Annals of Diagnostic Pathology 30 (2017) 12–16

Contents lists available at ScienceDirect

Annals of Diagnostic Pathology

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

Review Article

Chronic inflammation in refractory hippocampal sclerosis-related temporal lobe epilepsy

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ARTICLE INFO

Keywords:
Hippocampal sclerosis
Chronic inflammation
Temporal lobe epilepsy

ABSTRACT

Emerging evidence suggests chronic inflammation may play a role in hippocampal sclerosis-associated temporal lobe epilepsy. We sought to systematically evaluate for its presence in a group of 315 patients who underwent surgery for medically-refractory epilepsy and who had hippocampal sclerosis. Upon histologic review of hematoxylin and eosin stained tissue sections, 95 (41%) cases demonstrated the presence of lymphocytes within the perivascular region and diffusely within the brain parenchyma. Those cases with chronic inflammation evident on hematoxylin and eosin staining were significantly more likely to experience a post-operative seizure recurrence than those without it ($p = 0.03$). In 9 cases of hippocampi with chronic inflammation observed on hematoxylin and eosin stained sections, there was a mixture of both T (CD3 +) and B (CD20 +) lymphocytes located around blood vessels and interspersed within the brain parenchyma and a predominance of CD4 positive T cells versus CD8 positive cells. Ten hippocampi, apparently devoid of chronic inflammation upon inspection with hematoxylin and eosin stained sections, were stained with the lymphocyte common antigen CD45. In all 10 cases, scattered lymphoid cells were observed in the brain parenchyma, suggesting some level of chronic inflammation may be present in more cases than casual inspection might suggest. This study was the first to evaluate the incidence of chronic inflammation within a large temporal lobe epilepsy population. The study findings suggest chronic inflammation may be a more common component of hippocampal sclerosis -associated temporal lobe epilepsy than previously believed.

1. Introduction

Inflammation has not historically been described as a salient feature of hippocampal sclerosis and temporal lobe epilepsy. Emerging experimental and clinical evidence, however, suggests inflammation has effects on seizures and may play a role in overall epileptogenesis [1]. However, neuropathological literature regarding inflammation in the setting of hippocampal sclerosis and temporal lobe epilepsy remains limited. While some markers of inflammation such as microglial activation have been accepted as occasional findings among those with hippocampal sclerosis-associated temporal lobe epilepsy, the presence of a chronic inflammatory infiltrate has been documented only in small series [2-4]. Chronic inflammatory cells and contusion-related damage are well recognized sequela of previous invasive seizure monitoring. This study is the first to systematically evaluate for the presence of chronic inflammation in a large surgical series of hippocampal sclerosis patients who did not have prior invasive preoperative seizure monitoring.

2. Materials and methods

Institutional review board approval was obtained prior to commencement of the study. We searched the Cleveland Clinic Department of Anatomic Pathology surgical pathology files to identify cases of hippocampal sclerosis during the period 2000–2012 inclusive. Only cases of anterior temporal lobectomy performed for treatment of drug-resistant mesial temporal lobe epilepsy were considered. Criteria for refractory temporal lobe epilepsy were adopted from the 2010 International League Against Epilepsy (ILAE) consensus statement on drug resistant epilepsy [5]. All microscopic sections were reviewed for each case to confirm the diagnosis of hippocampal sclerosis. A total of 315 patients who underwent unilateral hippocampal and temporal lobe resections were screened for study inclusion. One hundred eighty (78%) of these cases had resected amygdala tissue available for pathologic review. All cases with known prior sources of chronic neuroinflammation were excluded from study. Sources of chronic inflammation included prior neurosurgical intervention (8 cases), prior stroke (9 cases), early-life cerebrovascular insult or anoxic injury (15 cases),

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http://dx.doi.org/10.1016/j.anndiagpath.2017.05.009

coexistent intracranial tumor (7 cases), prior brain irradiation (2 cases), arterio-venous malformation (1 case), neurocutaneous disease (3 cases) and pre-operative invasive seizure monitoring (39 cases). A final cohort of 231 cases met inclusion criteria for pathologic and clinical review.

In 219 (95%) cases, the hippocampus was totally submitted, with a mean of two slides available for histologic review [range, 1–5]. The ipsilateral temporal lobe cortical tissue was totally submitted for histologic review in 70 (30%) cases with a mean of six slides in each case [range, 1–13]. Among the 180 cases with ipsilateral amygdala tissue resected, 175 (97%) cases were totally submitted with a mean of one slide available for pathologic review [range, 1–4]. Classification of hippocampal sclerosis and focal cortical dysplasia were made using criteria outlined by the International League Against Epilepsy (ILAE) group [6,7].

A small sampling of nine cases of hippocampi with chronic inflammation observed on hematoxylin and eosin stained sections were further evaluated with antibodies against CD3 (prediluted; Ventana, Tucson, AZ), CD4 (prediluted; Ventana), CD8 (1:10 dilution; Biogenex, Fremont, CA) and CD20 (1:200 dilution; DAKO, Carpinteria, CA). Hippocampal sections from ten cases devoid of chronic inflammation upon inspection of hematoxylin and eosin stained sections were further stained with the pan-lymphocyte marker CD45 (1:100 dilution; DAKO, Carpinteria, CA).

Pre-operative patient data and post-operative outcomes were obtained via retrospective review of the medical record with the most recent data retrieval occurring in January 2016. Preoperative characteristics included the following: gender, surgical resection laterality, documented epilepsy risk factors, age of epilepsy onset, age at epilepsy surgery, and preoperative epilepsy duration. Post-operative measures included seizure recurrence, duration of post-operative seizure freedom, and percentage of individuals remaining free of disabling seizures at last clinical follow up. First post-operative seizure was defined per the definition used by Jehi et al. 2010, the first seizure occurring beyond the acute post-operative phase (> 7 days) [8]. Simple partial seizures (e.g. aura) alone were not considered a recurrence. Statistical analysis of all quantitative variables was performed using Fisher's exact test for independence with a significance level of $p \leq 0.05$.

3. Results

Gender and side of surgical resection were evenly represented within the study group with 101 (44%) males and 115 (50%) right-sided resections. Onset of habitual seizures occurred at an average age of 13 ± 12 [mean ± SD] years, with a mean preoperative duration of epilepsy of 24 ± 15 [mean ± SD] years. The average age at epilepsy surgery was 37 ± 15 [mean ± SD] years. One hundred seventy-eight (77%) cases carried a documented epilepsy risk factor including 35 (15%) with prior head trauma, 38 (17%) with prior central nervous system infection, 30 (13%) with first degree family history of epilepsy, and 83 (36%) with a history of childhood febrile seizures prior to onset of their habitual seizures. Clinical follow-up was available for all cases with a mean duration of postoperative follow-up of 13 ± 9 years [mean ± SD]. Ninety-seven (42%) subjects experienced a post-operative seizure recurrence. Among those subjects with seizure recurrence, the mean time to recurrence was 28 ± 23 months [mean ± SD]. Those individuals with evidence of chronic inflammation, as determined on routine analysis, were significantly more likely to experience a post-operative seizure recurrence than those without evidence on hematoxylin and eosin staining ($p = 0.03$). At final available clinic follow-up, 171 subjects (74%) were without disabling habitual seizures. A small minority required subsequent surgery for ongoing seizures, 3 (1%) cases. Clinicopathologic information is summarized in Table 1.

Ninety-seven cases (42%) demonstrated neuronal loss limited to the CA1, CA3 and CA4 hippocampal regions, otherwise known as the classic variant of hippocampal sclerosis (ILAE subtype Ia) (Fig. 1). One hundred eight cases (47%) demonstrated severe neuronal loss throughout the hippocampus, consistent with the severe phenotype (ILAE subtype Ib). A minority of hippocampal specimens demonstrated limited neuronal loss with 24 (10%) cases demonstrating a predilection for neuron loss within the CA1 region (ILAE subtype II). Two cases

Table 1
Population and pathologic descriptions.

	N (%)
Variable	
Final cohort	231 (100%)
Male gender	101 (44%)
Right laterality resection	115 (50%)
Historical epilepsy risk factor	178 (77%)
Prior head trauma	35 (15%)
Prior central nervous system infection	38 (17%)
Family history epilepsy	30 (13%)
Childhood febrile seizures	83 (36%)
Post-operative seizure recurrence	97 (42%)
Free from disabling seizures	171 (74%)
Reoperation	3 (1%)
Pathology variable	
Chronic inflammation	94 (41%)
Lymphocytes in hippocampus	25 (11%)
Lymphocytes in temporal lobe	50 (22%)
Lymphocytes in amygdala	46 (26%)
ILAE hippocampal sclerosis subtype	
Ia	97 (42%)
Ib	108 (47%)
II	24 (10%)
III	2 (1%)
Focal cortical dysplasia	187 (81%)
ILAE focal cortical dysplasia subtype	
Ia	5 (3%)
1b	79 (42%)
1c	102 (55%)
2a	0 (0%)
2b	1 (0.5%)
Perivascular white matter atrophy	182 (79%)
Vascular sclerosis	109 (47%)
Sub-pial gliosis	219 (95%)
Meningeal fibrosis	23 (10%)
Continuous variable	Mean [SD]
Age seizure onset (years)	13 [12]
Age at epilepsy surgery (years)	37 [15]
Epilepsy duration (years)	24 [15]
Duration post-operative follow-up (years)	13 [9]
Duration post-operative seizure freedom (months)	28 [23]

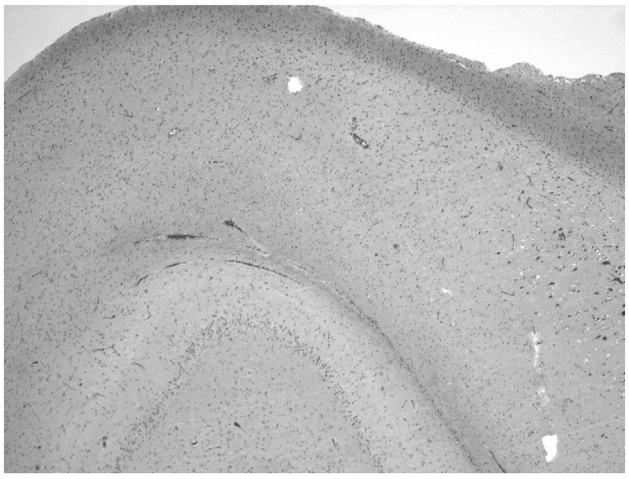

Fig. 1. Low magnification view of the hippocampus showing marked loss of neurons within the CA1 or Sommer section region (top center and left) as compared with the CA2 region (right). The patient also had a marked loss of neurons in the CA4 or endplate region and CA3 region, consistent with the classical subtype of hippocampal sclerosis (hematoxylin and eosin, original magnification 50 ×).