Epilepsy Research (2014) **108**, 1279—1285

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

Quantification of subfield pathology in hippocampal sclerosis: A systematic review and meta-analysis

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Received 28 May 2014; accepted 15 July 2014
Available online 23 July 2014

KEYWORDS
Temporal lobe epilepsy (TLE);
Neuropathology;
Mesial temporal sclerosis (MTS);
Ammon's horn sclerosis (AHS);
Neuronal density

Abstract
Background: The utility of MRI-based hippocampal subfield volumetry as a diagnostic test for hippocampal sclerosis (HS) is based on the hypothesis that specific hippocampal subfields are differentially affected in HS. While qualitative studies suggest selective involvement of certain hippocampal subfields in this condition, whether quantifiable differences exist remains unclear. Neuronal density measurement is the most widely used technique for measuring subfield pathological change in HS. Therefore, a systematic review and meta-analysis of studies reporting neuronal densities in temporal lobe epilepsy was performed in order to quantify subfield pathology in hippocampal sclerosis.
Methods: Studies were identified by searching the Medline and Embase databases using the search terms: cell count, hippocampus, and epilepsy. Of the 192 studies identified by the literature search, seven met all inclusion and exclusion criteria. Random effects meta-analyses were performed, comparing: (i) neuronal densities in control ($n = 121$) versus HS ($n = 371$) groups for subfields CA1-4; and (ii) amount of neuronal loss in HS between subfields CA1-4.
Results: Statistically significant neuronal loss was observed comparing HS to control groups in all subfields CA1-4 ($p < 0.001$ for all comparisons). Significantly greater neuronal loss was demonstrated in HS comparing CA1 versus CA2 ($p < 0.001$), CA3 ($p = 0.005$), and CA4 ($p = 0.003$). Greater pyramidal cell loss was also demonstrated in CA3 relative to the CA2 subfield ($p = 0.003$). No significant differences were identified comparing CA2 and CA4 ($p = 0.39$); or comparing CA3 and CA4 ($p = 0.64$).

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http://dx.doi.org/10.1016/j.eplepsyres.2014.07.003

Conclusions: HS is characterized by pathology in all hippocampal subfields. Quantifiable differences exist in the involvement of specific hippocampal subfields in HS. Neuronal loss is greatest in CA1, intermediate in CA3 and CA4, and least in CA2. Further studies are required to determine if this pattern can be detected using in vivo MRI.

Introduction

Hippocampal sclerosis (HS) is the most common pathological finding in drug resistant temporal lobe epilepsy (Thom et al., 2008). This entity is synonymous with mesial temporal sclerosis and Ammon's horn sclerosis, and consists of hippocampal neuronal loss and astrocytic gliosis. Identification of HS with preoperative MRI is predictive of favourable outcomes from temporal lobectomy (Berkovic et al., 1995). Reduction in MRI-measured hippocampal volume is strongly suggestive of HS as the underlying pathology (Cascino, 1995). However, recent studies have suggested that a significant proportion of pathologically proven HS cases remain undetected, even when whole hippocampal volumetry is normal (Bell et al., 2009).

High-field MRI (>1.5 T) yields images of sufficient resolution to delineate the internal architecture of the hippocampus in healthy individuals (Pan et al., 1995) and patients with HS (Eriksson et al., 2008). Preliminary studies have suggested that measurement of hippocampal subfields may detect atrophy in patients with normal whole hippocampal volumes (Mueller et al., 2009). Subfield volumetry may also allow detection of HS subtypes preoperatively (Henry et al., 2011), which might provide useful prognostic information (Blumcke et al., 2007). However, the utility of hippocampal subfield volumetry as a diagnostic test for HS is based on the hypothesis that specific hippocampal subfields are differentially involved in HS.

While qualitative analysis suggests that selective involvement of certain hippocampal subfields occurs in HS, whether quantifiable differences exist remains unclear. Qualitatively, pathologic change is most pronounced in the CA1 subfield (Sommer, 1880), while the CA2 subregion is relatively spared (Spielmeyer, 1927). Neuronal loss in hippocampal subfields can be quantified by measurement of pyramidal cell densities (Dam, 1980). However, such quantitative studies generally demonstrate significant neuronal loss in all hippocampal subfields (Babb et al., 1984; Van Paesschen et al., 1997; Thom et al., 2005); and the quantitative degree to which various hippocampal subfields are involved in HS therefore remains unclear (Wieser HG, 2004).

Due to limitations related to inadequate sample size, individual surgical series often lack statistical power to detect quantitative differences in involvement of hippocampal subfields (Andrioli et al., 2007). Therefore, a systematic review and meta-analysis of studies reporting neuronal densities in temporal lobe epilepsy was performed in order to quantify subfield pathology in hippocampal sclerosis.

Methods

This study was designed and conducted according to previously published guidelines for performing systematic reviews and meta-analyses (Moher et al., 2009). A structured screening form was used for selection of studies.

Literature search

Studies were identified by searching the Medline (1948 to present) and Embase (1974 to present) databases. The search strategy was as follows: [(cell count*.mp.) OR (exp cell count/)] AND [(hippocamp*.mp.) OR (exp hippocampus/)] AND [(epilep*.mp.) OR (exp epilepsy/)]; limited to humans. The last search was run on April 29th, 2014.

Eligibility criteria and study selection

Studies were eligible for this review if they met the following inclusion criteria: (a) both HS and control groups were studied; (b) neuronal cells in CA1-4 were identified by conventional staining techniques (hematoxylin and eosin, luxol fast blue and cresyl violet, or NeuN); (c) neuronal counts were reported as mean and standard deviation. Exclusion criteria were as follows: (a) sample size <4 in either group; (b) review articles; (c) animal studies; or (d) repeated analysis of subjects. In order to exclude the possibility of repeated analysis of subjects, only one study from a given epilepsy centre was eligible for inclusion. In this case, the study with the largest sample size in the HS group was selected. One reviewer (TS) performed the literature search, screened all studies (titles, abstracts, and full text articles), and extracted relevant data. Where inadequate quantitative data were included in the original report, corresponding authors were contacted via e-mail in an effort to obtain the relevant data.

Data collection

Data collected from each selected study included first author last name, year of publication, sample sizes of HS and control groups, neuronal counting technique employed, anatomical location of sampling from the hippocampus, and neuronal densities (mean and standard deviation) in subfields CA1-4.

Meta-analyses

Neuronal cell counts in HS versus control groups

A random effects meta-analysis comparing neuronal cell counts in HS versus control groups was conducted with Stata statistical software (Sterne JAC et al., 2011). Pooled standardized mean differences (SMDs) and 95% confidence intervals (95% CIs) were calculated comparing HS and control neuronal densities at each of the subfields CA1—4. Differences between HS and control groups were deemed