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Hamartia in hippocampal sclerosis-associated mesial temporal lobe epilepsy

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ABSTRACT

Hamartia are small collections of rounded glioneuronal cells that are thought to be due to aberrant cell migration. Their presence has been recognized in association with mesial temporal lobe epilepsy; their prevalence among cases of hippocampal sclerosis (HS) and any potential association with patient demographics and outcomes is unknown. This study examines hamartia in a series of 292 patients with pathologically confirmed HS. Medical records were reviewed for pertinent patient clinical information (follow-up mean 5 years). Hamartia were identified in 96 cases (33%) and were seen primarily in the amygdala (n = 88) and less commonly in the hippocampus (n = 10) and temporal lobe (n = 4). A statistically significant relationship was found between the presence of hamartia and male gender, younger age of seizure onset, and history of childhood febrile seizures and developmental delay. It is unclear if these associations represent a real association or are a result of the underlying pathologies related to chronic epilepsy. At follow-up, there were no significant differences between patients who had hamartia and those who lacked this finding. Hamartia were observed in all subtypes of HS and there was a significant difference found in subtype distribution as well as proportion of cases between subtypes, but no association with any specific subtype overall. The presence of hamartia was not associated with the coexistence of focal cortical dysplasia or any specific histologic pattern of dysplasia. Hamartia are a common concomitant finding in HS and indicates evidence of aberrant cell migration in the hippocampal and parahippocampal regions in these patients.

1. Introduction

The pathologic substrates underlying pharmacoresistent focal epilepsy are well established and most commonly include hippocampal sclerosis, focal cortical dysplasia, tumors, and remote ischemic events/infarcts [1,2]. Of these, hippocampal sclerosis (HS) is the most common neuropathological finding in surgical candidates for refractory mesial temporal lobe epilepsy. The incidence of HS in epilepsy ranges from 33.6%–66% in surgical series and 30–45% in post-mortem series in patients with epilepsy syndromes [3-6].

Abnormalities of the microarchitecture of the cortex and white matter, referred to as microdysgenesis, may often coexist with HS. Features of microdysgenesis are subtle findings with unknown significance that have been reported with increased frequency in brains of epilepsy patients [7]. Four features that have been described include marked clustering of neurons throughout cortical layers II-XI, perivascular clustering of oligodendrocytes in the white matter, heterotopic neurons in the deep white matter, and glioneuronal hamartia. Hamartia are composed of foci containing mature neuronal and glial elements, resembling oligodendroglial-like cells. Previous studies have reported the frequency of these lesions in 14.8–17% of mesial temporal lobe epilepsy brains [7,8].

Although hamartia are a known neuropathological feature associated with epilepsy, no previous studies report the prevalence of this lesion in patients with HS. We present a review of 292 cases to determine the frequency of hamartia in the brains of patients with HS who have undergone surgical resection.

2. Materials and methods

Institutional Review Board (IRB) approval was obtained prior to commencement of the study. The surgical pathology files were searched between 2000 and 2012 for cases diagnosed as HS in patients who underwent surgical resection for pharmacoresistent epilepsy. Only patients who underwent anterior temporal lobectomy accompanied by resection of the ipsilateral hippocampus were included for study (N = 292). Two hundred and thirty (79%) of those patients also underwent excision of the amygdala. Criteria for medically refractory temporal lobe epilepsy were defined in the 2010 International League Against Epilepsy (ILAE) consensus statement on drug resistant epilepsy [9].

For each case, all available microscopic sections were reviewed to

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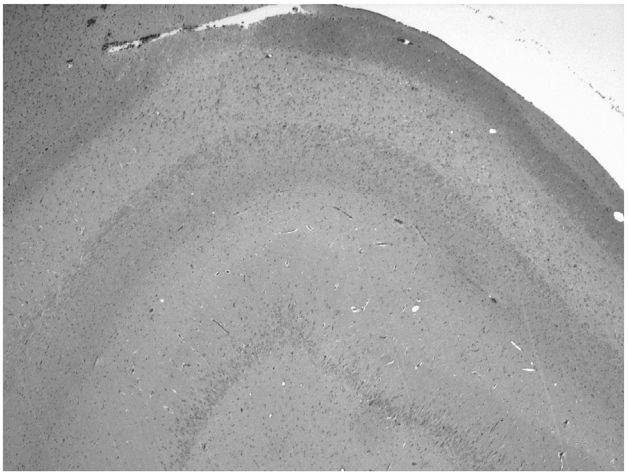

Fig. 1. Hippocampal section showing marked loss of neurons in the CA1 or Sommer sector region, consistent with hippocampal sclerosis; the patient had ILAE type Ia or classical type (hematoxylin and eosin, original magnification 50 ×).

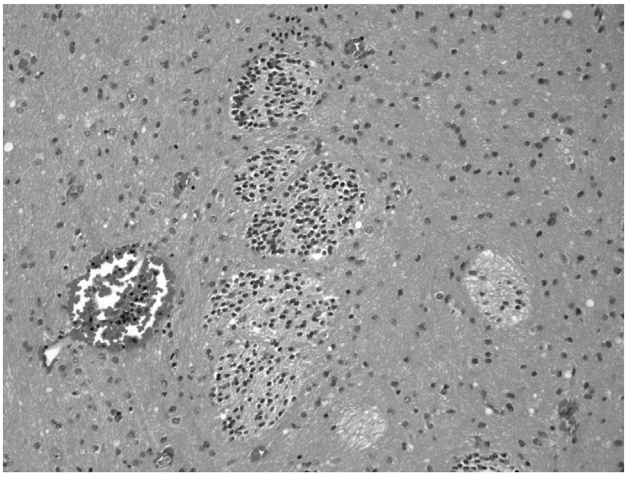

Fig. 2. Multiple small amygdalar hamartia marked by collections of rounded cells with scant cytoplasm and pericellular clearing (hematoxylin and eosin, original magnification 200 ×).

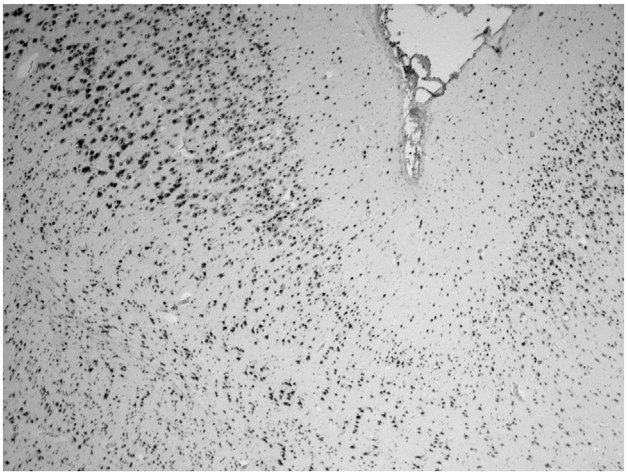

Fig. 3. Neu N immunostaining highlighting a focally underdeveloped cortical layer II and increased positive staining neuronal cells in the molecular layer (cortical layer I), consistent with focal cortical dysplasia (original magnification 50 ×).

confirm a diagnosis of hippocampal sclerosis and to subtype the hippocampal sclerosis, per ILAE guidelines [10]. Briefly, Type 1 HS refers to severe neuronal cell loss and gliosis predominantly in CA1 and CA4 regions (Fig. 1), while Type 2 and 3 show neuronal loss predominantly in CA1 and CA4, respectively. Of the 292 cases available for review, 279 (96%) hippocampal specimens were totally submitted for histologic analysis; each case had a mean of 2 slides available for review (range 1–6). Eighty (27%) of the adjacent temporal lobe specimen were totally submitted for histologic analysis; each case had a mean of 5 slides for review (range 1–13). Of the submitted amygdala specimens, 223 (76%) were totally submitted for histologic review; each case had a mean 1 slide for review (range 1–2). Cases were reviewed for evidence of concomitant hamartia, as defined by Yachnis, et al. [11]. To summarize briefly, hamartia are described by Yachnis et al. as poorly circumscribed cell clusters containing mature neurons with a random orientation and small cells with circular, hyperchromatic nuclei and scant cytoplasm (Fig. 2). Additionally, evidence of adjacent focal cortical dysplasia as outline by the ILAE was also noted when present and resemblance of observed patterns were categorized according to defined ILAE type I and II patterns [12] (Fig. 3), although technically, all cases of focal cortical dysplasia associated with hippocampal sclerosis are categorized as Type IIIa dysplasias in the ILAE schema.

Medical records were reviewed to obtain information regarding patient demographics, relevant past medical history, seizure history and postoperative seizure outcomes. All statistical analysis was performed using IBM SPSS Statistics for Windows, version 24.0 (Released 2016. Armonk, NY: IBM Corp.). Comparison of all categorical variables among study sub-groups was performed via contingency table analysis. Independence of variables was determined through the Fisher's exact test. Comparison of all continuous variables among study sub-groups was performed through comparison of means using independent samples t-testing. Post-hoc analysis involved pairwise comparisons using the z test of two proportions with a Bonferroni correction addressing multiple comparisons. Data are mean ± standard deviation, unless otherwise stated. For all analyses, differences were deemed significant at the 5% level ($p \leq 0.05$).

3. Results

The historical features and postoperative status of the patient cohort are outlined in Table 1. Overall, the cohort was composed of 55% females, with a mean age of seizure onset of 12.2 years and mean age at surgery of 36.6 years. This followed a mean epilepsy duration of 24 years.

Hamartia were found to be present in 96 cases (33%), and absent in the remaining 196 cases (67%). The majority of hamartia (88 cases) were located in the amygdala with the remainder in the hippocampus ($n = 10$) and temporal lobe ($n = 4$). Male gender showed a statistically significant relationship to the presence of hamartia ($p = 0.025$). The mean age of seizure onset varied significantly between the groups with and without hamartia, which presented at 9.5 and 14 years, respectively ($p = 0.001$); thus, earlier seizure onset may be associated with the presence of hamartia. In addition, childhood febrile seizures ($p = 0.05$) and developmental delay ($p = 0.002$) were also related to the presence of hamartia. There was no statistically significant differences between the groups regarding other historical factors (Table 1). There was no significant difference between the groups regarding number of past seizures; however, epilepsy duration was statistically significant between the two groups ($p = 0.001$), with hamartia cases having a duration of 18 years compared to 27 years in the cases without hamartia.

The follow-up period for the cohort was an average of 5 ± 4 years (Table 2). Overall, 44% ($n = 129$) of cases experienced postoperative seizure recurrence after an average of 21 ± 7 months, while 71% ($n = 206$) were free from disabling seizures at last follow-up. In comparing cases with and without hamartia, there were no statistically