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SHORT COMMUNICATION

Isolated febrile seizures are not associated with structural abnormalities of the limbic system

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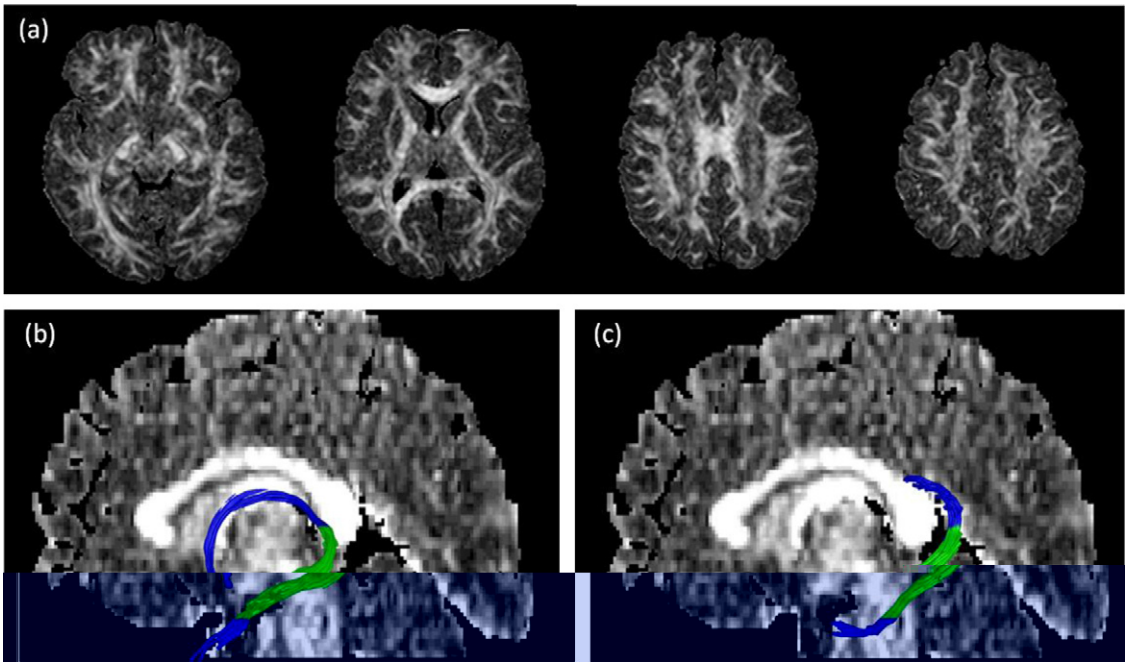

Figure 1 Axial fractional anisotropy maps and tractography of the fornix and cingulum in a subject with childhood febrile seizures axial fractional anisotropy maps (a), as well as DTI tractography of the (b) fornix and (c) cingulum of a representative subject with CFS. Quantitative analysis was performed on the segment of the tracts depicted in green. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

TLE and MTS. Based on this hypothesis, a preexisting brain abnormality creates a susceptible state that will result in the development of TLE and MTS in response to an initial precipitation event (such as a CFS) (Velisek and Moshe, 2003).

MTS is the most commonly observed structural abnormality in TLE, however, whether MTS is a cause or consequence of TLE remains controversial as does the relationship between MTS and CFS. More recently, TLE has been associated with extensive bilateral extratemporal white matter abnormalities (Seidenberg et al., 2005) including bilateral abnormalities of the fornix and cingulum as demonstrated with diffusion tensor imaging (DTI) (Concha et al., 2005). As with MTS, the basis of the association between these abnormalities and TLE remains unknown.

While uncertainty remains regarding the nature of the relationship between CFS, TLE and the structural findings observed in TLE, a better understanding of these relationships could provide insights into the pathogenesis of TLE. While most research has focused on subjects with TLE or acute studies following CFS, there has been limited investigation into structural changes in subjects who have experienced CFS but do not develop TLE with these studies focusing on the mesial temporal region. Evaluation of this group is necessary to test a number of hypotheses that have been put forward to explain the relationship between CFS and TLE. The purpose of this project was to determine whether limbic white matter and mesial temporal abnormalities seen in TLE are also present in adults who experienced CFS but did not develop epilepsy (i.e. to support or counter the hypothesis that these structural changes may predispose subjects to both TLE and CFS).

Methods

Approval of the project was obtained from the University of Alberta Health Research Ethics Board and informed consent was obtained from all participants. Subjects were recruited through posters and advertisements in local newspapers.

Subjects

Twenty-three adults who had experienced CFS but had no history of nonfebrile seizures (mean age: 23 years; range: 18—36 years; 8 male) and 21 control subjects with no history of seizures (mean age: 24 years; range: 18—31 years; 7 male) were studied with MRI. No significant difference in age was observed between the two groups (Student's t-test $p = 0.28$). For the CFS group, the median age at time of first CFS was 16 months (range: 5—36 months). The average length of first CFS was 4.8 min (range: 30 s to 30 min). Twenty-two of 23 subjects experienced seizures of less than 15 min duration. Twelve subjects experienced more than one CFS. All subjects experienced generalized tonic—clonic seizures without any ictal or postictal lateralized features. Twenty-two of 23 subjects had simple febrile seizures while one subject had a complex febrile seizure (duration greater than 15 min).

Image acquisition

All images were acquired on a Siemens Sonata 1.5 T MRI scanner (Siemens Medical Systems, South Iselin, NJ) using an eight element head coil. The study imaging protocol consisted of: axial fluid attenuated inversion recovery

Table 1 Imaging results for CFS and control subjects.

	Group	Mean	Std. dev.	Conf. int.	*p*-Value	*p*-Value (corr.)
T2 right hippocampus (ms)	Control	110.8	2.5	1.4	0.80	1
	CFS	111.0	4.0	1.2		
T2 left hippocampus (ms)	Control	111.3	4.4	1.8	0.54	1
	CFS	112.0	3.3	2.2		
Volume right hippocampus	Control	1.48×10^{-3}	2.2×10^{-4}	9.4×10^{-5}	0.39	1
Corrected	CFS	1.65×10^{-3}	2.8×10^{-4}	1.1×10^{-4}		
Volume left hippocampus	Control	1.47×10^{-3}	1.6×10^{-4}	6.8×10^{-5}	0.92	1
Corrected	CFS	1.55×10^{-3}	2.4×10^{-4}	9.8×10^{-5}		
MD right hippocampus	Control	0.85	0.05	0.021	0.59	1
(10^{-3} mm^2/s)	CFS	0.85	0.02	8.2×10^{-3}		
MD left hippocampus	Control	0.85	0.07	0.030	0.39	1
(10^{-3} mm^2/s)	CFS	0.86	0.03	0.012		
FA right fornix	Control	0.51	0.02	8.6×10^{-3}	0.64	1
	CFS	0.51	0.03	0.012		
FA left fornix	Control	0.52	0.03	0.013	0.49	1
	CFS	0.52	0.02	8.2×10^{-3}		
FA right cingulum	Control	0.48	0.02	8.6×10^{-3}	0.13	0.53
	CFS	0.47	0.03	0.012		
FA left cingulum	Control	0.47	0.02	8.6×10^{-3}	0.84	1
	CFS	0.46	0.02	0.012		

Corrected hippocampal volumes ratio of hippocampal volume (mm^3)/total intracranial volume (mm^3). Conf. int. — 95% confidence intervals. *p*-Value (corr.) — Bonferroni adjusted to account for repeated measures.

(FLAIR) DTI using parallel imaging mSENSE with acceleration factor of 2 with coverage of the limbic white matter and hippocampus (slices: 32, slice thickness: 3 mm, voxel size: 2 mm × 2 mm × 3 mm, *b*: 1000 s/mm^2, TR: 8700 ms, TE: 87 ms, TI: 2200 ms, diffusion directions: 6, averages: 6, scan time: 6:59 min), coronal T2 relaxometry of hippocampus (slices: 10, slice thickness: 3 mm, voxel size: 1.2 mm × 1.2 mm × 3 mm, TR: 4430 ms, TE: 32 echoes 9.1—291.2 ms, scan time: 8:13 min) and axial T1-weighted three-dimensional magnetization-prepared rapid-acquired gradient echoes (MPRAGE) of full brain (voxel size: 1 mm × 1 mm × 1 mm, TR: 1890 ms, TE: 4.38 ms, scan time: 6:03 min).

Image analysis

Hippocampal T2 was quantified using manually placed regions of interest on two coronal slices and using a mono-exponential fit (Concha et al., 2005). Hippocampal volumes were acquired by the manual outlining of hippocampi on the 3D MPRAGE sequence by a trained rater. The manual outlining was implemented on consecutive coronal images perpendicular to the long axis of the hippocampus by using itkSNAP software package (http://www.itksnap.org). The delineation of hippocampus included the cornu ammonis, subiculum and the dentate gyrus. More detailed methods have been previously reported (Li et al., 2007). Relative hippocampal volume was calculated using the ratio of hippocampal volume to total intracranial volume. To obtain hippocampal mean diffusivity (MD), the hippocampal volume mask from the T1 weighted MPRAGE dataset was transformed to the diffusion MRI. Fractional anisotropy (FA) of the fornix and cingulum were derived from a DTI deterministic streamline tractography based approach which has been previously described (Fig. 1b and c) (Concha et al., 2005). For all analysis the right and left sided structures were analyzed separately.

Statistical analysis

Student's two sample *t*-test was used to look for significant between group differences using Bonferroni correction to account for repeated measures with a corrected *p*-value <0.05 being considered significant. Correlations between MR data and clinical variables (age and duration of first CFS) were assessed using Pearson's correlation coefficient.

Results

Right-left comparisons: No right-left asymmetry was observed for any of the imaging variables (hippocampal volume, T2 and MD and fornix and cingulum FA) in either the control or CFS groups.

Control-CFS comparisons: No significant differences were observed between CFS and control groups for any of the imaging parameters using both uncorrected or Bonferroni corrected p values (Table 1). None of the CFS demonstrated hippocampal volume or T2 outside of the normal range (2SD or controls). Comparing patients that experienced one CFS ($n = 11$) and those that experienced multiple seizures ($n = 12$) yielded no significant between group differences. None of the correlations between MR and clinical data (duration, age of first seizure) approached significance.

Discussion

The primary results of this study were that adults who had experienced childhood febrile seizures but have no history of nonfebrile seizures did not demonstrate mesial temporal or limbic white matter abnormalities as compared to controls. The question of whether CFS can cause mesial temporal abnormalities remains controversial. Transient elevation of hippocampal abnormalities have been observed acutely following febrile status epilepticus (Scott et al., 2002) with hippocampal asymmetry observed at six months (Scott et al., 2003). One study reported no hippocampal differences between subjects with prolonged and simple CFS (Tarkka et al., 2003), while another group demonstrated hippocampal abnormalities in a small series of adults who had experienced simple CFS (Auer et al., 2008). Another study of two pedigrees with familial CFS demonstrated hippocampal asymmetries in family members with and without CFS (Fernandez et al., 1998). These findings suggest that hippocampal abnormalities could have a genetic basis and result in a predisposition to CFS. The association between CFS and mesial temporal abnormalities is most convincing for prolonged CFS (VanLandingham et al., 1998). The observation that prolonged CFS often exhibit focal manifestations suggests the possibility that structural abnormalities could predispose a child to prolonged CFS as opposed to prolonged CFS causing structural abnormalities (Shinnar and Glauser, 2002). In our study we performed extensive analysis of the hippocampus looking at: volume, T2 signal and diffusivity with the CFS group not demonstrating abnormalities in any of these parameters. As only one subject in the current study experienced a prolonged seizure, our results do not exclude the possibility of structural abnormalities associated with prolonged CFS. However, our findings do suggest that simple CFS may not be associated with mesial temporal abnormalities. These findings agree with Tarkka et al. (2003) but conflict with the findings of Auer et al. (2008). The difference in findings between our results and those reported by Auer et al. (2008) is potentially explained by differences in methodology (we analyzed the hippocampus as a whole whereas Auer et al. (2008) divided the hippocampus into subregions).

While many studies have examined mesial temporal abnormalities, no previous study has looked at cerebral white matter in CFS. We have demonstrated bilateral DTI abnormalities of the fornix and cingulum in TLE patients with unilateral MTS (Concha et al., 2005). In contrast, in the current study we found no limbic white matter abnormalities in the CFS group. While not directly compared to TLE patients, the negative results observed in the current study suggests that limbic white matter abnormalities are not an independent cause of both TLE and CFS. One possible explanation for the observed difference in findings between TLE with MTS and CFS groups is that limbic white matter abnormalities could be secondary to seizures (the TLE group having a much higher number of lifetime seizures and therefore greater white matter injury). However, the demonstration of significant limbic white matter differences between TLE with and without MTS (which both have similar seizure histories) goes against this explanation (Concha et al., 2009). An intriguing alternative explanation would be that limbic white matter abnormalities are an underlying substrate that can result in TLE following an initial precipitating incident such as a CFS. Although not definitive evidence, the absence of limbic white matter abnormalities in adults with a history of CFS but no history of nonfebrile seizures is compatible with this hypothesis.

The primary limitation of this study is the relatively small sample size (23 CFS and 21 control subjects). While no measure approached significance with corrected p values, uncorrected p values were also negative with only FA of the right cingulum approaching significance ($p = 0.13$). While it is not possible to confirm the absence of hippocampal and limbic white matter abnormalities in CFS based on the small sample size, our results suggest that the incidence of structural abnormalities in isolated CFS is very low. As all but one of the subjects in the CFS group had simple febrile seizures, the negative result cannot be generalized to CFS in general. Given the assumption that complex or prolonged CFS are more likely to be associated with structural abnormalities, further research on subjects with isolated prolonged CFS would be expected to provide further insight into the relationship between childhood febrile seizures and brain structure.

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