

ORIGINAL ARTICLE

Consensus Recommendations on Pathologic Changes in the Hippocampus: A Postmortem Multicenter Inter-Rater Study

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Abstract

There is no consensus on the pathologic conditions or severity implied by the term “hippocampal sclerosis” (HS). In this study, a panel of experienced neuropathologists evaluated inter-rater agreement for pathologic diagnoses in the hippocampus and proposes consensus recommendations on the use of the term “HS.” In a group of 251 cases of HS selected from a large autopsy cohort (1,388; 18%), a coordinating group identified 5 patterns of degenerative or vascular pathology. Four independent neuropathologists assessed a single set of hematoxylin and eosin–stained sections following descriptive definitions to classify the appearances and assign the diagnosis of HS, if appropriate. Diagnostic agreement (range, 36%–70%) was highest for vascular lesions. Subsequent joint review of all cases highlighted the need to identify neurodegenerative lesions using immunohistochemistry. Initial agreement in assigning the diagnosis of HS varied from 0% to 86%. After a joint review, the group recommended that the term “HS” should be applied to all cases with complete/near-complete neuronal loss and gliosis in the subfields of the cornu Ammonis but not to hippocampal microinfarction. Therefore, the etiology of HS must be defined in association with a neurodegenerative process or as “lacking neurodegenerative markers,” a pathologic condition presumed to arise from hypoxic/ischemic mechanisms.

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Key Words: Hippocampal sclerosis, Hippocampus, Postmortem, Immunohistochemistry, Inter-rater study.

INTRODUCTION

The hippocampus is a brain region that is most vulnerable to age-related pathologic alterations. In 1885, Bouchet and Cazauvieilh (1) (cited by Spielmeier [2]) observed changes in the hippocampus in subjects with epilepsy. Thereafter, the contemporary researcher, Sommer (3), reported that hippocampal changes in epilepsy were restricted to pyramidal cells of a region of the hippocampus, which has since been called “Sommer sector.” Sommer (3) also first introduced the term “Ammonshornsklerose” to define loss of pyramidal cells in Sommer sector of the cornu Ammonis (CA1 subfield). In 1899, Bratz (4, 5), also working on subjects with epilepsy, confirmed Sommer’s observations and additionally noted the involvement of the hippocampal dentate gyrus. Hippocampal pathologies are not only restricted to epilepsy but are also noted in many other disorders. The term “hippocampal sclerosis” (HS) has become increasingly adopted beyond the field of epilepsy to describe hippocampal alterations with various etiologies, including vascular and degenerative processes (6–9). Therefore, it is currently difficult to compare reported observations of HS in the literature because the definition of this entity is not standardized.

The objective of the present study was 2-fold. First, it was to assess inter-rater agreement in a diagnostic trial of hippocampal lesions using hematoxylin and eosin (H&E)–stained sections. Second, it was to assess the use of the term “hippocampal sclerosis” in current practice and to agree on consensus recommendations based on the experience gained in the diagnostic trial. A large collection of postmortem brain donors was screened to select all cases with hippocampal pathology based on H&E-stained sections. The pattern and details of the histopathologic alterations were defined by a coordinating group, and a diagrammatic and descriptive textual protocol was developed. A group of experienced neuropathologists at 4 centers independently examined the same H&E-stained sections and followed the diagrammatic and textual definitions to allocate the cases to a descriptive category. Finally, a joint assessment of all cases was carried out using a

multiheaded microscope. During this joint assessment, immunohistochemically stained sections of the cases were available for review. The ultimate goal was to develop and apply diagnostic criteria for different types of hippocampal pathology encountered in autopsy practice.

MATERIALS AND METHODS

The logistics of this study are summarized in the flow chart (Fig. 1). During a 10-year period, 1,900 postmortem neuropathologic examinations were carried out at the Kuopio University Hospital. In 1,388 (73%) of these cases, there was an available representative section of hippocampus taken at the level of the lateral geniculate body. At this coronal level, the entire posterior hippocampus, including all 4 CA subfields, and the dentate granule cell layer (GCL) are clearly identifiable. All sections were reviewed in an H&E-stained section by one observer (TR) who was blinded to the clinical and original neuropathologic data to identify cases with pathologic alteration in the hippocampal formation. In addition, 9 cases without any pathologic alterations (on H&E screening) were included as controls. The rapidity of death was estimated from medical records using published definitions as follows (10): almost instantaneous; death within 24 hours without evidence of cerebral hypoxia; death within 24 hours but with presumption of some cerebral hypoxia; slow death occurring more than 24 hours; and slow death with assisted ventilation. Clinical data regarding cognitive impairment and seizures were also obtained from medical records.

Definition of Hippocampal Lesions

The selected H&E-stained hippocampal sections showing lesional changes were assessed by the coordinating group (TR, MP, IA) several times using light microscopy without formal morphometric techniques. Five different patterns of histologic alterations were recognized and defined on the basis of vascular and degenerative pathology: Type +, recent diffuse hypoxic/ischemic degeneration of CA neurons; Type 1, small focal infarcts (single or multiple); Type 2, extensive infarction of CA1; Type 3, patchy diffuse neuronal degeneration in CA sectors associated with or without neuronal lesions of neurodegenerative origin; and Type 4, complete neuronal loss from CA1 because of neurodegeneration, most frequently associated with neurofibrillary tangle formation but sometimes without degenerative pathology. These patterns were schematically illustrated and described as instructions to 4 independent neuropathology reviewers (EE, PI, KJ, AP) (Fig. 2). For this purpose, the pathologic types were defined purely on the basis of histologic descriptions and named as Type +, 1, 2, 3, or 4 rather than using descriptors that implied the underlying pathologic process. This approach was adopted because the use of the term “HS” has pathogenetic implications. For example, it is unlikely that a pathologist would use the term “HS” to describe CA sector changes that were believed to represent an infarct. The method used for the diagnostic trial therefore had the best chance of capturing each pathologist’s view of HS, minimizing previous concepts and biases regarding the use of that term. The emphasis for defining alterations in the CA1 to CA4 regions was on the pattern of neuronal loss

(moderate, near complete, complete), alterations of the neuropil (vacuolization, cysts), and observation of neurodegenerative changes (pretangles, tangles, Lewy bodies, plaques) in H&E-stained sections.

Immunohistochemistry

Consecutive, deparaffinized, 7- μ m-thick sections of the hippocampus were stained using the immunohistochemical (IHC) methods and antibodies listed in Table 1. Staining was carried out manually; primary antibodies were incubated overnight; and the streptavidin-biotin method (Histostain-Plus kit; Zymed, San Francisco, CA) was used for detection with Romulin 3-amino-9-ethylcarbazole chromogen (Biocare Medical, Walnut Creek, CA). Sections were counterstained with Harris Hematoxylin (Merck, Darmstadt, Germany), dehydrated, and mounted with DePex (BDH Laboratory Supplies, Poole, UK). Immunohistochemical staining for hyperphosphorylated tau (HPTau) and ubiquitin binding protein p62 was carried out in all cases. In cases with p62-positive and HPTau-negative labeling, staining for transactive response DNA-binding protein 43 (TDP-43) and α -synuclein (α Syn) antibodies was performed. p62 and HPTau immunoreactivity was assessed in GCL and CA regions; TDP-43 immunoreactivity was assessed in GCL; and α Syn immunoreactivity was identified in CA regions as being present or absent.

Inter-Rater Assessment in Diagnostic Trial

Only H&E-stained sections of all included hippocampi were circulated among the 4 participating experts, and no clinical data were included except the age of the subjects. The observers were asked to categorize the type of alterations observed by light microscopy without the use of morphometric techniques following the instructions in Figure 2 and to state whether, in their opinion, the observed lesions represented HS. Completed assessment sheets were collated by the coordinating group for analysis.

Joint Assessment and Consensus Development

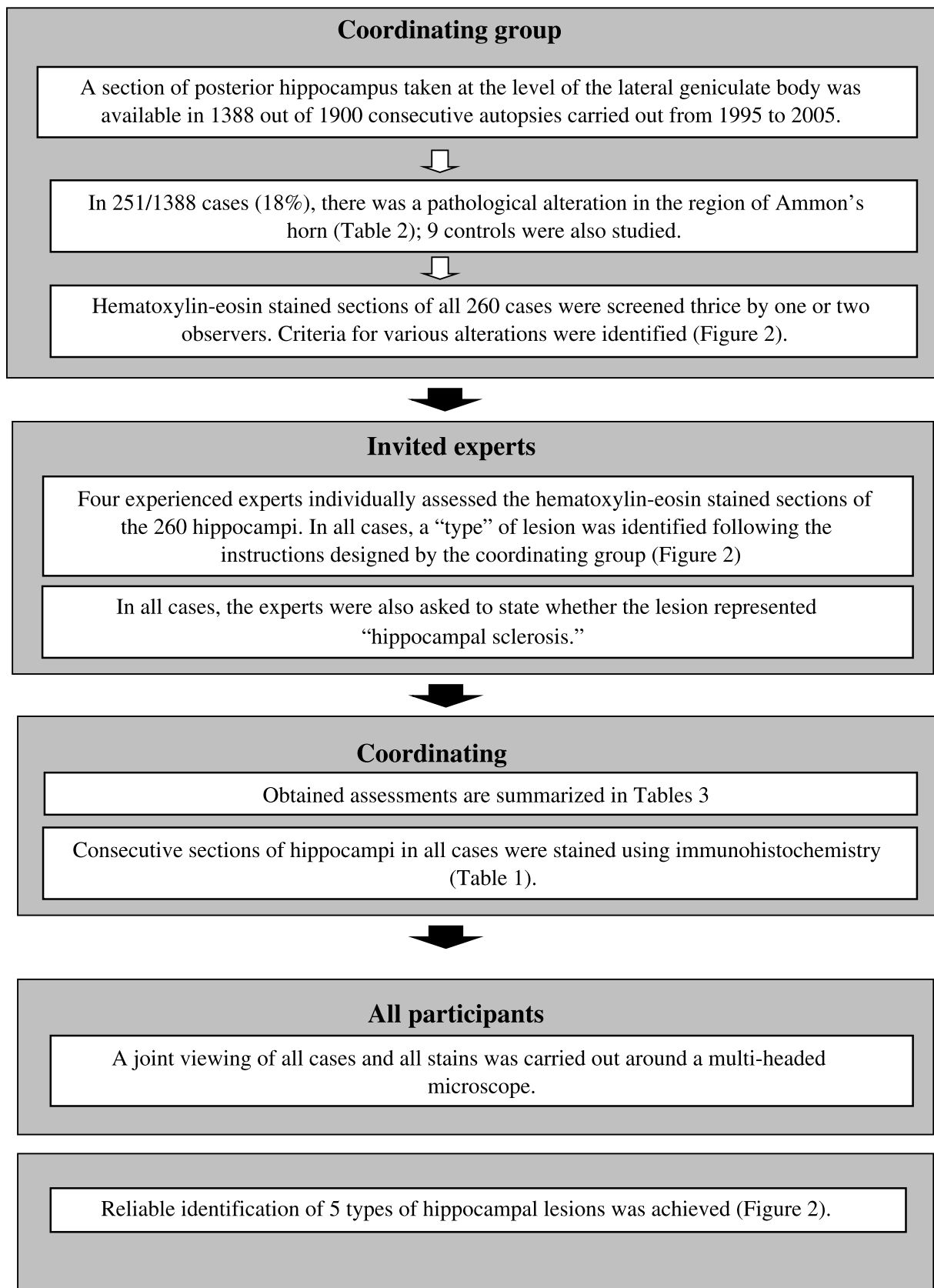
After the independent assessments of the H&E-stained sections by the expert observers, the whole study group met to jointly discuss all cases using a multiheaded microscope. At this session, both H&E- and immunohistochemically stained sections were available. The cases were reassessed jointly, and the inter-rater results were discussed. Cases with low agreement rates were discussed, and the pitfalls in assessment leading to disparate interpretations were identified. Based on these observations and discussions, the group agreed on operational definitions to recommend for the assessment of hippocampal pathology and for the use of the term “HS.”

Statistical Analysis

The statistical analyses were conducted with SPSS 17 for Windows (SPSS, Inc., Chicago, IL).

RESULTS

Pathologic alterations in the hippocampus were seen in 251 (18%) of the 1,388 cases (Fig. 1; Table 2). Fifty-nine percent of the subjects with hippocampal alteration were female;



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FIGURE 1. Flow chart summarizing the study design.

Types of hippocampal lesions illustrated and defined

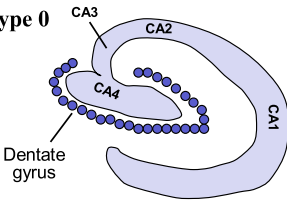

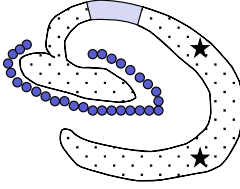

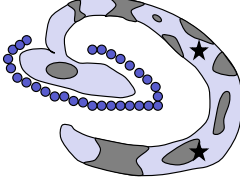

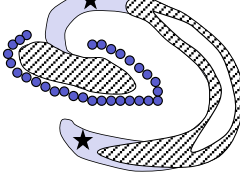


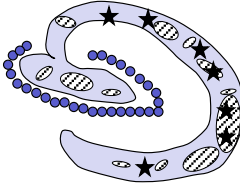

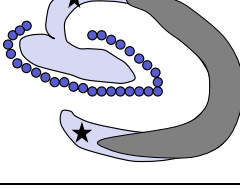

<p>Type 0</p> 	<p>The hippocampal formation with a special emphasis on the Cornu Ammonis (CA) region is unaffected. </p>
<p>Type +</p> 	<p>The hippocampal formation is preserved. Tissue and/or neuronal changes related to acute ischemia or acute infarct  are observed primarily in CA1 and CA3-4 regions. Degenerative lesions (★) such as neurofibrillary tangles, neuritic plaques, and Lewy bodies can also be noted. The extent of tissue changes does not fulfil the criteria for any of the types of lesions described below (Type 1 to Type 4).</p>
<p>Type 1</p> 	<p>There may be one or more foci of lesions in CA region separated by intact gray matter with identifiable pyramidal cells. The lesion with complete/near complete neuronal loss ranges from 0.01 mm to a maximum of a few mm in diameter. The margins of the lesion  towards the intact gray matter may display rounded edges. In some cases, the lesion may extend to the surrounding white matter. The neuropil is either relatively preserved or loosened with vacuolization. Occasional or numerous macrophages or prominent vascular profiles or gliosis can be noted. Concomitant degenerative lesions (★) can be seen.</p>
<p>Type 2</p> 	<p>A lesion is located in CA. In the Sommer's sector (CA1), moderate  cell loss and vacuolization of the neuropil and the vacuoles may merge and form cystic spaces of various sizes (cysts)  with complete neuronal loss is seen. Cell loss may even be seen in CA4 region. The lesion may extend to the surrounding white matter. Vascular proliferation, macrophages, and gliosis are usually seen.</p>
<p>Type 3</p> 	<p>An indisputable moderate to near total neuronal loss is identifiable already at low magnification in CA. The extent of neuronal loss differs and might be patchy or diffuse in CA regions. Neuronal loss is usually most prominent in CA1 or in CA3-4 regions . Clusters of neurons can be found in each CA region. Neuropil is mostly intact, but in some cases it may be loosened. Note, the neurodegenerative lesions (★) constitute the most prominent pathological feature, particularly in CA1. Gliosis is frequently seen in CA regions.</p>
<p>Type 4</p> 	<p>An indisputable complete neuronal loss is noted already at low magnification in CA. The extent of neuronal loss differs in various CA regions. Note that hardly any neurons are seen in the Sommer's sector (CA1) . Neuropil may be well preserved, slightly loosened, or collapsed/shrunk. Moderate to severe gliosis and corpora amylacea may be seen in CA regions. Vascular proliferation and macrophages are not observed.</p>

FIGURE 2. Illustration of the 5 defined types of hippocampal lesions.

TABLE 1. IHC Methods

Antigen	Clone	Source	Pretreatment	Dilution	Chromogen
TDP-43	2E2-D3	Abnova, Heidelberg, Germany	AC in water, 120°C; 80% FA, 5 minutes	1:1000	Romulin AEC
HPtau	AT8	Innogenetics, Ghent, Belgium, BR-03	None	1:500	Diaminobenzidine
α -Synuclein	KM51	Novocastra, Newcastle, UK NCL-ASYN	AC in 0.01 mol/L CB, pH 6.0 and 80% FA, 5 minutes	1:1000	Romulin AEC
p62 lck ligand	3	BD Biosciences Pharmingen, Franklin Lakes, NJ	AC at 120°C in 0.01 mol/L CB, pH 6.0	1:1000	Romulin AEC

Incubations were carried out at 4°C overnight.

AC, autoclave; AEC, 3-amino-9-ethylcarbazole (Biocare Medical); CB, citrate buffer; FA, formic acid.

the mean age at death of the subjects with hippocampal alteration was 77 years; and ages at death ranged from 7 months to 97 years. The mean brain weight of the subjects with hippocampal alteration was 1,300 g \pm 12 g (SE), and the postmortem delay was 68 hours \pm 3 hours (SE). The most common mode of death was “slow death over a period of more than 24 hours” (54%), followed by “death within 24 hours without evidence of cerebral hypoxia” (27%).

The coordinating group identified 5 different types of alterations (Fig. 3–7). The most common was Type 1, defined as focal or multifocal alteration of neuropil and/or neuronal changes related to acute ischemia or acute infarct (Fig. 4), followed by Type 3, defined by diffuse near-complete to complete neuronal loss with or without concomitant neurodegenerative lesions (Fig. 6; Table 2). Type 1 and 2 (Figs. 4, 5) alterations were considered to represent the consequences of vascular ischemic damage, that is, microinfarcts. Type 3 and 4 (Figs. 6, 7) alterations were considered to represent the consequences of a diffuse degenerative or chronic hypoxic process of variable severity. In the fifth, Type +, there were acute hypoxic/ischemic alterations (Fig. 3).

Assessment by Experts in Diagnostic Trial

The inter-rater assessment yielded an overall agreement of 48% across the 260 hippocampi (Table 3). The agreement

was 59% when the 9 cases defined by the coordinating group as being “controls” (i.e. lacking a lesion) were excluded. There was a 70% agreement regarding the Type 1 lesions, but only 50% agreement regarding Type 3 lesions. There was a poor agreement regarding the designation of HS: 86% of Type 4 lesions were assigned as representing HS; 44% of hippocampi with Type 3 lesions; 42% of Type 2 lesions; 14% of Type + lesions; and 1% of hippocampi with Type 1 lesions.

IHC Findings

p62 (63%) and HPtau (72%) immunoreactivity was commonly seen in the 260 hippocampi in the study (Table 4). Hyperphosphorylated tau pathology was observed in CA regions in 85% of Type 3 cases, 78% of the 9 controls, and 71% of Type 1 cases. Transactive response DNA-binding protein 43 pathology was noted in the neurons of the GCL in 56% of Type 4 cases versus 17% in the whole cohort. α -Synuclein pathology was seen in only 2% of the cases.

Joint Review Assessments and Consensus Development

As a result of the joint review, only 10 of 260 cases were reassigned to a type not originally assigned by the coordinating group. Five (55%) of 9 controls were reassessed as Type + or Type 3 because of the pathologic findings observed in IHC

TABLE 2. Cases Studied

Type Given by the Coordinating Group*	n	Percent of Total	Mean Age \pm SE, years	Sex (male/ female)		Clinical Manifestations, %		Brain Weight, Mean \pm SE, g	Rapidly of Death as Defined by Johnston et al [†] , %					Postmortem Delay, Mean \pm SE, hours	
						CI	Seizures		NA	2	3	4	5		NA
No lesions	9	4	77 \pm 3	3/6	33	10		1,318 \pm 77	33	44	22			94 \pm 10	
+	9	4	69 \pm 6	2/7	33	10		1,299 \pm 57	33		44	11	11	57 \pm 11	
1	143	55	77 \pm 1	67/76	26	4	4	1,343 \pm 12	27	10	54	6	3	67 \pm 4	
2	13	5	76 \pm 3	7/6	31	23	8	1,329 \pm 59	8	38	38	8	8	74 \pm 11	
3	59	23	77 \pm 1	18/41	71	7	3	1,260 \pm 24	29	7	61		3	72 \pm 8	
4	27	10	78 \pm 4	10/17	74	11		1,137 \pm 51	22	7	67		4	48 \pm 11	
Σ	260	77 \pm 1	107/153	42	7	4	1,300 \pm 12		27	11	54	4	69 \pm 3		

*Type of lesion as described in Materials and Methods and Figure 2: Type +, recent diffuse hypoxic/ischemic degeneration of cornu Ammonis (CA) neurons; Type 1, small focal infarcts (single or multiple); Type 2, extensive infarction of CA1; Type 3, patchy diffuse neuronal degeneration in CA sectors associated with or without neuronal lesions of neurodegenerative origin; Type 4, complete neuronal loss from CA1 caused by neurodegeneration, most frequently associated with neurofibrillary tangle formation but sometimes without degenerative pathology.

[†]Johnston et al (17).

CI, cognitive impairment; NA, not available.

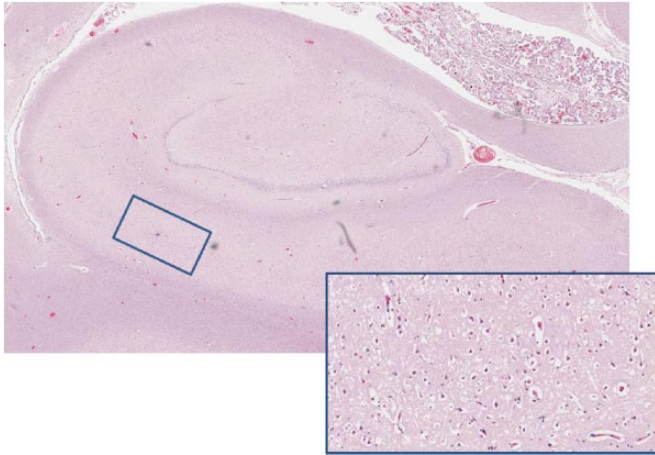


FIGURE 3. Scanned H&E-stained section of hippocampus obtained at autopsy from a 52-year-old man, brain weight 1,610 g. No macroscopic lesions were observed at sectioning. Histology and immunohistochemistry did not reveal neurodegenerative lesions. Neurons with eosinophilic cytoplasm in the Sommer sector (boxed area in large image shown in inset at magnification 40 \times) indicate irreversible ischemic/anoxic neuronal damage exemplifying Type + hippocampal lesion as illustrated and defined in Figure 2.

stains. Five (8%) of 59 Type 3 cases were reassigned either to Type + (1 case) or Type 4 (4 cases). In the remaining 250 cases (96%), the independent neuropathologists agreed with the assignment given by the coordinating group (Table 4). When the immunohistochemically stained sections were available for viewing, it became clear during the joint assessment that the neurodegenerative lesions (HPtau- and α Syn-associated alterations) were poorly seen in H&E-stained sections when they were sparse or moderate in extent and thus frequently missed. This emerged as the major contributor to diagnostic variation. The Type 4 lesions, a pattern

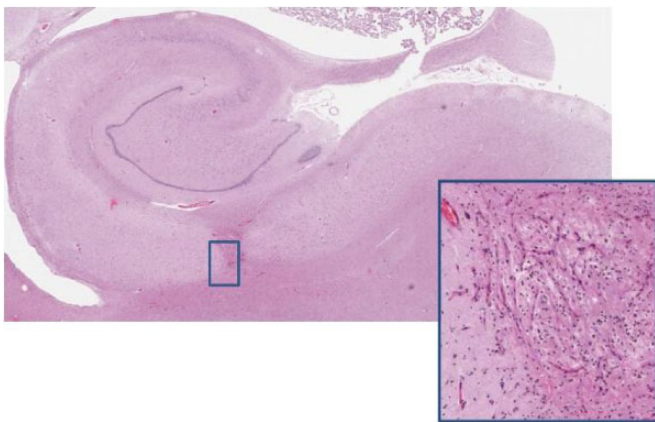


FIGURE 4. Scanned H&E-stained section of hippocampus obtained at autopsy from a 78-year-old man, brain weight 1,310 g. At brain sectioning, there was a grossly notable vascular lesion (a cyst) in the left striatum. The sharply demarcated area with numerous vascular profiles within the cornu Ammonis subfield 1 (boxed area in large image shown in inset at magnification 40 \times) is an infarct. This case exemplifies a Type 1 hippocampal lesion as illustrated and defined in Figure 2.

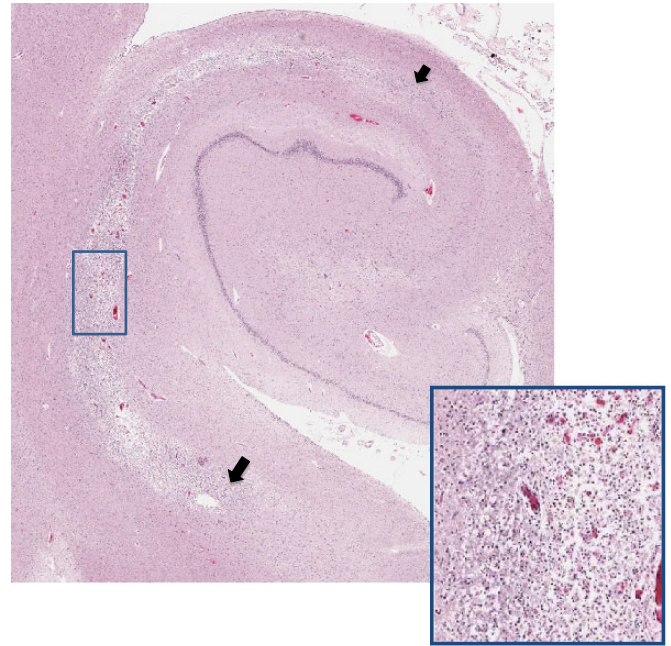


FIGURE 5. Scanned H&E-stained section of hippocampus obtained at autopsy from an 84-year-old man, brain weight 1,230 g. Grossly notable vascular lesions were seen in the right occipital cortex. In the section of the hippocampus, within almost the entire Sommer sector (arrows), there was a cystic space filled with macrophages (boxed area in large image shown in inset at magnification 40 \times). This large cystic infarct exemplifies the Type 2 hippocampal lesion as illustrated and defined in Figure 2.

of alteration that resembles that described by Sommer (3), yielded the highest agreement rate (86%) when assigning the concept of HS. In 56% of these cases, IHC revealed TDP-43 pathology in GCL neurons. Thirteen of 85 cases that were assigned as Type 3 or 4 (15%) lacked neurodegenerative pathology assessed here (e.g. non-TDP-43-, p62-, HPtau-, and/or α Syn-associated pathology). These 13 cases with other yet-unknown neurodegenerative or vascular pathology yielded poor agreement for assigning a pathologic alteration as an HS. In Type 2 cases with a vascular alteration, 42% of cases were initially assessed as HS.

DISCUSSION

Assessment of hippocampal pathology has not previously been subjected to analysis of inter-rater agreement. Such pathology is commonly seen in neuropathologic practice. In the overall cohort of predominantly elderly individuals assessed here, hippocampal pathology was seen in 18% of patients.

Because of the lack of stringent detailed definitions of hippocampal pathologies, the coordinating group defined and illustrated 5 different types of hippocampal alterations based on observations seen in 260 cases. The Type 4 pathology resembles a lesion previously described by Sommer and defined by him as “HS” (3, 11, 12) but in the context of epilepsy. The overall agreement between the independent assessments by 4 experts was 59%. It became obvious during the joint assessment

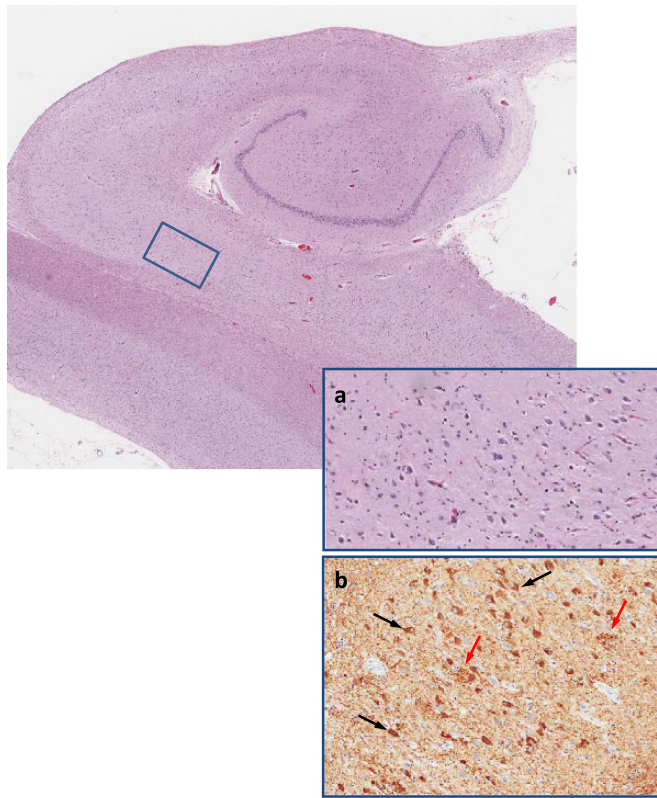


FIGURE 6. Scanned H&E-stained section of hippocampus obtained at autopsy from an 85-year-old woman. She had clinical dementia for 2 years before her death. The brain weight was 1,140 g. There were no focal macroscopic lesions, but limbic structures were atrophic. Note the marked loss of neurons and gliosis in region 1 of Sommer sector. The neurodegenerative lesions were poorly visualized in H&E stain (inset [a]; magnification, 40×) when compared with the IHC stain using an anti-hyperphosphorylated tau antibody (inset [b]; magnification, 40×). Note the numerous neurofibrillary tangles (black arrows) and neuritic plaques (red arrows) surrounded by pathologic neuropil threads (brown). This exemplifies the Type 3 hippocampal lesion as illustrated and defined in Figure 2.

process that one of the major limitations of assessing microscopic pathology in the hippocampus in the context of elderly people is the limited visualization of many lesions in H&E-stained sections. Degenerative lesions such as neurofibrillary tangles or Lewy bodies were frequently missed, particularly if they were sparse. This was particularly noted while assessing the 9 cases designated as controls. In addition to neurofibrillary tangles and Lewy bodies, many cases had TDP-43-positive inclusions that are not seen in the H&E-stained sections. The joint assessment, therefore, confirmed that IHC should be included when assessing hippocampal pathology and should be used to qualify the subtype of HS. The use of p62 antibody as a screening tool to limit laboratory costs before specific staining for HPTau, αSyn, and TDP-43 is also recommended. The only drawback regarding p62 as a screening marker is that pretangles and grainy αSyn aggregates are not visualized, as previously reported (13).

During the joint assessment review of H&E and IHC stains in which pathologists from 5 centers assessed the cases around a multiheaded microscope, the agreement rate was 96% with the pathology type assigned originally by the coordinating group. It is noteworthy that the typing assigned by the coordinating group was based only on the observations seen in the H&E-stained sections. Thus, 96% agreement by the independent pathologists indicates that a high agreement rate can be achieved for the assessment of hippocampal alterations in H&E-stained sections when the instructions provided are followed. However, it was noted during the joint assessment that some neurodegenerative alterations were not seen and registered during individual assessments of the H&E-stained

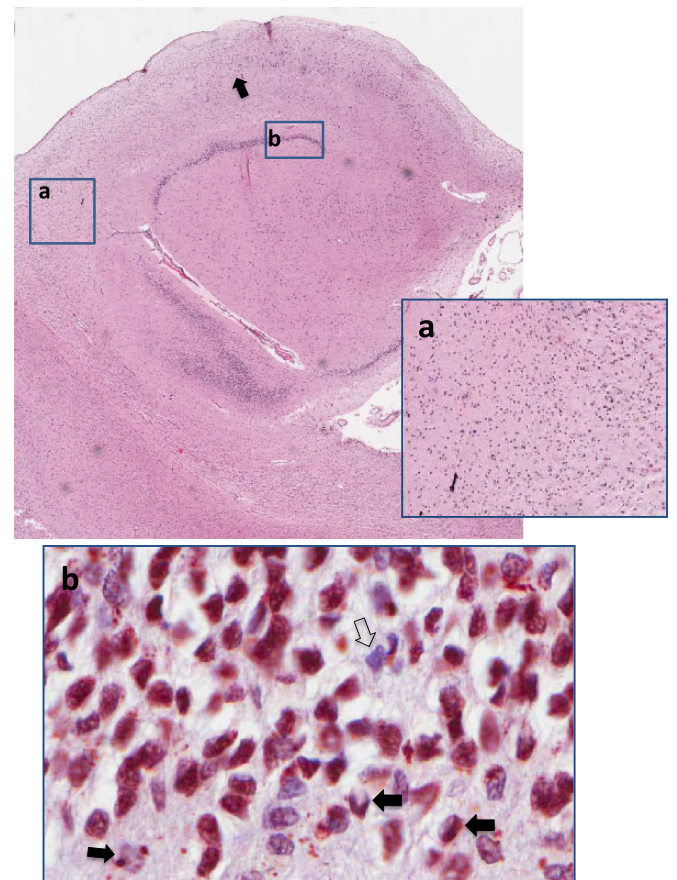


FIGURE 7. Scanned H&E-stained section of hippocampus obtained at autopsy from a 93-year-old woman. She had clinical dementia for 6 years before her death. The brain weight was 900 g. There were no focal macroscopic lesions, whereas there was severe frontotemporal atrophy. Note the near-complete loss of neurons and gliosis in Sommer sector (arrow in large panel, inset [a]; magnification, 40×). There were no lesions observed with immunohistochemistry for HPTau (not shown). Some pathologic inclusions (black arrows) were demonstrated with immunohistochemistry for TDP-43 (inset [b]; magnification, 400×). Note the normal brown staining of most nuclei and the pathologic lack of TDP-43 in some neuron nuclei (open arrow) with cytoplasmic inclusions (black arrows). This exemplifies the Type 4 hippocampal lesion as illustrated and defined in Figure 2.

TABLE 3. Results When 4 Experts Assessed H&E-Stained Sections Individually Following Detailed Assessment Instructions

Type Given by the Coordinating Group*	No. Cases	Agreement Rate in % When Assessed by 4 Experts					Type 4
		No Lesion	Type +	Type 1	Type 2	Type 3	
No lesions	9	36	19	19		17	6
Type +	9	8	44	15	8	19	6
Type 1	143	9	4	70	7	4	3
Type 2	13	—	8	2	67	—	19
Type 3	59	2	5	12	10	50	22
Type 4	27	1	2		25	3	51

*Type of lesion as described in Materials and Methods and in Figure 1.

sections. Thus, although it is possible to achieve good agreement by only assessing H&E-stained sections, the recommended protocol includes a review of at least a p62 IHC stain.

The participating experts were asked to state whether the alteration seen was HS according to their individual understanding of the term and local practice; HS is increasingly reported in older and cognitively impaired subjects. The frequency of HS in previous autopsy series of demented patients varied from 2.8% to 14% (14–19); in a very old (>80 years) cohort of demented subjects, it was reported to be as high as 26% (6). These publications and the findings in the present study underline the lack of consensus about the use of the term “HS” outside its application in surgical pathology to epilepsy-associated mesial temporal sclerosis. A high agreement rate (86%) was obtained in applying the term HS to Type 4 lesions. The definition of Type 4 lesion resembles that which was originally described by Sommer (3) in epilepsy patients and more recently by Thom et al (12). However, 56% of our Type 4 cases showed TDP-43 pathology, an observation that is in line with previous studies reporting a high incidence of TDP-43-immunoreactive pathology in subjects with HS (50%–89.9%) (7, 19, 20), and none showed the characteristic abnormalities of dentate dispersion that characterize surgical material in epilepsy-related mesial temporal sclerosis (12). In contrast, there was poor agreement around the assignment of HS to cases with Alzheimer disease (AD)-type neurodegen-

eration, primarily Type 3 cases. Numerous reports have assessed HS in subjects with a neurodegenerative disorder such as AD. The poor agreement between the 4 centers participating in this study in the assessment of HS in subjects with AD-related pathology may reflect the widely differing incidence of HS previously reported by different groups because of lack of application of stringent diagnostic criteria (6, 9, 14–16, 20–22).

Type 2 pathology was considered to be HS in 42% of cases. This finding was somewhat surprising because the Type 2 lesion represents extensive cystic lesion seen in the CA1 subfield and was assumed to be ischemic by the coordinating group. This problem justified the study design and use of purely descriptive categories because all the pathologists agreed that HS should not be used when infarcts are present. Very few of the cases with Type 1 pathology (1%), that is, focal microinfarcts, were categorized as HS in this study. Hippocampal sclerosis has been suggested to be the consequence of vascular disease, for example, after cardiac arrest or severe hypotension, but this implies diffuse neuronal ischemic/hypoxic change rather than focal infarction (23). It has been suggested that hippocampal vasculopathy with fibrosis and calcification has a predilection for the middle hippocampal artery and may result in patchy neuronal loss or in almost complete neuronal loss in the area of impaired blood supply, possibly linking hippocampal vasculopathy to HS, at

TABLE 4. Summary of Results Following Joint Assessment and Additional IHC Stains

Type Given by Coordinating Group*	No. Cases	Agreement Between Experts and the Coordinating Group†, %				No. Cases With				Type Given at Joint Assessment‡, No. Cases	
		p62		HPtau		TDP-43		αSyn		Control	No. Cases
		GCL	CA	GCL	CA	GCL	CA	GCL	CA		
No lesions	9	36	1	7	3	7	1	0	0	Control	4
+	9	44	1	4	2	5	0	0	0	+	15
1	143	70	13	92	14	102	4	1	1	1	143
2	13	67	2	4	1	6	1	0	2	2	13
3	59	50	41	50	34	51	24	4	3	3	54
4	27	51	16	7	10	17	15	0	4	4	31
Σ	260	48	74	164	64	188	45	5	Σ	Σ	260

*Type of lesions as described in Materials and Methods and Figure 2.

†Results as in Table 3.

‡Reassessment of case type based on joined assessment of H&E-stained sections and IHC stains.

GCL, granular cell layer of CA region of Ammon horn; p62, ubiquitin binding protein 62.

least in some cases (24). There were only 13 cases assigned as Type 3 or 4 that lacked any of the assessed neurodegenerative changes, suggesting that, in only few aged subjects, HS might be purely vascular in origin. Other studies have failed to detect an association between hippocampal infarcts and cerebrovascular risk factors (25). A recent study indicates that children with late intrauterine stroke developed HS, suggesting that HS might indeed be caused by circulatory failure (26). It was reported that 16% of HS cases within the State of Florida Brain Bank had coexisting vascular dementia (15); Dickson and coworkers (6) reported risk factors for cerebrovascular disease in all 13 cases with HS. Furthermore, HS has also been associated with subcortical ischemic vascular disease (8, 27). Whether noninfarct HS can occur on the basis of cerebrovascular/cardiovascular abnormalities was not addressed in the present study.

The participants debated the use of the term ‘‘HS’’ when assessing hippocampal alterations. It was agreed that Type 1 and 2 lesions, that is, those obviously arising on the basis of infarct, should not be called HS. Alterations of Types 3 and 4 can be referred to as ‘‘HS,’’ in line with previous practice, although pathologists should take into account the severity of the overall degenerative change. The present study did not identify precise guidelines for determining the

severity of neuronal loss that should warrant the diagnosis of HS. There was general agreement that the term is best reserved for cases with severe pathology with total or subtotal loss of CA neurons and appreciable loss of volume in either the presence or the absence of neurodegenerative pathology. The term ‘‘HS’’ in diagnostic and research radiology is principally associated with volumetric changes, and the approach recommended here would seem to best harmonize the use of this diagnostic term across pathology and radiology. Because it is important to define the underlying mechanisms leading to marked cell loss and gliosis in the CA subfields, it is recommended that Type 3 or 4 alterations with HPtau pathology should be referred to as ‘‘HS in association with HPtau pathology,’’ and Type 4 alteration with TDP-43 pathology in GCL neurons should be referred to as ‘‘HS in association with FTD-TDP pathology’’ (28). Cases with Type 4 alteration lacking TDP-43, HPtau, or α Syn pathology might be referred to as ‘‘HS lacking known neurodegenerative markers.’’

We recommend that the term ‘‘HS’’ should be used when the lesion is encountered in elderly subjects in the absence of a long-standing history of epilepsy, whereas the term ‘‘mesial temporal sclerosis’’ should be applied when the lesion is encountered in subjects with temporal lobe epilepsy

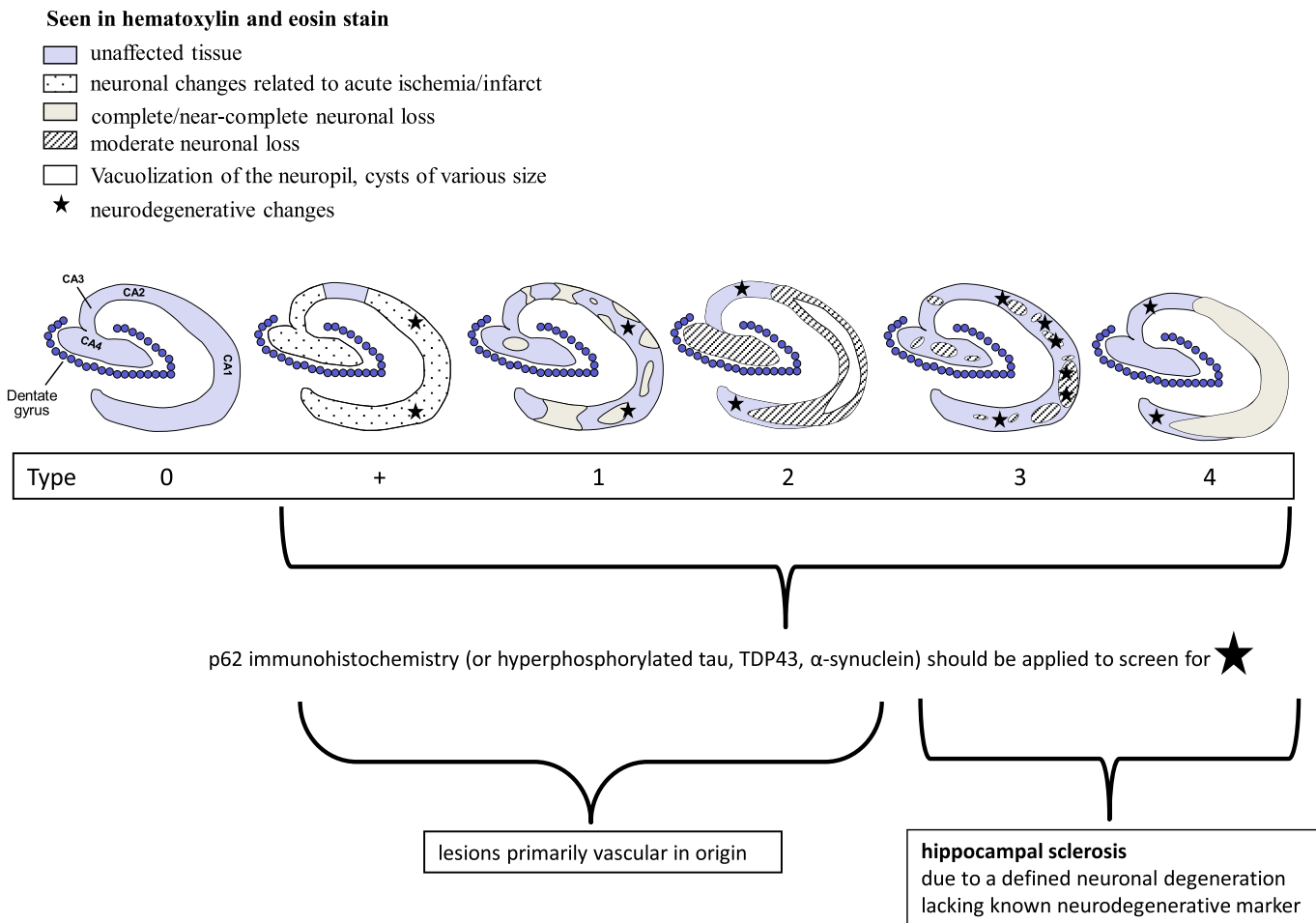


FIGURE 8. Schematic representation of the defined categories of hippocampal pathology seen in the aged population.

(12). This recommendation is based on the likelihood that, although the 2 pathologic entities seem similar, they are etiologically different (29). It is recognized that seizure activity is encountered in advanced AD, so this distinction may not be completely clear. Classical changes of epilepsy-associated mesial temporal sclerosis are not yet described in AD patients in the absence of a previous long-standing history, but they might occur. The review group does not expect that this pathology occurs in the context of late-stage seizure activity in AD, but additional research is needed to provide an evidence base for this assumption.

These results emphasize the general need for joint assessment and reassessment studies in the field of pathology and neuropathology to reach high agreement rates for the interpretation of emerging lesion concepts and also in the interpretation of their significance.

In conclusion, we report agreement ranging from 10% to 76% for the diagnostic assessment of hippocampal alterations in H&E-stained sections using a combination of diagrammatic and textual definitions of 5 subtypes of lesion. The highest agreement rate was reached for assessments of alterations that were vascular in origin (74% and 76%). We propose that hippocampal alterations found in autopsy practice can be divided into 5 types based on cell loss, neuropil changes, evidence of infarction, and the presence of neurodegenerative lesions (Fig. 8). Immunohistochemical staining should always be used routinely to visualize neurodegenerative lesions, and p62 IHC is an appropriate screening method. The use of the term “HS” should be restricted to specific types of pathology, and the underlying etiology should be specified (AD-related HS, FTD-TDP-related HS, etc.). “HS lacking known neurodegenerative markers” should be reserved for cases of Type 4 pathology lacking HPTau, TDP-43, fused in sarcoma, or α Syn lesions. Mesial temporal sclerosis is best restricted in routine and research pathology to cases associated with temporal lobe epilepsy.

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