	-0.64	0.528	-0.66
Postcentral	1.25	0.21	1.21	-0.20	0.846	-0.20
Paracentral	0.48	0.08	0.59	1.35	0.193	1.38
Superior parietal	1.82	0.25	2.09	1.05	0.307	1.08
Inferior parietal	1.82	0.29	1.79	-0.09	0.933	-0.09
Supramarginal	1.44	0.19	1.55	0.59	0.563	0.60
Precuneus	1.34	0.18	1.32	-0.12	0.904	-0.13
Isthmus of the cingulate	0.36	0.05	0.31	-1.03	0.314	-1.06

Region	Control subjects (%)		Patient (%)	<i>t</i>	<i>P</i>	<i>z</i> [†]
	Mean	SD				
Transverse temporal	0.15	0.04	0.16	0.38	0.707	0.39
Superior temporal	1.50	0.19	1.45	-0.26	0.801	-0.26
Banks superior temporal sulcus	0.31	0.04	0.31	-0.05	0.959	-0.05
Middle temporal	1.47	0.19	1.37	-0.48	0.637	-0.49
Inferior temporal	1.40	0.24	1.60	0.83	0.419	0.85
Entorhinal	0.27	0.05	0.29	0.48	0.640	0.49
Parahippocampal	0.30	0.06	0.33	0.45	0.658	0.46
Fusiform	1.37	0.18	1.66	1.56	0.137	1.59
Lingual	0.92	0.12	0.79	-1.07	0.297	-1.10
Pericalcarine	0.29	0.06	0.22	-1.09	0.290	-1.12
Cuneus	0.40	0.06	0.38	-0.33	0.748	-0.33
Lateral occipital	1.63	0.18	1.46	-0.97	0.344	-0.99
Cerebellum	6.66	0.63	5.95	-1.09	0.289	-1.12

Regional volumes are expressed as percentages of intracranial volume.

* $P < 0.05$.

[†] *z*-score effect size estimate.

Table 3

Regional white matter volume of our patient and our control subjects

Region	Controls (%)		Patient (%)		t	p	z [‡]
	Mean	SD	Mean	SD			
<i>A priori</i> region of interest							
Splenium [*]	0.06	0.01	0.03	0.03	-2.13	0.023	-2.18
Exploratory regions of interest							
Anterior corpus callosum	0.06	0.01	0.06	0.06	0.25	0.808	0.25
Mid anterior corpus callosum	0.03	0.01	0.03	0.03	-0.21	0.835	-0.22
Central corpus callosum	0.03	0.01	0.02	0.02	-1.43	0.169	-1.47
Mid posterior corpus callosum	0.03	0.01	0.02	0.02	-1.65	0.115	-1.69
Superior frontal	2.44	0.17	2.49	0.34	0.34	0.737	0.35
Precentral	1.82	0.17	1.85	0.20	0.20	0.840	0.21
Caudal middle frontal	0.81	0.09	0.92	1.18	1.18	0.255	1.20
Rostral middle frontal	1.74	0.14	1.59	-1.02	-1.02	0.320	-1.05
Pars opercularis	0.46	0.06	0.41	-0.97	-0.97	0.345	-0.99
Pars triangularis	0.41	0.04	0.42	0.26	0.26	0.795	0.27
Pars orbitalis	0.14	0.01	0.11	-1.55	-1.55	0.138	-1.59
Lateral orbital frontal	0.87	0.06	0.79	-1.31	-1.31	0.207	-1.34
Medial orbital frontal	0.50	0.06	0.44	-0.97	-0.97	0.347	-0.99
Insula	1.22	0.09	1.19	-0.36	-0.36	0.726	-0.36
Rostral anterior cingulate	0.33	0.04	0.34	0.27	0.27	0.787	0.28
Caudal anterior cingulate	0.39	0.05	0.33	-1.13	-1.13	0.271	-1.16
Posterior cingulate	0.58	0.04	0.51	-1.74	-1.74	0.098	-1.78
Postcentral	0.98	0.11	0.85	-1.14	-1.14	0.267	-1.17
Paracentral	0.55	0.06	0.52	-0.50	-0.50	0.621	-0.51
Superior parietal	1.64	0.11	1.67	0.25	0.25	0.804	0.26
Inferior parietal	1.43	0.16	1.29	-0.88	-0.88	0.392	-0.90
Supramarginal	1.17	0.14	1.30	0.92	0.92	0.371	0.94
Precuneus	1.26	0.10	1.21	-0.41	-0.41	0.690	-0.42
Isthmus of the cingulate [‡]	0.47	0.04	0.32	-3.25	-3.25	0.004	-3.33

Region	Controls (%)		Patient (%)	<i>t</i>	<i>p</i>	<i>z</i> [‡]
	Mean	SD				
Transverse temporal	0.09	0.01	0.09	0.38	0.707	0.39
Superior temporal	0.97	0.08	0.95	-0.24	0.815	-0.24
Banks superior temporal sulcus	0.36	0.07	0.25	-1.58	0.132	-1.62
Middle temporal	0.78	0.09	0.80	0.20	0.841	0.21
Inferior temporal	0.82	0.09	0.88	0.73	0.475	0.75
Entorhinal	0.11	0.03	0.13	0.43	0.675	0.44
Parahippocampal	0.23	0.03	0.20	-1.09	0.289	-1.12
Fusiform	0.93	0.10	0.95	0.21	0.834	0.22
Lingual	0.74	0.08	0.58	-2.06	0.054	-2.11
Pericalcarine	0.47	0.09	0.29	-1.92	0.070	-1.97
Cuneus	0.34	0.05	0.25	-1.69	0.107	-1.74
Lateral occipital	1.28	0.15	1.02	-1.67	0.112	-1.71
Cerebellum [†]	2.18	0.19	1.53	-3.36	0.003	-3.45

Regional volumes are expressed as percentages of intracranial volume.

* $P < 0.05$,

[†] $P < 0.01$.

[‡] *z*-score effect size estimate.