Epilepsy & Behavior Case Reports 10 (2018) 86–91

Contents lists available at ScienceDirect

Epilepsy & Behavior Case Reports

journal homepage: www.elsevier.com/locate/ebcr

Case Report

Working memory deficit in drug-resistant epilepsy with an amygdala lesion

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ARTICLE INFO

Article history:
Received 28 March 2018
Received in revised form 22 June 2018
Accepted 6 July 2018
Available online 17 July 2018

Keywords:
Amygdala lesion
Temporal lobe epilepsy
Cognitive functions
Working memory

ABSTRACT

This study compared temporal lobe epilepsy (TLE) patients with amygdala lesion (AL) without hippocampal sclerosis (HS) (TLE-AL) with patients with TLE and HS without AL (TLE-HS). Both subtypes of TLE arose from the right hemisphere.

The TLE-AL group exhibited a lower Working Memory Index (WMI) on the Wechsler Adult Intelligence Scale, third edition (WAIS-III), indicating that the amygdala in the right hemisphere is involved in memory-related function. [18F]fluorodeoxyglucose positron emission topography (FDG-PET) showed glucose hypometabolism limited to the right uncus for the TLE-AL group.

The results suggest the importance of considering cognitive functions in the non-dominant hemisphere to prevent impairment after surgery.

1. Introduction

The most common cause of drug-resistant mesial temporal lobe epilepsy (TLE) is hippocampal sclerosis (HS) [1–3]. Epileptogenesus originating from the pathological hippocampus, however, often involve the amygdala that is anatomically adjacent to the hippocampus [4]. For example, Graebenitz and his colleague reported that epileptiform network of TLE with HS involved the amygdala [5]. In some cases, amygdala sclerosis coexists with HS in patients with TLE [6]. Wieser, furthermore, reported a patient with amygdala epilepsy without HS [7]. Recent reports have indicated that enlargement of the amygdala without HS can be epileptogenic [8–10].

As for the characteristics of seizures, both similarities and differences between the TLE with amygdala lesion (AL) without HS (TLE-AL) and TLE with HS without AL (TLE-HS) are more or less understood [8, 11]. Reports regarding interictal conditions also exist. Tebartz van Elst and his colleagues reported an association between bilateral amygdala enlargement with affective disorders in some patients with TLE [12]. Some researchers reported memory impairment associated with HS in TLE-HS [13, 14]. To our knowledge, however, neither systematic investigation on the effects of unilateral amygdala lesion nor report that deals with effects of AL on cognitive functions in TLE-AL exists. Hence, functional influence of both TLE-AL and TLE-HS are still to be delineated, particularly in the interictal state.

The main function of hippocampus is memory formation. The main function of the amygdala, by contrast, is considered to be related to emotion and drives, and not memory itself. The amygdala plays a role in memory enhancement in emotional conditions. The amygdala is also related to olfaction and autonomic control mediated by connection with the olfactory bulb, hypothalamic and brainstem centers [15–19]. A lesion in the hippocampus, therefore, is considered to be associated with memory impairment. As for lesions in the amygdala, however, no report so far demonstrated a clear implication of memory impairment.

In the present study, we intended to clarify the effects of the right amygdala lesion on higher order functions and explore whether the amygdala lesion causes deficits of cognitive function among drug-resistant TLE-AL in comparison with TLE-HS. The right hemisphere typically tends to be regarded as not crucial in language-related functions because the left hemisphere is usually dominant for speech. Understanding the functions and roles of such brain areas as the amygdala and hippocampus in the non-dominant hemisphere, however, is still incomplete, and thus, this study also explores the aspect of cognitive functions in the non-dominant hemisphere.

2. Material and methods

2.1. Subjects

Among patients with drug-resistant TLE in an epilepsy surgery program at National Epilepsy Center, Shizuoka Institute of Epilepsy and Neurological Disorders between 2007 and 2013, 148 patients were

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https://doi.org/10.1016/j.ebcr.2018.07.003

diagnosed with mesial temporal lobe epilepsy in the right hemisphere based on multimodal preoperative evaluation. Before admission to the surgery program, psychiatrists saw each patient to confirm that the patient had no psychiatric contraindications to epilepsy surgery.

The studies used for the diagnosis of TLE included ictal and interictal scalp video-EEG, 1.5-Tesla MR images, and Iomazenil-SPECT. Iomazenil-SPECT was included as a standard clinical procedure based on its usefulness [20, 21]. Video-EEG confirmed clinical features of the seizures with impaired awareness within the category suggestive of mesial TLE [22]. Interictal Iomazenil-SPECT showed decreased perfusion unilaterally in the right mesial temporal area compared with the left.

The 148 consecutive patients were then screened based on inclusion criteria for amygdala lesion (AL) without hippocampal sclerosis (TLE-AL) and for hippocampal sclerosis (HS) without AL (TLE-HS). They were required to be left hemisphere language-dominant confirmed by intracarotid-propofol (Wada) test, to be between 15 and 50 years old at surgery, to be a native speaker of Japanese, to have no neurological or psychiatric disorders other than epilepsy, and to possess preoperative Full Scale IQ > 80. In the MRI evaluation for TLE-AL, we confirmed that fluid attenuated inversion recovery (FLAIR) images showed no hyperintensity and volume increase in the right amygdala compared with the left, and no difference in the right and the left hippocampus in terms of signal intensity and volume. In MRI evaluation for TLE-HS, we confirmed that FLAIR images showed hyperintensity and volume decrease in the right hippocampus compared with the left without any abnormality in bilateral amygdalae. The inclusion criteria found 12 TLE-AL patients and the first 12 consecutive TLE-HS patients.

All patients were taking anti-seizure drugs at the time of evaluation. Of the twelve patients in the TLE-AL group, three were treated with monotherapy consisting of carbamazepine, one with levetiracetam, and the remaining eight with 2 or 3 drugs, including carbamazepine, valproate, levetiracetam, zonisamide, phenobarbital, gabapentin, or clobazam. All twelve patients in the TLE-HS group were treated with more than 2 drugs out of the drugs mentioned above, at the time of evaluation.

In statistical imaging studies of [18F]-fluorodeoxyglucose positron emission tomography (FDG-PET), 19 right-handed healthy volunteers (mean age ± SD, 34.1 ± 4.6; 9 females) recruited for the present study also participated as normal controls.

The present study was approved by the Ethics Committee of National Epilepsy Center, Shizuoka Institute of Epilepsy and Neurological Disorders, and written informed consent was obtained from all participants.

2.2. Neuropsychological and imaging studies

The TLE patients, both with AL without HS (TLE-AL) and with HS without AL (TLE-HS), took the Japanese version of two standardized neuropsychological tests, Wechsler Adult Intelligent Scale, third edition (WAIS-III) [23] and Wechsler Memory Scale, revised (WMS-R) [24]. The WAIS-III, designed to evaluate global cognitive functioning and specific domains of cognition, provides four index scores. The WMS-R provides four memory-related index scores. Since these evaluations were conducted as part of presurgical examination, the objective was cross-sectional study at a specific point in time, between 3 and 6 months before surgery.

Eight out of 12 subjects in each patient group who gave informed consent for PET study and 19 normal controls underwent 18F-FDG PET by using Discovery ST Elite PET scanner (GE Healthcare Japan, Tokyo). They received an intravenous injection of 3.7 MBq/kg 18F-FDG and were scanned after a 60-min bed rest. The patients had no seizure at least for 12 h before the PET scan. Positron count was acquired in 128 × 128 matrix (5.47 × 5.47 × 3.27 mm) and reconstructed in VUE Point Plus (3D-OSEM) procedure (GE Healthcare Japan) with post Gaussian filter of 2.19 mm. Slice thickness of reconstructed images was 3.27 mm with FOV of 256 mm. Anatomical T1-weighted MR images of each subject were acquired on a 1.5 Tesla Signa HDxt Optima Edition Twin Speed system (GE Healthcare Corporate) with 3D fast spoiled gradient-recall (FSPGR) sequence (TR = 7.856 ms, TE = 2.996 ms, FOV = 24.0 cm, 1.3 mm slice thickness, 124 slices). Before group analysis, an experienced radiologist (KM) inspected the FDG-PET images of each patient and confirmed unilateral glucose hypometabolism in the right temporal area. The inspection of the FDG-PET and anatomical MR images of each normal control found no abnormality.

2.3. Analysis

2.3.1. Demographic and neuropsychological data

Demographic data of the TLE-AL and TLE-HS groups were compared by using t-test and Fisher's exact test. Cognitive performance of the patients was compared between the TLE-AL and TLE-HS groups by using eight index scores obtained from WAIS-III and WMS-R. The Kruskal–Wallis test was used to test the null hypothesis between groups. For multiple comparisons, p-value adjusted by the Bonferroni method ($p < 0.00625$) was considered statistically significant. Subtest scaled scores of WAIS-III and WMS-R were also compared between the two groups. Analyses were conducted with SPSS version 19.0 (IBM).

2.3.2. Imaging data

We evaluated differences in glucose metabolism between TLE-AL group and the normal control (NC) group between TLE-HS group and NC group, and between TLE-AL group and TLE-HS group, using parametric mapping software SPM 8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). Individual FDG-PET images were co-registered with his/her structural T1-weighted MR images, spatially normalized to the Montreal Neurological Institute (MNI) space, and smoothed with an 8-mm full-width and half maximal (FWHM) Gaussian kernel. Whole brain voxel-wise group comparison was conducted for the TLE-AL vs. the NC and the TLE-HS vs. the NC. A two-sample t-test was performed to find regions with glucose hypometabolism. Statistically significant clusters corrected for Familywise Error (FWE) (T value > 5.45; voxel per cluster >64 for TLE-AL vs. NC, T value > 5.48; voxel per cluster >60 for TLE-HS vs. NC) ($p < 0.05$, FWE corrected) were anatomically referenced by using Talairach Client [25], and Anatomy Toolbox version 2.1 implemented in SPM 8 [26].

2.3.3. Correlation between cognitive and imaging data

To investigate the relation between cognitive test results and localized glucose hypometabolism in each patient, we evaluated the severity of regional glucose hypometabolism of each patient using three-dimensional stereotactic surface projections software (3D-SSP, AZE, Tokyo) [27]. The same NC data that we used in SPM 8 analysis were used as the normal database for 3D-SSP. After spatial normalization, each patient's radiotracer uptake at each 3D pixel was compared with the corresponding 3D pixel in the NCNormal database. The comparison was quantified as numerical Z-score:

$$\text{Z score}\,(x,y,z) = (\text{Normal mean}\,(x,y,z) - \text{Patient}\,(x,y,z))/\text{Normal SD}\,(x,y,z).$$

SD = standard deviation

Extent of glucose hypometabolism in each gyrus was analyzed using a stereotactic extraction estimation method (SEE) [28], which automatically yielded the ratio of 3D pixels of glucose hypometabolism within each classified anatomical structure. For the classification of anatomical structures, SEE applied the definition of Talairach Daemon database [25]. SEE also showed the severity of decreased glucose metabolism in each anatomical structure by means of Z-score. We defined a severity score of each patient as his/her Z-score multiplied by his/her extent ratio of 3D pixels.

Pearson's correlation coefficient was used to assess for association between index scores and severity scores after the test of normality