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Hippocampal Sclerosis and Epilepsy in Elderly Population

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Abstract

Objective: In temporal lobe epilepsy, hippocampal sclerosis (HS) and Alzheimer's disease (AD) pathological alterations in the hippocampus are frequently observed.

Methods: We assessed the clinicopathological characteristics of 30 aged subjects with HS originating from a large unselected autopsy cohort including 1,388 individuals.

Results: Overall, in 22 subjects AD related pathology and in 17 subjects TDP43 pathology, from mild, moderate to severe was seen. Five subjects out of 30 (17%) with HS had epilepsy.

Conclusion: A higher percentage compared to the reported prevalence of epilepsy in 0.6 percent of the adult population was observed, but more post mortem studies are urgently needed to investigate the pathological substrate for epilepsy in AD.

Keywords: Hippocampus; Postmortem; Hippocampal sclerosis; Epilepsy; Alzheimer

Introduction

In both epilepsy (EP) and in Alzheimer's disease (AD), pathological alterations are seen within the neuroanatomical region of the hippocampus formation [1,2]. In AD, the hippocampal formation displays substantial pathology including AD related hallmark lesions such as neurofibrillary tangles and neuritic plaques [3]. Furthermore, many reports have indicated that a substantial number of AD subjects, in addition to the AD related lesions, also display TAR DNA binding protein 43 (TDP43) within the hippocampus [4-14]. TDP43 related pathology is primarily seen in subjects with frontotemporal lobar degeneration (FTLD) [15]. It has been reported that when TDP43 pathology is seen in the FTLD, severe loss of neurons is frequently observed within the Cornu Ammonis region 1 (CA1) of the hippocampal formation, a change reminiscent of hippocampal sclerosis (HS) [16]. In subjects with temporal lobe EP HS is the most common lesion [17,18].

In a recent study, assessing the hippocampal formation in a large unselected cohort including 1,388 aged subjects, we noted that a pathological alteration in the hippocampal region was present in 18% of the subjects. The alterations ranged from mild to severe and from vascular to degenerative. Interestingly, in 31 out of these 260 (12%) subjects with an alteration in the hippocampus, the lesion was reminiscent of HS with indisputable neuronal loss especially in the CA1 region and moderate to severe gliosis [19]. Thirty of the subjects with this particular type of HS lesion were adult to aged.

Thus, it became of interest to assess whether aged subjects with HS, alteration reminiscent of what is seen in young subjects with temporal lobe EP, display EP.

Materials and Methods

30 subjects with HS included derive from a large unselected cohort of 1388 subjects who underwent an autopsy with a systematic neuropathological evaluation between the years 1995-2005 in the Department of Pathology of the Kuopio University Hospital [19], both medical and autopsy findings were reviewed. The clinical medical records were reviewed by a clinical neurologist and the pathology reports by a neuropathologist. The original assessment included samples from at least 16 regions: frontal, temporal, parietal, precentral, occipital cortices, cingulate gyrus, striatum, basal forebrain including amygdala, thalamus, anterior and posterior hippocampus, midbrain including substantia nigra, pons including locus coeruleus, medulla, cerebellar vermis and cortex. All neuropathological diagnostic slides were re-assessed and the findings were re-evaluated according to the present generally accepted diagnostic standards and recommendations. HS lesion here was defined as substantial to complete neuronal loss in the hippocampal CA1 region with well-preserved neuropil and moderate to severe gliosis [19]. The demographics of the subjects fulfilling these criteria are summarized in Table 1.

Results

The clinicopathological findings are summarized in Table 1. The mean age at death was 80 ± 2 (standard error, S.E.) years and the majority of subjects were female (19 subjects). The most common cause of death was pneumonia (n=8), followed by infection/sepsis

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Case	Gender	Age at death	Cause of death	Brain weight (g)	Cognitive impairment	Seizures	Neuropathological findings, other than "hippocampal sclerosis	TDP 43 in hippocampus	Significant general autopsy findings
1	f	38	6	1400	No	Yes	Acute brain hemorrhage and infarct	no	Renal transplant
2	m	62	5	1440	No	Yes	No	no	Pneumonia
3	f	68	6	1320	No	No	Acute brain infarct	no	Skull base chondroma
4	m	73	1	1425	No	No	Primary Age Related Tauopathy (PART) Braak II	no	Pericarditis
5	m	79	2	1660	No	No	PART Braak I	no	Gastrointestinal stromal tumor
6	f	88	4	1255	No	No	PART Braak I	no	Generalized tuberculosis
7	m	94	4	1300	No	No	Cerebral amyloid angiopathy (CAA)	no	Peritonitis
8	m	78	5	1270	Yes	No	AD related Braak II (bilateral HS)	no	Cardiac infarct
9	m	81	2	1375	Yes	No	AD related Braak II, CAA	no	Generalized atherosclerosis
10	m	88	1	1330	Yes	No	AD related Braak III	yes	Diffuse large B-cell lymphoma
11	m	61	1	900	Yes	No	FrontoTemporal Lobar Degeneration (FTLD)-TDP43	yes	Pneumonia
12	f	68	1	970	Yes	No	FTLD-TDP43	yes	Generalized atherosclerosis
13	f	70	1	830	Yes	No	FTLD-TDP43	yes	Generalized atherosclerosis
14	f	83	7	1340	Yes	No	FTLD-TDP43, PART Braak I	yes	Generalized atherosclerosis
15	f	93	1	795	Yes	No	FTLD-TDP43	yes	Cardiac granulomatous inflammation
16	f	79	5	1190	Yes	No	Alzheimer's disease (AD) Braak VI	no	Generalized atherosclerosis
17	f	82	1	740	Yes	No	AD Braak VI, cerebral amyloid angiopathy (CAA)	yes	Generalized atherosclerosis
18	f	85	3	840	Yes	No	AD, Braak VI, Lewy body disease (LBD) Braak 5, CAA	yes	Pulmonary tuberculosis
19	f	85	1	1030	Yes	No	AD, Braak VI, LBD Braak 3, CAA	yes	Cardiac ischaemic scars
20	f	86	1	970	Yes	No	AD Braak IV, multiple old infarcts	yes	
21	f	88	1	1190	Yes	No	AD Braak VI, LBD Braak 3	yes	Cardiac ischaemic scars
22	f	90	4	820	Yes	No	AD Braak VI	yes	Pyelonephritis
23	f	97	6	965	Yes	No	AD Braak V, Status post multiple old infarcts	yes	Generalized atherosclerosis, cachexia
24	f	83	4	1300	Yes	No	Dementia with Lewy Bodies (DLB) Braak 4, PART Braak stage II	no	Metastatic adenocarcinoma
25	m	89	3	1280	Yes	No	DLB Braak 4, AD Braak II, CAA	yes	acute myocardial infarct, lung small cell carcinoma
26	f	83	4	1200	Yes	Yes	Multiple old infarcts, AD related Braak III, CAA	no	Chronic pyelonephritis
27	f	84	4	975	Yes	Yes	Multiple old infarcts, PART Braak I	yes	Cardiac ischaemic scars
28	m	84	1	1345	Yes	No	Multiple old infarcts, AD related Braak II	yes	Cardiac ischaemic scars
29	f	86	4	875	Yes	No	Multiple old infarcts, PART Braak I	no	Cholangitis, liver abscesses
30	m	89	2	1360	Yes	No	Multiple old infarcts, AD Braak I	yes	Generalized atherosclerosis

m: male; f: female; TDP43: TAR DNA-Binding Protein 43)
Cause of death (1 pneumonia, 2 cardiac infarction, 3 neoplasia, 4 infection/sepsis, 5 pulmonary embolism, 6 brain infarction, 7 circulatory failure)

Table 1: Demographics of hippocampal sclerosis and epilepsy.

(n=6), cardiac insufficiency (n=6), cardiac infarction (n=3), central nervous system infarction (n=4), neoplasia (n=2) and pulmonary embolism (n=1). Five out of 30 cases with HS (17%) had a history of EP. Seven subjects were cognitively unimpaired and displayed mild AD related pathology, i.e., primary age related tauopathy (PART) (20) or vascular alterations. None of these subjects displayed TDP43 pathology. Two out of these seven (21%) subjects with HS of unknown origin [#1,2] displayed EP. Noteworthy, the medical records of these two cases revealed a complicated and long medical history. Twenty-three out of the 30 subjects displayed cognitive impairment, and the primary cause for this clinical alteration, based on the neuropathological examination, was AD in eight subjects, FTLD in five subjects, dementia with Lewy bodies (DLB) in two subjects, and vascular brain alterations in five cases. Neuropsychiatric disorders were observed in three subjects. In one subject [#10], mild AD related pathology with concomitant TDP43 pathology was seen, and the medical records revealed a history of a severe head trauma. In two subjects, only mild AD related pathology was observed, #8 had a history of cardiac infarct resulting in insufficiency, and [#9] was clinically diagnosed as having a late-onset psychosis. Concomitant pathologies (AD with DLB or TDP43 or vascular pathology) were seen in 13 out of 23 cognitively impaired subjects. Hippocampal TDP43 pathology was seen in seven out of eight (88%) subjects with primary AD, in one out of two (50%) subjects with primary DLB, and in three out of five (60%) subjects with primary vascular brain alterations. Three cases with cognitive impairment (11%) had a clinical history of seizures. One of these cases with EP [#16] fulfilled the clinicopathological criteria for AD. Two cases with dementia and seizures displayed extensive vascular lesions and concomitant AD related pathology on neuropathological examination. Five cases [#11-15] displayed neuropathological findings consistent with FTLD-TDP43, but none of these subjects displayed EP.

Discussion

Seventeen percent of the adult/aged subjects with HS, as defined here, displayed EP during life. Two of these subjects were cognitively unimpaired. Out of the remaining three cognitively impaired subjects, AD related changes were observed in one and vascular alterations in two. Thus, one out of eight AD patients with HS (13%) had suffered from EP during life. It has been reported that the incidence of EP in the elderly (65+ years) eastern Finnish population was 145,4/100000 in 2008 [21]. Furthermore, the incidence has been shown to increase with age in the Nordic population [21-23]. The reported prevalence of EP in dementia and AD varied from 5% to 64% [24-34]. When all cognitively unimpaired subjects with HS were lumped together here, three out of 23 (11%) had displayed EP during life, thus indicating a high frequency, when compared to the general population.

However, our results are not directly comparable with previously published reports. Here we assessed only those subjects that displayed HS independent of the final diagnosis. This selection was chosen due to the strong association found between EP and HS. Post-mortem studies on elderly patients with EP are sparse or include only a small number of subjects [24,29,35-37].

In 2013, it was reported that while assessing the post-mortem brains of 122 EP patients, HS was seen in up to 45% of the adult subjects [37], thus, indicating that HS is fairly common in adults with EP. In this study neurodegeneration was also common in the elderly subjects but was not considered causative for EP.

Noteworthy, TDP43-pathology has been reported to be relatively common in AD [4-14] and in line with this, TDP43-pathology was observed in as many as 88% of our cases with severe AD related pathology (Braak stages V-VI). It should be noted that clinical studies reporting that EP is common in AD include all subjects with AD diagnosis. Whether EP is associated with AD related pathology within the hippocampal formation was not assessed here.

In three of our subjects with EP, the primary brain alteration was vascular in origin. EP in these cases is most likely related to the tissue damage and might be regarded as symptomatic EP [38] and not related to neurodegeneration or HS. Noteworthy, five of our 23 demented subjects had a final diagnosis of FTLD-TDP, and none of these subjects had displayed EP during life. Thus, our observations are in line with previous reports indicating that TDP43 pathology, even if being associated with HS, does not increase the risk for seizures [39,40].

Conclusion

In summary, our findings indicate that 17% of the subjects with HS displayed EP, and that one out of eight AD patients with HS (13%) suffered from EP, but that none out of the five FTLD patients with TDP43 pathology and HS had EP. Additional clinopathological studies are certainly merited to investigate the pathological substrate for EP in AD.

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