Neurological consequences of diabetic ketoacidosis at initial presentation of type 1 diabetes in a prospective cohort of children.

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Objective: The study aimed to investigate the impact of new onset diabetic ketoacidosis (DKA) upon brain morphology and function.

Research Design and Methods: Patients aged 6-18 years with and without DKA at diagnosis were studied at four time points: <48 hours, five and 28 days, and six months post diagnosis. Patients underwent magnetic resonance imaging and spectroscopy with cognitive assessment at each time point. Relationships between clinical characteristics at presentation and magnetic resonance imaging and neurologic outcomes were examined using multiple linear regression analyses, repeated measures and ANCOVA analyses.

Results: Thirty-six DKA and 59 non-DKA patients were recruited between 2004-9. With DKA, total white matter volume was increased at baseline and decreased over six months with altered diffusion measures in the frontal, temporal and parietal cortices on day one relative to non-DKA patients. For grey matter in DKA patients, total volume was lower at baseline and increased over six months. Lower levels of N-acetyl aspartate were noted at baseline in the frontal grey matter and basal ganglia. Mental state scores were lower at baseline and at five days. Importantly, changes in total and regional brain volumes over the first five days were associated with poorer delayed memory recall, and focused, sustained, and divided attention at six months. Multiple regression analysis demonstrated that pH and age at the time of presentation were strong predictors of the aforementioned outcomes.

Conclusions: DKA at type 1 diabetes diagnosis results in morphologic and functional brain changes that are associated with adverse neurocognitive outcomes in the medium term.

The incidence of childhood onset type 1 diabetes varies from 0.1 to 57.6 per 100,000 and is increasing worldwide(1). Long-term cognitive consequences of type 1 diabetes and associated fluctuations in glycemia during childhood and adolescence are well documented (2). Developing strategies to prevent or ameliorate these adverse outcomes requires an understanding of the nature and timing of the neurological insults associated with diabetic dysglycemia.

The most severe acute diabetes-related central nervous system complication in type 1 diabetes is cerebral oedema associated with diabetic ketoacidosis (DKA) (2) with 10-25% of affected children experiencing chronic CNS morbidity (3). Whilst the frequency of DKA at diagnosis is relatively high (15-70% depending upon age and geographic region), fulminate clinical cerebral oedema in this context is relatively rare with an incidence rate of only 0.5-0.9% (4) and hence documented brain injury is also rare. The more frequent, milder alterations in brain function and chemistry in newly diagnosed DKA have been assumed to be transitory with normalisation after metabolic stabilisation (5-8), but this assumption has not been formally tested. We hypothesized that just as there exists a continuum of clinical and sub-clinical cerebral oedema (9), there may also be a continuum of brain injury in DKA and that brain injury outside the context of cerebral oedema may be more common than previously recognised. The purpose of this study in children with new onset DKA was two-fold – firstly, to document acute alterations in magnetic resonance imaging (MRI) measures of cerebral structure and cognitive function and correlate these with clinical parameters; and secondly, to study the evolution of these alterations in brain structure and cognitive functioning over the first six months.

RESEARCH DESIGN AND METHODS

We conducted a prospective, longitudinal cohort study at the Royal Children's Hospital (RCH), Melbourne, Australia between June 2004 and October 2009 of English-speaking children aged between 6-18 years who presented with a new diagnosis of type 1 diabetes. The diabetes clinic at RCH provides services to approximately 75% of children in Melbourne (population of 4.17 million) with diabetes living within a large, socio-demographically and ethnically diverse region. The type 1 diabetes clinic population consists of 1650 children and adolescents aged up to 19 years with 2-3 children being diagnosed at our centre each week. Patients were recruited sequentially as they presented to RCH at diagnosis. The patients underwent MRI, magnetic resonance spectroscopy (MRS) and cognitive evaluation at four time points: "Baseline" was within 48 hours of presentation, "Day 5" was

between 5 and 7 days, “Day 28” was between 26-30 days and “6 months” was 25-27 weeks after presentation. Exclusion criteria were pre-existing neurological abnormality, neurologic impairment, evidence of any congenital abnormality or established brain injury on MRI, clinical signs consistent with a diagnosis of cerebral oedema (headache with obtundation or deterioration in Glasgow Coma scale score, bradycardia with hypertension), the presence of metal-wired orthodontic braces and inability to undergo MRI without general anaesthesia. Of 205 eligible children, 95 children were enrolled in the study - 36 with DKA, defined as serum pH <7.30, and 59 without DKA. Clinical status of participants (DKA vs non-DKA) was classified unambiguously according to parameters that were measured biochemically in a NATA (National Association of Testing Authorities- Australia) accredited laboratory. The device that was used to measure pH was a Siemans Rapidlab 1260 machine with a measurement of uncertainty is +/- 0.02. All patients were treated as per standard hospital protocol (http://www.rch.org.au/clinicalguide/guideline_index/Diabetes_Mellitus). The study was approved by the Royal Children’s Hospital Human Research Ethics Committee.

Measures

Clinical and Demographic Information

Clinical information collected from all children at diagnosis included age, sex, weight, height, blood pressure, pulse rate and serum biochemical measures (pH, CO_2, HCO_3, base excess, glucose, osmolality, sodium, urea). Percent dehydration was calculated according to: [(discharge weight minus admission weight)/discharge weight] x 100. Socioeconomic status (SES) was rated according to Victorian geographical postal area using the Australian Bureau of Statistics Socio-Economic Indices for Areas (10). Parents also provided information on their child’s developmental and academic history.

The following data were collected at each assessment: height, weight, number of severe hypoglycemia reactions, number of episodes of recurrent DKA, co-morbidities, insulin dose and regimen, and glycated hemoglobin. Severe hypoglycemia was defined as hypoglycemia associated with loss of consciousness and/or seizure or altered conscious state that required therapy from another person. DKA was defined in the same way (serum pH < 7.30) as at presentation. Insulin dose adjusted A1C levels were calculated as an index of degree of residual endogenous insulin secretion (11).

Magnetic resonance imaging

Brain imaging was performed using a Siemens Trio 3T scanner. Images were acquired using the standard quadrature head coil at four time points. Transverse, T2-weighted images were acquired using a turbo spin echo sequence (TR/TE 6400/93 ms, echo train length 17, slice thickness 3.5 mm, in-plane resolution 0.51 x 0.51 mm). T1-weighted images were acquired using an MPRAGE sequence with contiguous slices (TR/TE/TI 1900/2.19/900 ms, flip angle 9°, contiguous slices 1 mm^3 isotropic spatial resolution). Diffusion data were acquired with a spin-echo EPI sequence using one of two image parameter sets. The first was TR/TE 6000/97 ms, slice thickness 3 mm, in-plane resolution 1.5 x 1.5 mm, b amplitude 1000 x 10^{-3} s/mm^2 with 20 directions. The second was TR/TE 4000/89, slice thickness 4 mm, in-plane resolution 1.7 x 1.7 mm, b amplitude 1000 x10^{-3} s/mm^2 with 24 directions plus five b=0 acquisitions.

Cortical and volumetric segmentation were performed with Freesurfer 4.4 (http://surfer.nmr.mgh.harvard.edu/) using the T1 weighted images. Volumes were determined for both cortical and subcortical regions (12). Parcellated brain volumes were combined into larger regions matching the regions for diffusion analysis. These included frontal, temporal and parietal regional volumes (Appendix 1), and expressed as a proportion of the total brain volume (TBV) to normalise for age-related variations in brain size.

Raw data from the diffusion acquisitions were phased using a Bayesian procedure (13) to provide images with Gaussian noise centred about zero. The images were aligned to the corresponding T2-weighted image data set. Diffusion encodings corrupted by subject motion were automatically identified and removed. Parametric maps were generated for mean diffusivity (MD) and fractional anisotropy (FA). Diffusion Tensor Imaging (DTI) parameter sampling was performed using Analyze, version 9·0 (Mayo Clinic, Rochester, MN). A data analyst blinded to subject status placed regions of interest in the grey and white matter of the frontal, temporal, and parietal lobes (Figure 1, Appendix 1).

Magnetic resonance spectroscopy

Single-voxel, water-saturated spectra were acquired using a standard PRESS sequence. Regions of interest included the left frontal white matter, frontal grey matter, and left basal ganglia, each previously identified as vulnerable (7, 14). The ROIs were positioned using T1-weighted scout images. Basal ganglia ROIs were

positioned over the lentiform nuclei; frontal lobe white matter ROIs were positioned above the anterior tip of the left lateral ventricle, and frontal lobe grey matter ROIs were placed in the same plane as the white matter voxel, anterior to and at the level of the corpus callosum within cingulate grey matter. Acquisitions comprised 80 transients recorded with a TE/TR = 30/3000 ms. The voxel placed in the basal ganglia was 20 x 20 x 10 mm and the frontal lobe voxels were 25 x 20 x 15 mm. All measurements were made using the same 3T Siemens instrument ustilising a quadrature head coil. Metabolite concentrations are presented relative to creatine concentration. The values for N-acetylaspartate (NAA) reported here include its NAA-glutamate component (reported as NAA). NAA is considered a marker of neuronal density. Myoinositol concentration is an endogenous osmolyte that is considered a marker of gliosis. Tissue metabolite content was determined using LCModel (15) with a basis set of 21 metabolites prepared using reference solutions.

Cognition

Mental state: At Day 1 tests were limited to those that could be administered bedside to unwell children. Hence the only tests administered were the Mental State School-Years Screening Test for the Evaluation of Mental Status (SYSTEMS) (16) and a paired associate verbal learning task. The SYSTEMS was developed as a child-appropriate alternative to the adult Mini-Mental State Examination (17) on which it is based. It was developed in a pediatric hospital to measure subtle changes in mental state and cognition in the context of both acute and chronic illness or brain injury. The SYSTEMS was administered at days one and five after admission. Responses were classified using age-specific cut-off scores (16).

Intelligence: The Wechsler Intelligence Scale for Children - Fourth Edition (WISC-IV) (18) was administered six months after admission. An age-standardised summary Full Scale IQ score (M=100, SD=15) was calculated.

Memory: Verbal memory was assessed at each time point using a paired associate learning task requiring children to learn novel word pairs and recall them after a delay (19). Alternative forms of the test were used to minimise practice effects. The numbers of words remembered after a delay was reported.

Attention: Four tasks (Sky Search-focused attention; Sky Search Dual Task – dual modality divided attention; Score Dual Task – single modality divided attention; and Walk/Don't Walk – sustained attention/impulsivity) from The Test of Everyday

Attention for Children (TEA-Ch) (20) were administered at five days, 28 days and six months after acute presentation. Age and gender standardised scores were reported.

Statistical Analysis

All data (Appendix 2) were analysed using SPSS version 20 (SPSS Inc.). Groups (DKA/non-DKA) were compared using ANOVA and ANCOVA (continuous variables) and χ^2 (categorical variables) analyses. Age at presentation and gender were added as covariates in all analyses involving non-age and non-gender adjusted variables. Change in neurologic outcome over time was investigated using repeated measures ANCOVA. Relationships between clinical characteristics at presentation and neurologic outcomes were examined using multiple linear regression analyses with age at presentation and gender entered as additional predictors. Regression diagnostics were performed and no issues of multicollinearity among independent variables were identified. Data for this model are also presented in terms of percentage of variance accounted for by the individual predictor (sr^2). Proportionate changes in brain measures at presentation were calculated according to (measured value at day five minus measured value at day one/value at day five). The proportionate volume changes were correlated with cognitive outcome variables at six months. All analyses were two-sided and a Bonferroni correction was applied resulting in an alpha level of 0.01.

RESULTS

The characteristics of the participants are described in Table 1. Participant numbers were 36/59, 29/46, 27/46 and 25/44 (DKA/non-DKA) at the four time points respectively. There were no differences between the DKA and non-DKA groups in age, duration of symptoms, SES and educational history. Following diagnosis, the groups did not differ in frequency of severe hypoglycemia, recurrent DKA, thyroid or celiac disease, or by insulin regimens or glycated hemoglobin (raw or insulin adjusted).

Magnetic resonance imaging and spectroscopy measures

Total Cerebral Volumes: Total supratentorial brain volumes did not differ with DKA at any time point (Figure 1) and did not change over time in either group.

White Matter: Relative total white matter volume was increased in the DKA group at baseline (F=7·43, p=0·008, Figure 1) and decreased over six months (F=25·72, p<0·001). For regional analysis, relative frontal white matter volume was increased with DKA at baseline (F=10·84, p=0·002, Figure 2) and decreased over six months

(F=16·56, p=0·001). A decrease in relative parietal white matter volume also occurred over six months in the DKA group only (F=9·19, p=0·008). For diffusion measures, with DKA white matter diffusivity at baseline was higher in the frontal lobe (F=18·78, p<0·001, Figure 2), temporal lobe (F=18·12, p<0·001) and parietal lobe (F=13·42, p<0·001). Reductions in white matter diffusivity occurred over six months with DKA in the frontal (F=11·08, p=0·006, Figure 2), temporal (F=42·20, p<0·001) and parietal (F=16·63, p=0·002) lobes. Fractional anisotropy changed in the opposite direction, but parallel to the diffusivity over all analyses. Spectroscopy revealed frontal white matter NAA levels were lower with DKA at Time 4 (F=8·51, p=0·005, Figure 2). There was a trend toward an increase in frontal white matter NAA levels over six months in the non-DKA group (F=6·186, p=0·02), but no change in the DKA group.

*Grey Matter:*Relative total cortical grey matter volume was decreased with DKA on day one (F=7·64, p=0·008, Figure 1) and increased over six months (F=10·18, p=0·005). Regionally, the relative temporal cortical grey matter volume was decreased with DKA on day one (F=8·66, p=0·005), with a trend to increase over six months. For diffusion, parietal lobe grey matter diffusivity was higher with DKA on day one (F=10·2, p=0·002). Grey matter diffusivity in the frontal lobes decreased over six months with DKA (F=50·232, p<0·001, Figure 2) and was lower at six months (p=0·01). For spectroscopy, frontal grey matter NAA levels were lower on day one with DKA (F=8·73, p=0·005, Figure 2), while myoinositol levels decreased over six months (F=14·827, p=0·002).

Hippocampus and basal ganglia: Relative hippocampal and basal ganglia volumes did not differ with DKA at any time point. There was no change in either volume over six months. In the left basal ganglia, NAA levels with DKA trended lower on day one (F=5·24, p=0·03) and day five (F=7·29 and p=0·01).

Cognition

The mental state score was lower with DKA on day one (Figure 3, F=10·14, p=0·002), with both groups showing a similar improvement by day five (DKA F=28·77, p<0·001; non-DKA F=21·42, p<0·001). There were no group differences on Full scale IQ at six months. Memory scores were lower with DKA on day one (F=14·58, p<0·001) and improved by six months (F=8·22, p=0·009, Figure 3). No differences in memory, divided or sustained attention were noted with DKA at six months. Focused attention improved between day five and six months in the non-DKA group (F=13·73, p=0·001, Figure 3), but not in the DKA group.

Clinical parameters on admission and MRI and cognitive outcomes

Lowest pH and age at presentation were the strongest predictors of MRI and MRS measures and cognitive outcomes. The day one lowest pH was positively related with change in total brain volume by day five (sr^2=7·1%, p=0·008); negatively associated with day 1 white matter diffusivity in the frontal (sr^2=41·3%, p<0·001), temporal (sr^2=33·03%, p<0·001) and parietal regions (sr^2=24·07%, p<0·001); but positively associated with six month frontal grey matter diffusivity (sr^2=119·66%, p=0·015). Day one lowest pH was also positively associated with day one frontal grey matter NAA levels (sr^2=16·86%, p=0·001) and day one memory (17·47%, p<0·001).

Age at presentation was positively related to diffusion measures on day one in frontal and parietal grey matter diffusivity (sr^2=22·84%, p<0·001 and sr^2=21·87%, p<0·001) and negatively associated with day one frontal and temporal white matter diffusivity (sr^2=10·36%, p<0·001; sr^2=11·46%, p=0·001 respectively). Age at presentation was positively associated with six month frontal (sr^2=17·91%, p=0·001) and parietal grey matter diffusivity (sr^2=19·70%, p=0·001).

In the DKA group univariate and multivariate analyses of MR outcomes and the timing of the first scan (expressed as hours between the time of commencement of intravenous resuscitation and time of scan) showed there were no significant associations between any of the volumetric and spectroscopic outcomes and time of first scan. There was a significant association between the time of the scan and parietal grey matter MD seen on univariate analysis that was not significant on multivariate analysis. There were no other significant associations between MD and timing of scan.

MRI measures in the first week and 6 month cognitive outcomes

The reduction between days one and five in total white matter volume (an indirect measure of swelling) was negatively associated with performance on dual modality divided attention (r=-0·46, p=0·002) and sustained attention (r=-0·40, p=0·007) at six months. Frontal white matter volume reduction was negatively associated with dual modality divided attention (r=-0·43, p=0·004); temporal white matter volume reduction was negatively associated with long-term memory (r=-0·49, p=0·0009); and parietal white matter volume reduction was negatively associated with sustained

attention (r=-0·47, p=0·002). Parietal grey matter volume increase was negatively associated with sustained attention (r=-0·45, p=0·002).

CONCLUSIONS

This study highlights the common nature of focal cerebral oedema, and associated impairment in mental state, at the time of presentation with new-onset type 1 diabetes in middle childhood. We demonstrate that these alterations occur most markedly throughout the cerebral white matter, particularly in the frontal lobes and are most prominent in the youngest children with the most dramatic acidemia. Changes in cerebral MRI measures over the first week after diagnosis were associated with persisting alterations in attention and memory functioning six months later. Children with DKA did not otherwise differ in age, sex, SES, pre-morbid learning difficulties or in post-diagnosis clinical trajectory. Earlier diagnosis of type 1 diabetes in childhood may avoid the complication of DKA, with the neurological consequences documented in this study, and is worthy of a major public health initiative.

This study utilizes several MRI techniques to define cerebral structure and biochemistry. All regional brain volume data were normalized to account for differences in absolute volume related to varying subject age. Thus, the measures from day one showed a relative increase in white matter volume and decrease in grey matter volume. With DKA, white matter volume expansion was greatest within the frontal white matter but a more widespread reduction in parietal and frontal white matter volume was seen over the first six months following diagnosis. Unlike volumes, diffusion values were not normalized, as they are comparatively stable throughout childhood (21). Diffusion values in the DKA group were high on day one throughout all white matter regions evaluated, but returned to non-DKA levels by day five. We postulate that increases in both volume and diffusivity within the white matter were due to increased tissue water, and this is supported by strong correlations between the reduction in volume and decrease in diffusivity. It is notable that the diffusivity appeared to be more sensitive than volume, as an increase in white matter volume was detected only for frontal white matter. This finding also suggests a greater vulnerability for the frontal white matter in DKA, which may represent a maturational vulnerability as the frontal white matter remains immature at this period of cerebral development.

We propose two explanations, which are not necessarily mutually exclusive, for the increased volume and altered diffusion that is prominent acutely in the white matter: 1) the osmotic effects caused by relatively rapid restoration of blood glucose (and osmolarity) in the face of slower loss of idiogenic osmoles in axons and myelin leading to cell swelling; and/or 2) the breakdown of the blood brain barrier leading to extravasation of fluid into the white matter interstitium with extracellular (vasogenic) oedema. These disturbances in brain water balance can be viewed as being analogous to those associated with extrapontine myelinolysis, which is typically found in conjunction with fluid/electrolyte disturbances and has been associated with diabetes (22, 23). Our findings are consistent with other studies suggesting brain water shifts associated with DKA (9) including increased diffusion in the frontal white matter in the first hours of management (14). Further evidence of white matter pathology was demonstrated in two atypical comatose, pediatric DKA cases without cerebral edema in which subcortical white matter micro-hemorrhage and inflammation were noted (24).

Additional insight is provided from the MRS. Acutely, frontal grey matter demonstrated a reduction in NAA which recovered. This may reflect neuronal dysfunction, emphasizing neuronal impact from DKA. Over the first six months following diagnosis, the greatest alterations on spectroscopy were reductions in frontal white matter NAA. Whereas a typical maturational increase in NAA occurred in children without ketoacidosis (25), this was not seen in the children who presented with DKA. Reductions in frontal white matter and basal ganglia NAA have previously been associated with impaired cognition (26) and DKA (27-29). In addition from the MRS, lactate was present in approximately 10% of both DKA and non-DKA subjects in any voxel. This low incidence of an elevation in lactate may relate to the delay in imaging after the initiation of therapy.

Two recent cross-sectional retrospective studies have highlighted a negative impact of ketoacidosis on cognitive performance in school-aged children with existing diabetes (30-31). For the current study, the strength of examining patients with new onset diabetes has allowed the window of dysglycemia to be simplified to a single period of hyperglycemia with or without one episode of ketoacidosis. Interestingly, our findings replicate a similar uni-dimensional model of cognitive performance in rats after one episode of DKA (32).

In relation to clinical risk factors, the degree of acidosis and younger age appeared to be the greatest risk factors for alterations in cerebral structure. Younger age has been previously described as being associated with greater degree of cognitive impairment in type 1 diabetes (2). These previous studies have included children exposed to various aspects of diabetes dysglycemia, including hypoglycemia. Specific studies of DKA in children have been thus far limited to cerebral oedema. In these, the risk of cerebral oedema was associated only with elevation in serum urea and low partial pressures of arterial carbon dioxide (33). In children and adults with DKA without cerebral oedema, the degree of acidosis was the determinant of impaired conscious state (6, 34).

Finally, cerebral volume changes in the frontal, temporal and parietal regions in the first week after diagnosis were associated with lower attention and memory scores six months later. This suggests new onset DKA in childhood may have irreversible impacts on the brain, with functional information processing difficulties persisting after resolution of tissue water increases in cerebral white matter. These findings have not been reported to date, but are consistent with the growing concern over academic performance in school-aged children with diabetes (2).

The lack of pre-morbid data on MR brain volumes, diffusivity, spectroscopy and cognition is an unavoidable limitation of this study. There are currently no screening programs that practically identify those children and adolescents destined to develop type 1 diabetes in low risk populations. If there were such screening programs, it would be unethical to allow such children to develop DKA. However, given the fact that the DKA and non-DKA groups did not differ in any demographic variables or previous history of learning difficulty and that the variations in brain morphology aligned temporally and statistically to the episode of acidosis, we surmise that the likelihood of significant pre-morbid differences in brain structure and function between the two groups is low. Another possible limitation relates to the period of DKA prior to admission. Given the severity of the clinical phenotype of DKA any variation in duration would be a matter of hours rather than days and is to some extent reflected by the degree of acidosis, however exact duration remains unknown. An additional limitation relates to the short follow up period of 6 months. However the longer the follow-up period, the greater the likelihood of post-diagnosis glycemic events (recurrent episodes of DKA, episodes of severe hypoglycemia, prolonged periods of hyperglycemia etc) contributing to brain injury. Thus, balancing the need for allowing for time for recovery yet avoiding additional clinical confounders, 6

months was chosen as the follow-up period to provide the best picture of the neurological sequelae of the initial DKA insult. A final limitation relates to the fact that only three quarters of the subjects completed all data collection. This may introduce some bias in the later evaluations.

Conclusions and clinical implications

This study demonstrates common and widespread alterations in brain structure and chemistry in new-onset type 1 diabetes with ketoacidosis in a paediatric and adolescent cohort from a socio-economically and ethnically diverse population. There are several implications that arise from these findings. First, the imperative to avoid ketoacidosis in children through improved public and professional awareness. Reductions in the rates of ketoacidosis at diagnosis are possible, as has been demonstrated with public health campaigns in Italy and Australia (35, 36). Secondly, any neuroprotective strategy developed in the future must be prioritized at initial diagnosis. Finally, we should focus greater attention on neuropsychological evaluation of children with diabetes – both by performing a brief mental state examination in all newly diagnosed patients and with cognitive follow-up. It would appear sensible for clinicians to defer educational activities in patients with a suboptimal mental state for at least 1-2 weeks. Brain injury should no longer be considered a rare complication of DKA. This study has shown that it is both frequent and persistent.

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Table 1: Patient characteristics

	Non-DKA Group mean (range) n = 59	**DKA Group mean (range) n = 36**	**p value**
Age (yrs)	11.52 (6.17-16.16)	11.52 (6.05-17.87)	0.99
Percentage male	54.2	47.2	0.5
Duration of polyuria/polydypsia (days)	23.41 (2-168)	19.46 (1-56)	0.4
SES (percentile)	61.51 (5-99)	60.58 (4-100)	0.99
Percentage requiring school assistance	15.8	16.7	>0.99
At presentation:			
Lowest pH	7.37 (7.30-7.44)	7.12 (6.72-7.29)	<0.001
Highest blood glucose (mmol/l)	25.77 (13.00-45.10)	31.00 (16.00-81.00)	0.03
Highest corrected serum sodium (mmol/l)	139.69 (134-146)	147.99 (124-198)	<0.001
Lowest corrected serum sodium (mmol/l)	136.00 (133-141)	142.56 (128-169)	0.075
Highest urea (mmol/l)	5.15 (2-8)	6.21 (3-13)	0.006
Serum osmolality (mmol/l)	298.39 (285-318)	312.80 (264-394)	<0.001
Percent dehydration*	N/A	7.84 (0-14)	N/A
At 6 month follow-up:			
Percentage of patients with 1 or more episodes of severe hypoglycaemia	(1.7%)	(2.8%)	0.3
Percentage of patients with 1 or more episodes of subsequent DKA.	0%	0%	-
Percentage on: BD regimen MDI regimen	 78% (n=46) 22% (n=13)	 74% (n=26) 26% (n=9)	 0.7
TDD (units/kg/day)	0.7 (0-1.4)	0.8 (0.3-1.7)	0.016
HbA1c - at 6 months	7.52 (5-12)	7.40 (5-9)	0.617
IDAA1C	10.2 (5.6-15.7)	10.6 (6.9-14.8)	0.205

*Calculated as weight at discharge minus weight at presentation/weight at discharge.

Figure 1: Total brain volumes

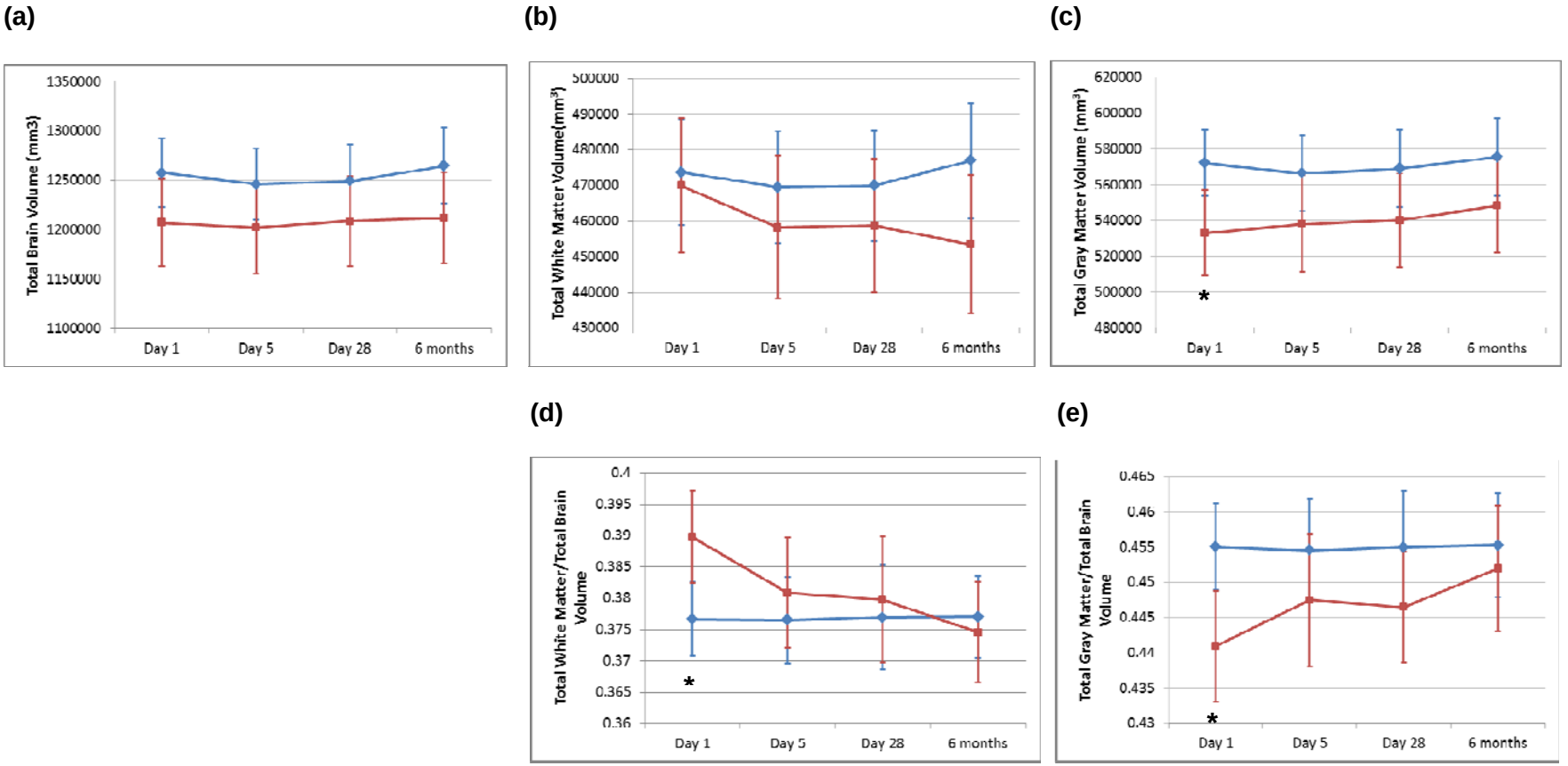

Figure legend: Data are presented as estimated means and 95% confidence intervals at each time point: (a) total supratentorial brain volumes; (b) total supratentorial white matter volume; (c) total supratentorial grey matter volume * p=0.14; (d) total cortical white matter volume/total brain volume * p=0.008; (e) total cortical grey matter volume/total brain volume * p=0.008. The non-DKA group is depicted in blue and the DKA group is depicted in red.

Figure 2: Frontal lobe volumes, diffusivity and spectroscopy

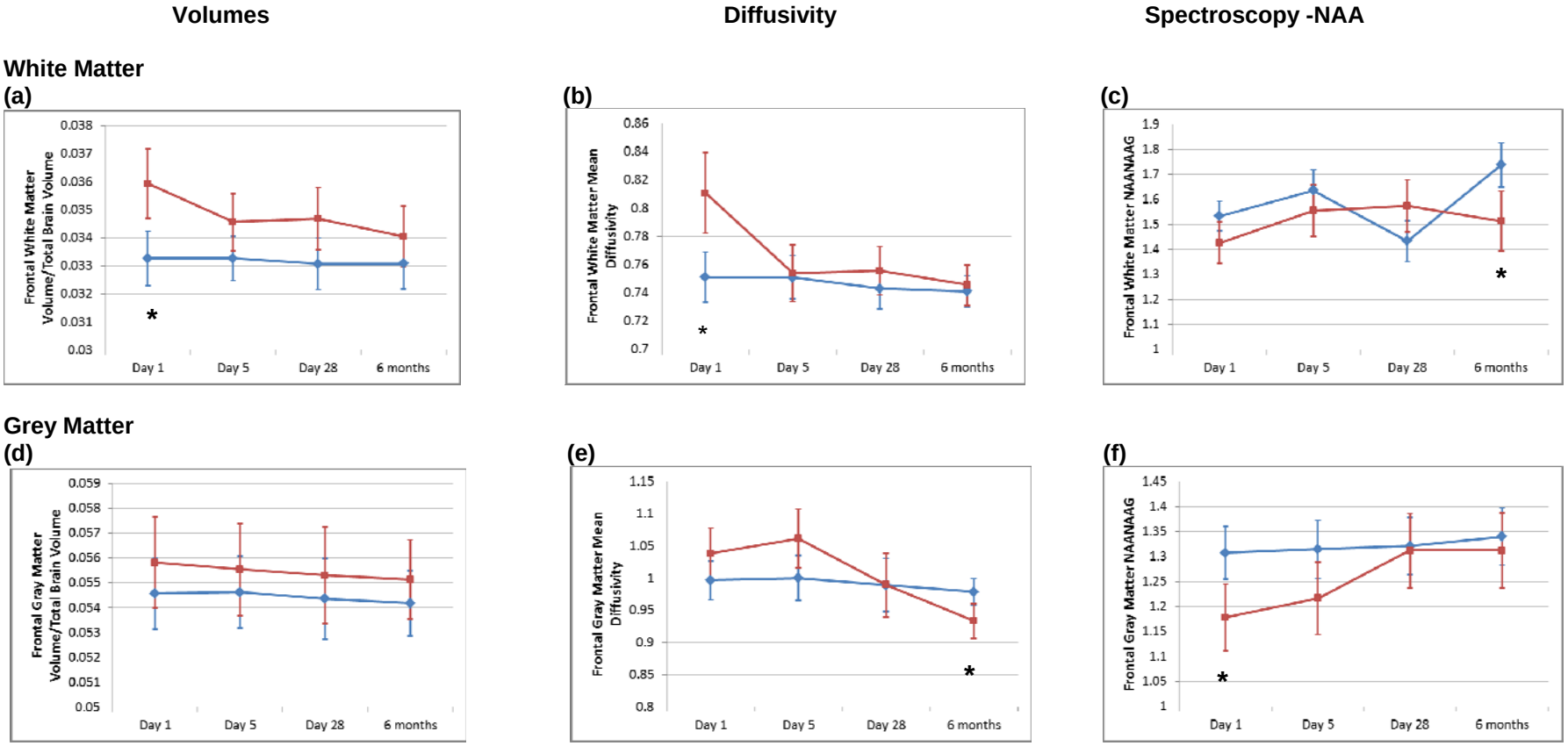

Figure legend: Data are presented as estimated means and 95% confidence intervals at each time point: (a) frontal lobe white matter relative volume *p=0.002; (b) frontal lobe white matter diffusivity *p<0.001; (c) frontal lobe white matter NAA *p=0.005; (d) frontal lobe grey matter relative volume; (e) frontal lobe grey matter diffusivity *p=0.013; (f) frontal lobe grey matter NAA *p=0.005. The non-DKA group is depicted in blue and the DKA group is depicted in red.

Figure 3: Mental state and cognition

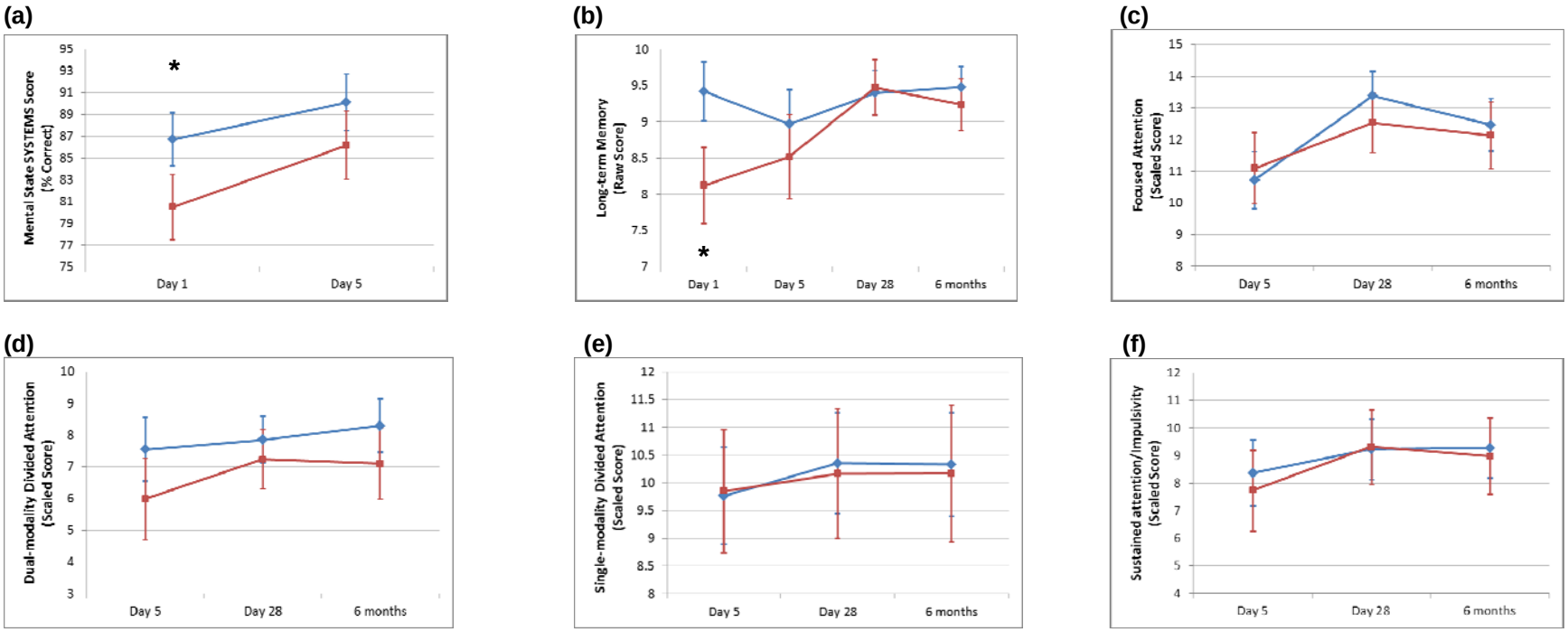

Figure legend: Data are presented as estimated means and 95% confidence intervals at each time point: (a) mental state (SYSTEMS) score *p=0.002; (b) long term memory score *p=0.002; (c) focused attention (Sky Search) score; (d) dual-modality divided attention (Sky Search DT) score; (e) single-modality divided attention (Score DT) score; (f) sustained attention/impulsivity (Walk/Don't Walk) score. The non-DKA group is depicted in blue and the DKA group is depicted in red.