SHORT REPORT

Corpora amylacea in hippocampal sclerosis

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Abstract

Corpora amylacea have been reported in around 60% of hippocampal sclerosis specimens. The aim was to determine whether there are clinical and quantitative hippocampal MRI differences between hippocampal sclerosis with and without corpora amylacea. Corpora amylacea density was determined in 46 resected hippocampi of patients with temporal lobe epilepsy, using a three dimensional microscopical counting technique. Forty one hippocampi had hippocampal sclerosis. Twenty six of the 41 (63%) hippocampal sclerosis specimens contained corpora amylacea, which were found in highest numbers in the CA1 subregion of the hippocampus. Corpora amylacea density in the CA1 correlated inversely with the neuronal density in CA1. Hippocampal sclerosis with corpora amylacea had the same clinical and quantitative hippocampal MRI characteristics as hippocampal sclerosis without corpora amylacea, and did not affect seizure outcome after surgery adversely. In conclusion, formation of corpora amylacea seems to be a pathological response to neuronal cell loss in most hippocampal sclerosis specimens, with no clear clinical and quantitative hippocampal MRI correlates.

(*J Neurol Neurosurg Psychiatry* 1997;**63**:513–515)

Keywords: corpora amylacea; hippocampal sclerosis; epilepsy; neuronal density

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Received 27 January 1997 and in revised form 14 May 1997
Accepted 30 June 1997

Corpora amylacea are globular basophilic bodies, 10-50 μm in diameter, which may stain deeply with iodine. They are commonly seen in the subpial tissue of the brains of elderly subjects. Corpora amylacea develop in astrocytic processes and are associated with neurodegeneration.[1]

Corpora amylacea can be found in temporal lobe epilepsy in the hippocampus[2] and extrahippocampal tissue with a predilection for the temporal white matter.[2-4] MacKenzie[5] reported corpora amylacea in 15 of 40 cases of temporal lobe epilepsy, half of them with hippocampal sclerosis. Chung *et al*[2] reported hippocampal corpora amylacea in 22 of 38 (58%) hippocampal sclerosis specimens. Loiseau *et al*[4] postulated that many corpora amylacea in a patient with hippocampal sclerosis might represent a localised form of a glycogen storage disease. Clinical correlates and MRI features of hippocampal sclerosis with and without corpora amylacea have not been reported.

We have used a three dimensional cell counting technique to quantify corpora amylacea and neuronal cell densities in hippocampal neuronal and granular cell layers of patients who underwent temporal lobectomy for intractable temporal lobe epilepsy.[6] The aim was to study the presence of corpora amylacea systematically and quantitatively in a consecutive series of resected hippocampi of patients with temporal lobe epilepsy and to determine whether there are clinical and quantitative hippocampal MRI differences between hippocampal sclerosis with and without corpora amylacea.

Methods

STUDY POPULATION

Forty six patients (18 men, 28 women; median age 31, range 17-51 years) with intractable temporal lobe epilepsy who underwent anterior temporal lobe resection were included in the study. The body of the hippocampus of all of these patients was available for histopathological examination. Qualitative microscopical assessment of 41 hippocampi showed hippocampal sclerosis and five hippocampi showed mild gliotic changes confined to the end folium.[7] Six control hippocampi of people (three men, three women; median age 31, range 14-52 years) who had died from non-neurological causes were obtained at necropsy. None of the control hippocampi showed hypoxic or other neuropathological changes.

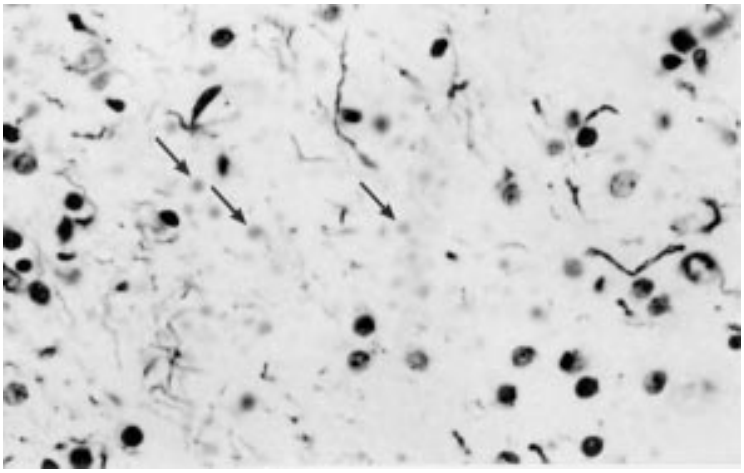
CLINICAL EVALUATION

Age at onset of habitual epilepsy, duration of epilepsy, a history of febrile convulsions and meningoencephalitis, age at the time of these events, family history of febrile convulsions and epilepsy, seizure types and description, average frequency of each seizure type during the year preceding the operation, and total number of secondary generalised seizures in their lifetime were established. In those who had a postoperative follow up of at least one year, outcome was rated as 1, no seizures or auras only, 2 >90% reduction in seizures, 3 >50% reduction

Table 1 Corpora amylacea densities in hippocampal subregions

Hippocampal subregion	*Controls (n=2; 33%)*	*Hippocampal sclerosis (n=26; 63%)*	*Endfolium sclerosis (n=2; 40%)*
CA1	288 (176–400)	17 544 (800–1 340 000)	0
CA2	0	0 (n=17)	0
CA3	0	800 (0–43 636)(n=16)	705 (0–1410)
Hilus	176 (0–352)	0 (0–181 319)	287 (0–574)
GCDG	0	0 (0–35 000)(n=25)	0

The median (range) corpora amylacea density for hippocampal subregions CA1, CA2, CA3, hilus, and granular cell layer of the dentate gyrus (GCDG) are shown for hippocampal specimens that had corpora amylacea in at least one hippocampal subregion. Corpora amylacea density is expressed in corpora amylacea/mm^3; n=number of hippocampal sclerosis specimens for which a particular hippocampal subregion was available for counting studies. In the other specimens, these regions were damaged during surgical removal. In one hippocampal sclerosis specimen, the GCDG was almost completely destroyed and technically difficult to count.



Numerous corpora amylacea in the CA1 hippocampal subregion of a patient with hippocampal sclerosis; Luxol fast blue-cresyl violet stain; magnification originally×750. The patient had a history of prolonged febrile convulsions at the age of 11 months and onset of habitual refractory left temporal lobe epilepsy associated with hippocampal sclerosis at the age of 1 year. He was operated on at the age of 27 years. He has been seizure free for more than three years after surgery. Pathological examination of the resected temporal lobe disclosed hippocampal sclerosis and numerous corpora amylacea in the hippocampus and extrahippocampal tissues. The density of corpora amylacea in the CA1 (arrows) was approximately 1 300 400/mm^3 (the highest density of the present study), in the hilus 181 319/mm^3, and none were found in the GCDG. The CA2 and CA3 regions were not available for pathological examination.

in seizures, or 4 no improvement. Clinical evaluation of patients, quantitative hippocampal MRI, and quantitative neuropathological studies were performed by the same observer.

QUANTITATIVE MRI

Presurgically, MRI based hippocampal T2 (HCT2) and volumes (HCV) were determined as described previously.[8] Mean control (SD) HCT2 was 102.4 (2.8) ms, and mean control HCV corrected for intracranial volume (SD) was 5180 (416) mm^3.

NEUROPATHOLOGY

Hippocampi were removed en bloc during surgery and were fixed immediately in formalin for one week. After fixation each specimen was sliced into 3 mm thick tissue blocks. The plane of sectioning was perpendicular to the long axis of the hippocampus. Sections of each paraffin embedded block, 5 to 7 μm thick, were stained with haematoxylin and eosin, luxol fast blue, and glial fibrillary acidic protein for neuropathological assessment. For quantification of corpora amylacea, one 20 μm thick luxol fast blue-cresyl violet stained section of the body of the hippocampus with the characteristic C shaped appearance of the cell layers, corresponding to the HCT2 map, was selected. A direct three dimensional counting method was used.[9] We used a Zeiss microscope fitted with a Zeiss drawing tube, a digital length gauge (Heidenhain) with a sensitivity of 0.5 μm that was firmly attached to the stage, and an oil immersion lens with a magnification of ×100 and numeric aperture of 1.3 with a depth of field of 0.22 μm. For measurements of corpora amylacea density, a counting box of 50×50×10 μm was used, unless the specimens had high densities of corpora amylacea, when the counting box was 20×20×10 μm. We followed the counting rules recommended by Williams and Rakic.[9] Corpora amylacea completely inside the counting box were counted, and those completely outside the counting box were not. Corpora amylacea that touched the forbidden planes—that is, bottom, front, and left side of the counting box—were excluded, and those that touched the top, right side, and rear of the counting box were counted, provided that they did not touch any of the forbidden planes. Corpora amylacea were defined as globular bodies which stained blue with luxol fast blue. For the definition of the neuron containing layers of the hippocampus, we used the descriptions of Lorente de Nó,[10] Duvernoy,[11] and Amaral and Insausti.[12] Corpora amylacea densities were determined for the pyramidal cell layer of CA1, CA2, CA3, hilus, and the granular cell layer of the dentate gyrus (GCDG). Each hippocampal subregion was counted using 50 counting boxes with a random and systematic sampling strategy. Using similar methodology, neuronal cell densities were determined in the same hippocampal subregions, as reported previously.[6] Statistical analysis was performed using SPSS for Windows, release 6 (SPSS Inc, Chicago, IL,

Table 2 Neuronal densities in hippocampal subregions

Hippocampal subregion	*Controls (n=6)*	*Hippocampal sclerosis with corpora amylacea (n=26)*	*Hippocampal sclerosis without corpora amylacea (n=15)*
CA1	20.3 (15.6–23.4)	2.6 (1.2–8.9)	2.8 (1.7–9.6)
CA2	30.2 (25.7–38.0)	20.0 (12.3–28.1)(n=17)	20.2 (14.8–30.4)(n=7)
CA3	16.4 (15.6–25.9)	4.9 (1.1–16.5)(n=16)	7.9 (3.8–8.4)(n=7)
Hilus	12.0 (8.6–14.9)	2.7 (0.9–8.6)	1.5 (0.6–9.6)
GCDG	482 (295–635)	180 (80–490)(n=25)	152 (41–270)(n=14)

Neuronal densities of five hippocampal subregions for control, hippocampal sclerosis with corpora amylacea and hippocampal sclerosis without corpora amylacea specimens; n=number of specimens for which a particular hippocampal subregion was available for counting studies. In the other specimens, these regions were damaged during surgical removal and therefore not available for quantitative neuropathological studies. In two hippocampal sclerosis specimens, the GCDG was almost completely destroyed and technically difficult to count. Neuronal densities are number of cells × 10^3/mm^3. Neuronal density is expressed as median (range). The neuronal densities of hippocampal sclerosis specimens with and without corpora amylacea are comparable.

USA). Spearman's correlation coefficient (r) was used for correlation of corpora amylacea and neuronal cell densities, a χ^2 test for comparison of categorical variables, and a Mann-Whitney U test for comparison of continuous variables in patients with and without corpora amylacea. This study was approved by the ethics committee of the National Hospital for Neurology and Neurosurgery.

Results

Two control hippocampal specimens (33%), two end folium sclerosis specimens (40%), and 26 hippocampal sclerosis (63%) specimens contained corpora amylacea. Table 1 shows the corpora amylacea densities for the specimens that had corpora amylacea in at least one hippocampal subregion. The hippocampal subregion with the highest density of corpora amylacea was CA1 (figure). Table 2 shows the neuronal cell densities of control, hippocampal sclerosis with corpora amylacea, and hippocampal sclerosis without corpora amylacea. Neuronal cell densities of hippocampal sclerosis specimens with corpora amylacea were comparable with those of hippocampal sclerosis specimens without corpora amylacea. Using all available data from control, end folium sclerosis, and hippocampal sclerosis specimens, the corpora amylacea density of CA1 correlated with that of CA3 (r=0.61; P<0.001) and the hilus (r=0.63; P<0.001), and inversely with the neuronal density of CA1 (r=−0.42; P=0.02).

Clinical characteristics of the 15 patients with hippocampal sclerosis and no corpora amylacea and the 26 patients with hippocampal sclerosis and corpora amylacea in at least one hippocampal subregion were compared. There were no significant differences in median age of onset of habitual epilepsy (2 *v* 7 years), duration of epilepsy (24 *v* 21 years), a history of febrile convulsions (60% *v* 58%) and meningoencephalitis (7% *v* 7%), family history of febrile convulsions and epilepsy (13% *v* 20%), median number of complex partial seizures a month during the year preceding the operation (2 *v* 2.5), estimated median number of secondary generalised seizures in their lifetime (6 *v* 13), and seizure outcome after anterior temporal lobe resection. Median HCT2 (125 ms *v* 125 ms) and median MR based HCV (3698 mm^3 *v* 3686 mm^3) did not differ between these two groups.

Discussion

Corpora amylacea are often found in hippocampal sclerosis. Chung *et al*[2] reported the presence of corpora amylacea in 58% of hippocampal sclerosis specimens, which is similar to the 63% in the present study. We found no evidence that hippocampal sclerosis with corpora amylacea had clinical and MRI characteristics that differed from hippocampal sclerosis without corpora amylacea. Chung *et al*[2] reported that the distribution of corpora amylacea paralleled the characteristic neuronal loss in hippocampal sclerosis, which we confirm quantitatively in the present work. When present, corpora amylacea are therefore seen in the highest numbers in the CA1 hippocampal subregion, which is the most severely affected region in hippocampal sclerosis.[6] The inverse correlation of corpora amylacea density with neuronal cell densities supports the hypothesis that corpora amylacea may be the result of neuronal cell loss. The lack of clinical differences between hippocampal sclerosis with and without corpora amylacea indicate that corpora amylacea are an epiphenomenon of the pathogenetic process of hippocampal sclerosis.

We thank Action Research for financial support and Mister William Harkness for performing the surgical resections.

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