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Evidence for brainstem network disruption in temporal lobe epilepsy and sudden unexplained death in epilepsy

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ABSTRACT

The symptoms witnessed in unexplained death in epilepsy (SUDEP) suggest a breakdown of central autonomic control. Since the brainstem plays a crucial role in autonomic control, the objectives of this study were 1. To investigate if temporal lobe epilepsy (TLE) is associated with brainstem atrophy and to characterize it using graph Analysis 2. To compare the findings with those in two probable TLESUDEP. T1 images were obtained from 17 controls, 30 TLE (16 with mesial-temporal-sclerosis (TLE-MTS) and 14 without (TLE-no)) and from 2 patients who died of SUDEP. The brainstem was extracted, warped onto a brainstem atlas and Jacobian determinants maps (JDM) calculated. SPM8 was used to compare the JDMs at the group level, z-score maps were calculated for single subject analysis. Brainstem regions encompassing autonomic structures were identified based on macroscopic landmarks and mean z-scores from $5 \times 5 \times 5$ voxel cubes extracted to calculate a new measure called atrophy-similarity index (ASI) for graph analysis. TLE-MTS had volume loss in the dorsal mesencephalon. The SUDEP cases had severe and more extensive volume loss in the same region. Nodal degrees and participation coefficients were decreased and local efficiency increased in SUDEP compared to controls. TLE is associated with volume loss in brainstem regions involved in autonomic control. Structural damage in these regions might increase the risk for a fatal dysregulation during situations with increased demand such as following severe seizures.

1. Introduction

Descriptions of epilepsy patients dying unexpectedly after seizures have existed since the 19th century, but only recently has it been recognized that sudden unexplained death in epilepsy (SUDEP) is the leading cause of premature death (10-50%) in epilepsy patients (Shorvon and Tomson, 2011, Tomson et al., 2008, Ryvlin et a., 2013). The observations in patients dying of SUDEP in epilepsy monitoring units suggest that a postictal breakdown of central autonomic control characterized by a severe alteration of the respiratory and cardiac function that leads to a generalized EEG suppression and finally to a terminal cardio-respiratory arrest might play a major role (Bateman et al. 2010, Seyal et al., 2012). This raises the question to what degree epilepsy associated structural alterations in brain structures involved in central autonomic control could contribute to such a breakdown.

The central autonomic system can be divided into two subsystems. One is the brainstem/medulla system that responds typically to non-conscious stimuli from internal sensors, i.e., baro- and chemoreceptors, etc, and encompasses the nuclei (ncl.) of the solitary tract, ambiguous ncl, dorsal vagal ncl, pre-Bötzinger/Bötzinger complex, parabrachial and Kölliker-Fuse ncl, the rostral and caudal ventral respiratory group, the serotoninergic raphe and the mesencephalic periaqueductal gray/reticular formation. The other is the cortical and subcortical autonomic system which responds conscious stimuli, e.g., fear or anxiety caused by external stimuli, by initiating the appropriate response via the brainstem/medulla system. Its main components are the hypothalamus and thalamus, particularly the ventral posterior medial and lateral nuclei and the mesial prefrontal cortex and the insular cortex. Animal studies but also human clinical studies suggest that the posterior insula might play a prominent role in cortical and cortical/brainstem autonomic integration (Nagai et al., 2010).

The progress in quantitative image analyses in recent years has led to the insight that even well defined epilepsy types, e.g., temporal lobe epilepsy (TLE) with mesial temporal sclerosis (MTS), are associated with brain structural abnormalities beyond the epileptogenic focus that encompass remote but anatomically connected cortical and subcortical regions and most importantly regions belonging to the central autonomic system, e.g. prefrontal mesial cortex, insula (Scanlon et al., 2013; Mueller et al., 2009; Bernhardt et al., 2008). To our knowledge there is no study that investigated if there are also structural abnormalities in brainstem structures in TLE. The first objective of this study was

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therefore to investigate if TLE with (TLE-MTS) and without MTS (TLE-no) is associated with volume losses in the brainstem and to compare the findings in these two groups with those in two TLE patients who had been studied with the same MR protocol but had later died under circumstances consistent with SUDEP. It was hypothesized that a subset of TLE-MTS and TLE-no patients would have regional brainstem atrophy as would the two SUDEP patients but that the atrophic changes in the latter would be more severe.

The fact that abnormalities in the cortical autonomic control system are apparent at the level of group analyses indicates that they are probably fairly common at the single subject level. This suggests that structural abnormalities within the autonomic control system per se are eventually not enough to cause serious disturbances of the autonomic control but that they need to fulfill very specific characteristics, e.g., to be particularly severe or to encompass very specific regions, to become critical. The second objective was therefore to use graph analysis and a new measure, the atrophy similarity index (cf. Methods for details) that was designed to capture differences in the severity and the spatial extent of atrophic changes to further characterize brainstem volume losses in TLE and SUDEP TLE. It was hypothesized that SUDEP TLE patients would have a different pattern of graph analytical abnormalities than TLE-MTS or TLE-no that would be consistent with a reduced interaction between atrophic brain regions.

2. Methods

2.1. Study population

The committees of human research at the University of California San Francisco (UCSF), California Pacific Medical Center, San Francisco (CPMC) and VA Medical Center, San Francisco approved the study, and written informed consent was obtained from each subject according to the Declaration of Helsinki. The study population consisted of 49 subjects. Seventeen were controls (mean age: 39.0 ± 13.9 years, female/male: 11/6, no current neurological or other condition affecting brain function or structure, no history of epilepsy or other neurological or psychiatric diseases, normal MRI reads by a board certified neuroradiologist). Sixteen were patients suffering from TLE with mesial temporal seizure origin and ipsilateral mesial-temporal sclerosis (TLE-MTS) (mean age: 41.1 ± 11.0 years, female/male: 8/8, left/right/bilateral onset: 10/5/1, mean age at onset: 7.9 ± 6.6 years, mean epilepsy duration: 33.1 ± 12.3 years) and 14 were patients suffering from TLE with unilateral mesial-temporal seizure origin and normal MRI (TLE-no) (mean age: 34.6 ± 11.4 years, female/male: 10/4, left/right onset: 9/5, mean age at onset: 23.3 ± 11.6 years, mean epilepsy duration: 12.1 ± 9.7 years). Finally, there were two TLE patients who later died under circumstances consistent with probable SUDEP. One of them was a 48 years old male TLE-no patient (bilateral onset, age at onset 40 years, duration 8 years), and the other one a 39 years old male TLE-MTS patient (left onset, age at onset 25 years, duration 14 years). The identification of the epileptogenic focus was based on seizure semiology and prolonged ictal and interictal Video/EEG/Telemetry (VET) in all patients. The presence/absence of MTS in TLE was based on a visual inspection of a T2 weighted high resolution image of the hippocampal formation and confirmed by subfield volumetry (Mueller et al., 2009). None of patient's MRI showed other lesions besides the MTS. The two epilepsy groups and the controls did not differ in age. TLE-MTS were significantly younger at onset and had longer duration of their epilepsy than TLE-no ($p < 0.05$). All patients reported having been seizure free for at least 24 h before the 4T study.

2.2. MRI acquisition

All studies were performed on a Bruker MedSpec 4T system controlled by a Siemens Trio™ console and equipped with a U.S.A. instruments eight channel array coil. The following sequences, which were part of a larger research imaging and spectroscopy protocol, were acquired: 1) T1-weighted whole brain gradient echo MRI TR/TE/TI = 2300/3/950 ms, 1.0 × 1.0 × 1.0 mm^3 resolution, acquisition time: 5.1 min. 2) 3D T2-weighted turbo spin-echo sequence, TR/TE = 3500/356 ms, 1.0 × 1.0 × 1.0 mm^3 resolution (for calculation of intracranial volume), acquisition time: 3.4 min. 3) high resolution T2 weighted fast spin echo sequence for hippocampal subfield volumetry (TR/TE: 3500/19 ms, 0.4 × 0.4 mm in plane resolution, 2 mm slice thickness, 24 interleaved slices, angulated perpendicular to the long axis of the hippocampal formation, acquisition time: 7.30 min. Total acquisition time for structural MRIs: ~20 min.

2.3. Image Processing and Voxel-Based Group comparisons

The processing/analysis procedures are depicted as a flow chart in Supplementary Fig. 1. The T1 images were processed in Freesurfer 5.1 (http://surfer.nmr.mgh.harvard.edu). The labels cerebellum gray and white, brainstem, left and right diencephalon, left and right thalamus that are produced in the Freesurfer subcortical segmentation stream (Fischl et al., 2002) were used to generate a brainstem mask for each subject that encompassed the brainstem, the cerebellum and the diencephalon including the thalami. This mask was used to generate a T1 brainstem image by extracting the corresponding regions from each subject's gray scale image. The template building routine from DARTEL toolbox (Ashburner et al., 2007) as implemented in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) and running Matlab (version 8.1.0.604) was used to generate a brainstem template from the T1 brainstem images of the control group. Each subjects T1 brainstem image was warped onto this template using the high dimensional warping algorithm of the DARTEL toolbox and the Jacobian determinants calculated from the resulting transformation matrices. The resulting Jacobian determinant maps (JDM) were masked to suppress the background and corrected for differences of head size using the intracranial volume that had been calculated from the skull-stripped T2 images.

2.4. Single subject analyses

The JDM were converted into z-score maps using the following formula: z-score = (JDMsubject – mean JDMcontrols/standard deviation of JDMcontrols). The resulting z-score maps were processed in two ways:

A Voxel-wise atrophy whole brainstem analysis: Atrophy maps were generated for each subject by thresholding them at z-score ≤ −2. Subjects with more than 504 subthreshold voxels (504 = mean subthreshold voxelscontrols + 2 standard deviation controls) were considered to have pathological z-score maps (Crawford and Howell, 1998).

B Definition of autonomic system for graph analysis: A 5 × 5 × 5 voxel grid was overlaid on each z-score map to divide it into equally sized cubes. Brainstem nuclei/regions involved in the autonomic control are not distinguishable on in vivo 4T T1. Therefore macroscopic landmarks based on the atlas of histological and 9.4 T high resolution sections of the brainstem/medulla by Naidich et al. (2009) were used to identify altogether 16 cubes of interest (COI) with a high probability to encompass the following structures: COIs 1–4: Caudal Autonomic region with a ventral (CAV) and a dorsal (CAD) aspect that contain the caudal parts of ambiguous, solitary tract and dorsal vagal nuclei. COIs 5,6: Caudal Respiratory (CR) region that contains the pre-Bötzinger and Bötzinger Complex. COIs 7,8: Rostral Autonomic (RA) region that encompasses the rostral parts of the ambiguous nucleus. COIs 9–12: Rostral Respiratory (RR) region which encompass the parabrachial and Kölliker-Fuse nuclei and a section of the reticular formation (lateral tegmental field) and COIs 13–16: Periaqueductal gray (Periaqc) that encompasses the periaqueductal gray and parts of the