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NEUROPATHOLOGICAL CHANGES IN RESECTED TEMPORAL LOBE OF PATIENTS WITH CRYPTOGENIC EPILEPSY

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The study was performed on cerebral tissue resected during temporal lobectomy in 16 patients whose long-standing cryptogenic epilepsy did not submit to anticonvulsive drugs. Cases presenting definite etiological factors such as CNS trauma, infection or neoplasm were excluded. Neuropathological investigations disclosed microangiomas and focal vascular malformations in the meninges and tissue in 7 patients. Neuronal heterotopias in the white matter and of the white matter in the cortex were observed in 3 cases. Main cortical changes were: neuronal loss, chronic neuronal degeneration, perineuronal satellitosis, and GFAP-positive submeningeal gliosis, especially at the bottom of sulci, perivascular gliosis and laminar or diffuse gliosis. The changes in the hippocampus were most enhanced in the end-plate and in the sector H3 of the pyramidal layer. Astrocytic gliosis in the white matter presented distinct GFAP and S-100 immunostaining; the latter involved in some cases a wider area than the GFAP reaction.
The above named changes are analysed with regard to the presumed epileptogenic factors and to the postepileptic damage.

Key words: *temporal lobectomy, epilepsy, neurons, gliosis.*

The problem of idiopatic epilepsy engaged a good deal of attention, especially devoted to the explanation of the morphological ground of temporal epilepsy. Cases of spontaneous epilepsy raise the question whether morphological alterations are the consequence or the cause of epileptic seizures, a question probably impossible to answer. With the purpose of explaining the origin of temporal epilepsy in a selected group of patients in whom symptomatic epilepsy had been eliminated, we took an interest in patients treated with temporal lobectomy. These patients suffered of long-standing drug-resistant epileptic seizures.

MATERIAL AND METHODS

Clinical data

The material under study was obtained from 11 male and 5 female patients. Their age at the time of operation was 8—50 years (mean 21.8) for men and 20—38 (mean 25.4) for women. At the outset of the first temporal seizure the age of patients ranged from 4 months to 28 years (mean 10.3), whereas the duration of the medically treated illness till surgical intervention was 3—22 years. In the majority of cases the etiology of the epilepsy remained obscure; perinatal traumas such as asphyxia, forceps delivery, premature delivery were established in 3 patients. Slight mechanical traumas were discovered in 2 cases, twice in 2-year-old child and once in 28-year-old man with brief period of unconsciousness. In one case meningitis in a 1-year-old baby preceded epilepsy by 8 years. In the early period of the illness generalized maximal seizures were observed in 11 patients, whereas simple partial and complex partial seizures were not frequent and in only 4 cases associated with grand-mal. In this early stage the number of all types of seizures could not be established, the number reported by the patients was 1—70 per year. At the time preceding lobectomy only 7 patients complained of grand-mal but the fits increased in number as well as increased the number of seizures of other types, so the patients complained of 50-1000 seizures per year. Neurological examinations in 3 patients revealed some minor abnormalities but no definite neurological symptoms, whereas psychological tests established emotional and intelectual disturbances in 11 patients. Neuroradiological examination (Rtg, CT) showed also some minor pathological changes without distinct relation to the etiology of epilepsy (5 patients). EEG investigations demonstrated foci of slow waves or foci of sharp waves or both types in all 16 patients. Applied pharmacological treatment consisted of the following anticonvulsant drugs: Amizepam, Dipromal, Phenydantin, Luminal, Tegretol, Mizodin.

Right-side temporal lobectomy was performed in 9 patients, left-sided in 7. The extent of lobectomy in all cases depended on the ECoG results at the outset and during the operation and on the local conditions. Radical lobectomy was performed in 10 cases, in 6 cases it covered the anterior part of the temporal lobe. The majority (8 out of 10) of radical lobectomies was performed in the right hemisphere, whereas resection of anterior parts was done mainly (5 out of 6) in the left lobe. Only in one case temporal lobe resection did not comprise the hippocampus: in 8 cases the lobectomized tissue included total or partial hippocampal structure, in 2 cases temporal lobectomy comprised also the hippocampus and nucleus amygdalae. In 5 cases temporal lobectomy including the hippocampus covered additionally (due to ECoG) other epileptogenic areas (frontal parietal, parieto-occipital and occipital cortex). Two of the patients had to be operated twice because of persistence of epileptic seizures, one after 4 years, another after 10 months.

The cerebral surface was normal in 11 patients whereas in four widening of temporal gyri was distinct; in 2 of them the medial temporal gyrus was twice the normal size.

Opacity of leptomeninges over the temporal lobe was observed in 2 pa-

tients, one of them presented additionally some cortical atrophy. A superficial cyst involving the middle part of the temporal lobe and extending to the parieto-occipital area was found in one case. Adhesions between dura mater and leptomeninges were observed in 3 cases (twice in reoperated patients). The appearance and consistence of the cerebral tissue removed during lobectomies seemed altogether unchanged in nine out of 16 patients.

Neuropathological methods

Cerebral tissue obtained from 16 patients was fixed in formalin and embedded in paraffin. The 10 μ thick paraffin sections were stained routinely with HE, Klüver-Barrera method, some also with cresyl violet. Immunohistochemical investigations were performed on mirror sections from the same paraffin blocks. Antisera against protein S-100 and against glial fibrillary acidic protein (GFAP) were obtained from Dacopatts (Copenhagen). The former was used in 1:5000 solution with use the APAAP method, the latter in 1:500 solution by the ABC method.

RESULTS

In the temporal cortex and subcortical white matter of all 16 patients pathological alterations were present. Most of them took the form of neuronal changes and astrocytic gliosis. The cortex displayed most frequently neuronal loss, dark neurons, chronic neuronal degeneration, sometimes combined with perineuronal satellitosis. In all the cases the enhanced cortical GFAP-positive subpial fibrous gliosis, in particular at the bottom of sulci (Fig. 1), perivascular gliosis (Fig. 2) and gliosis either haphazardly disseminated or distributed in some cortical layers (Figs 3, 4) were observed. GFAP-positive astrocytes were also S-100 immunostained, but in some cases the area of S-100 astrocytic immunoreactivity extended beyond the fields of GFAP-positive astrocytes and involved the whole cortex. In two cases reactive astroglia did not show any GFAP reaction in spite of marked S-100 reactivity.

In the white matter diffuse astrocytic gliosis of various intensity appeared in 11 cases, whereas 3 cases presented only marked fibrous gliosis restricted to the cortical-subcortical junction (Fig. 5). Similarly as in the cortex, perivascular GFAP-positive gliosis was distinct and appeared in all cases and often was most prominent around small lacunae (Fig. 6). As in the cortex, reactive astrocytes showed both GFAP and S-100 immunostaining, the latter spreading over a wider area in 4 cases (Figs 7, 8).

Discrete inflammatory changes such as mononuclear perivascular infiltrations in the meninges, cortex, and in the white matter, and the glial-lymphocytic nodules were found in 2 cases. These changes remain obscure in one case; others concern the patient reoperated after 10 months.

Vascular changes were found in 7 cases. They took the form of meningeal microangiomas (Fig. 9) or microscopical size arterio-venous malformations in the meninges and at the meningo-cerebral interface (Fig. 10). Abnormal arteries with thick hyalinized walls in the cortex and white matter were found in a 50-year-old man with 22 years long history of epilepsy.

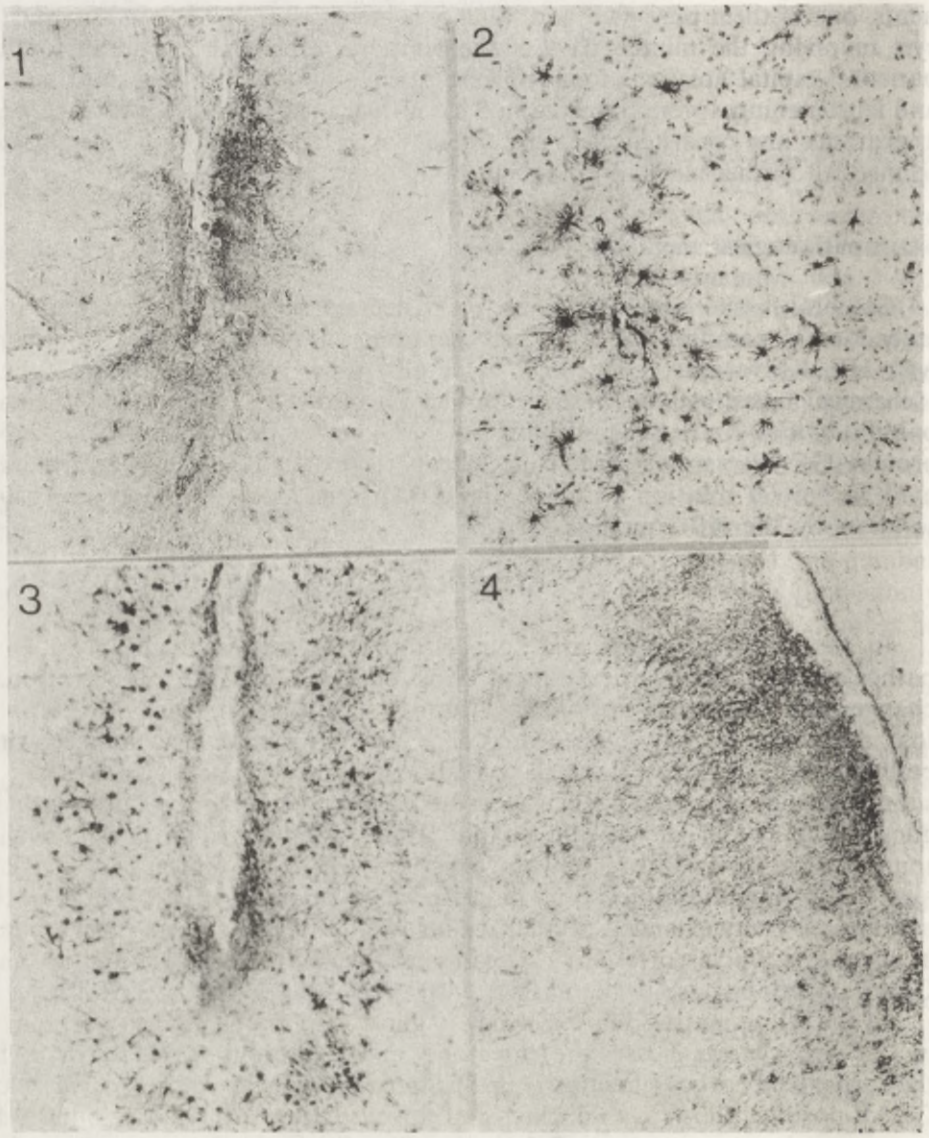


Fig. 1. Temporal cortex. Submeningeal GFAP-positive fibrous gliosis at bottom of sulcus. × 100
Fig. 2. Temporal cortex. GFAP-positive perivascular astrocytic gliosis. × 100
Fig. 3. GFAP-positive astrocytic gliosis, mostly in II cortical layer. × 60
Fig. 4. GFAP-positive fibrous gliosis spread from submeningeal region to deeper cortical layers. × 100

Distinct developmental abnormalities of brain tissue appeared in the case of abortive microgyria in the abnormally wide middle temporal gyrus, associated with white matter heterotopia in the cortex (Fig. 11) and neuronal dystopias in the cortical layers II and III (Fig. 12). In other two cases heterotopias of small groups of neurons occurred in the white matter, but in a 24-year-old patient suffering of temporal epilepsy for 4 years they coexisted with persisting matrix cells.

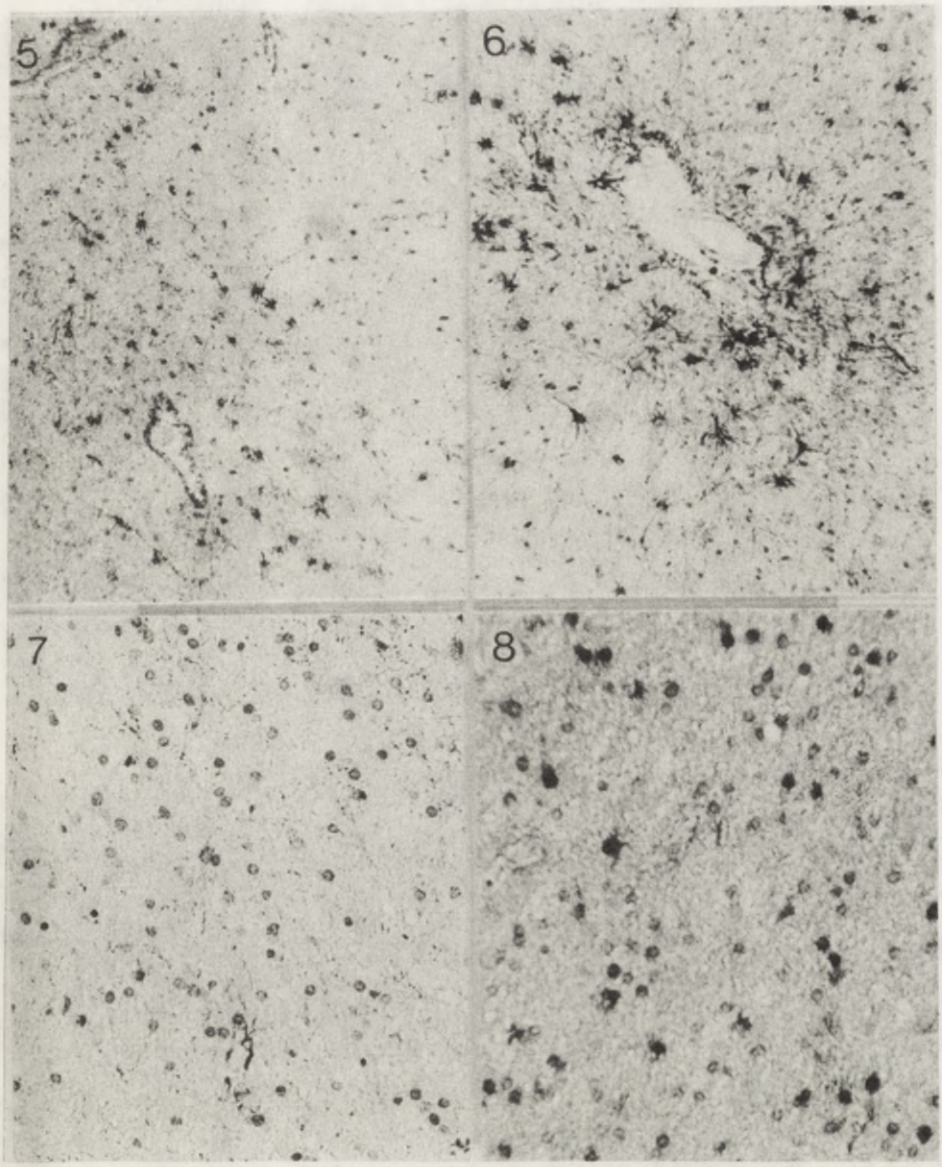
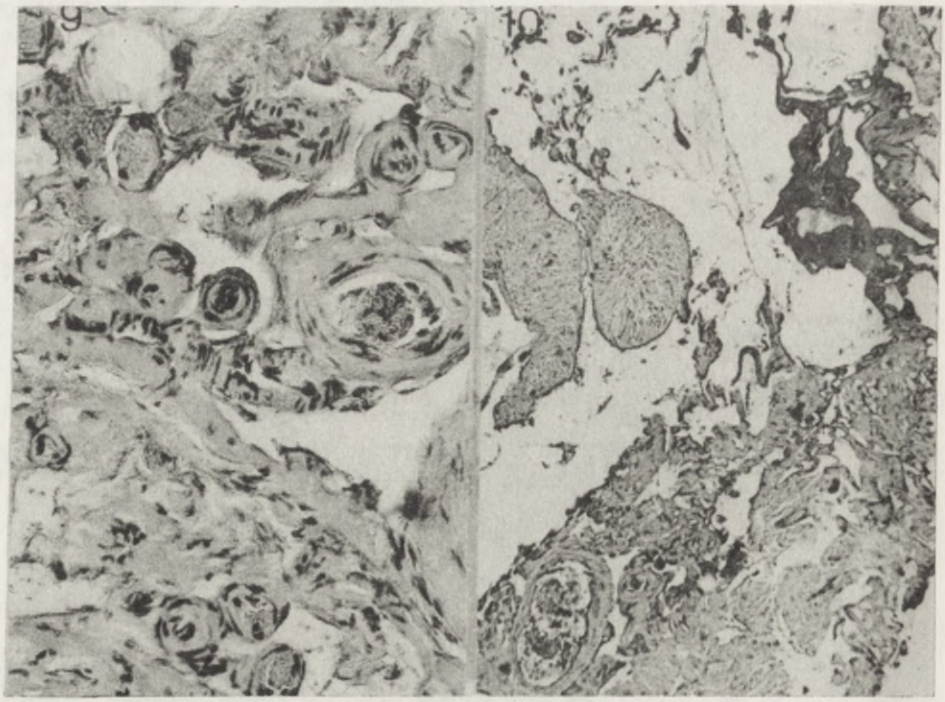


Fig. 5. Cortico-subcortical border. GFAP-positive astrogliosis. × 60
Fig. 6. White matter. GFAP-positive gliosis around perivascular lacuna. × 100
Fig. 7. White matter. Low GFAP-positive reaction. × 180
Fig. 8. White matter. Distinct S-100 protein reaction. × 200

The hippocampus was examined in 9 patents, but fragments of all hippocampal structures were available in 5 cases only, in 3 specimens preserved were only some fragments of *gyrus dentatus* including the *hilus* and in another one – some parts of the *subiculum* and *gyrus dentatus.*

The density of neurons in the hippocampal pyramidal cell layer was either decreased or the neurons revealed neuronal degeneration of chronic type (Fig. 13). In sector H1 and hilus (Fig. 14) beside dark, shrunken neurons, swollen



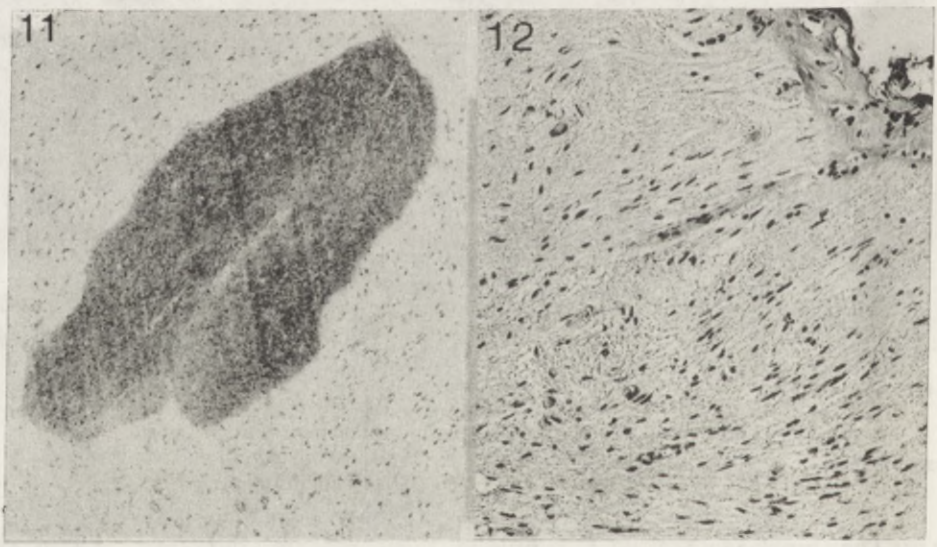


Fig. 9. Angioma in leptomeninges. HE. × 250
Fig. 10. Cortico-meningeal vascular malformation. HE. × 120
Fig. 11. Focal white matter heterotopia in temporal cortex. Klüver–Barrera. × 50
Fig. 12. Cortical layers disturbances. Fibrosis of arachnoidea. HE. × 120

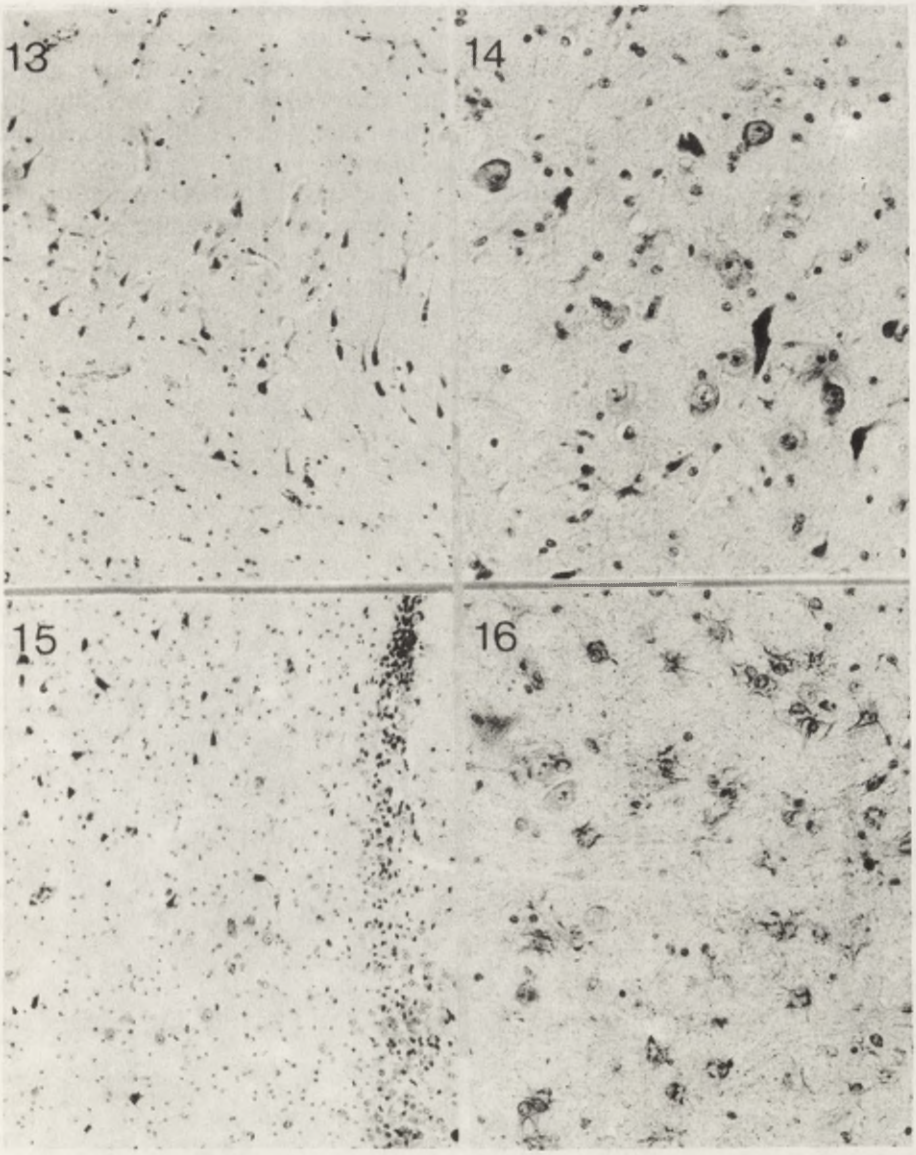


Fig. 13. Hippocampus. Neuronal loss and chronic degeneration of pyramidal neurons in H1 sector. HE. × 120

Fig. 14. Hippocampus. Chronic degeneration, swelling and vacuolization of hilar neurons. HE. × 90

Fig. 15. Hippocampus. Segmental loss of granular cells, neuronal chronic degeneration in hilus. HE. × 90

Fig. 16. Hippocampus. Diffuse GFAP-positive astrocytic gliosis in hilus. HE. × 200

nerve cells against the background of edematous perenchyma were seen. Cellular rarefaction and dark neurons were also visible in some segments of the granular cell layer of *gyrus dentatus* (Fig. 15). GFAP-positive fibrous gliosis was restricted selectively to the whole hilus of the dentate gyrus including the H3 sector of the pyramidal layer (Fig. 16). In other parts of the hippocampus gliosis was observed in the alveus, *s. lacunosum-moleculare* and once in *s. infrapyramidale*. In the H1 sector of *s. pyramidale* the GFAP reaction was almost negative (Fig. 17). S-100 protein immunostaining was enhanced in this sector only twice. Besides, enhanced diffuse GFAP-positive gliosis was present in the neighboring periventricular white matter in 5 cases.

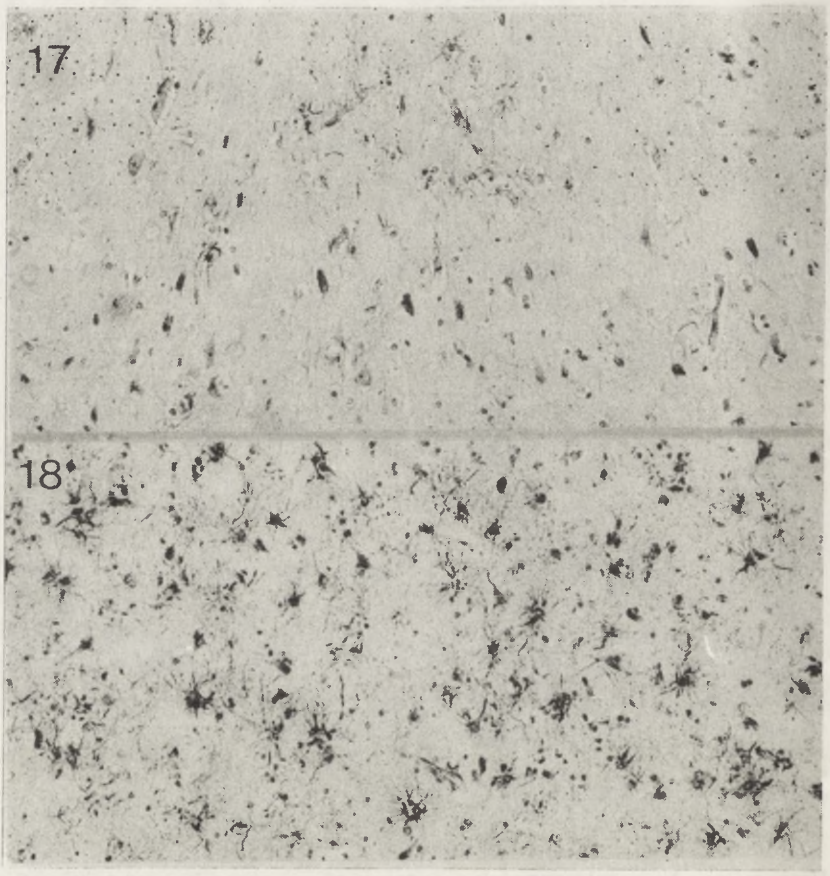


Fig. 17. Hippocampus. Trace of GFAP reaction in pyramidal cell layer in H1 sector. × 120
Fig. 18. Nucleus amygdalae. Distinct GFAP-positive astrocytic gliosis. × 120

Fragments of *nucleus amygdalae* were found in 2 specimens. *N. amygdalae* showed all types of alterations as neuronal loss, chronic neuronal changes, neuronal swelling and cytoplasmic vacuolization. Nerve cell abnormalities were associated with perineuronal satellitosis and diffuse cellular gliosis which in one case was represented by strongly GFAP-positive, astrocytic hypertrophy (Fig. 18).

DISCUSSION

Our results reveal two types of pathological changes which can be the primary cause of abnormal stimuli releasing epileptic seizures. These are vascular changes (7 cases) and maldevelopment of the nerve tissue of temporal lobes (4 cases). Both kinds of focal lesions were seldom reported in the literature as a cause of long-year standing, drug-resistant epileptic seizures. In a large collection of lobectomized patients both lesions amounted to 10% and 7%, respectively, whereas the preponderance of neoplastic changes (55%) in the temporal lobe has been striking (Plate et al. 1990). According to Cavanagh and Meyer (1956), one third of their lobectomy material showed focal abnormalities. Similar data are reported by other authors (Sager, Oxbury 1987). By initial elimination of the patients suspected of symptomatic epilepsy, our material became enriched in a large number of developmental changes. The vascular changes in meninges and at the meningo-cerebral interface consist mainly of microangiomas and small vascular malformations diagnosed neither clinically nor during lobectomy. The vascular changes together with macro- and micro-heterotopias support the opinion of Alzheimer and Vogt (1907) of maldevelopmental alterations being the ground of epilepsy. However, such observations do not explain late epilepsy in patients with congenital changes characterized by a low degree of evolution (neuronal dystopias).

So far as vascular malformation can be directly responsible for initiation of epileptic focus, the epileptogenic mechanism originating in irregular synaptic terminals between ectopic neurons and regular neurons is unknown. Complex or separate vascular and ectopic malformations have been found in more than half of the examined patients (9) what seems to corroborate Penfield's opinion (1956) about participation of expansive lesions in psychomotor epilepsies. Also studies of Gastaut et al. (1959) presented in autopsy material numerous vascular and atrophic changes underlying temporal lobe epilepsy. Six of our patients did not reveal such obvious changes. We believe their lack can depend to some extent on the surgical procedure or on the way of collecting the tissue for histological processing.

Changes in the cortex of the temporal lobe, in the hippocampus and in the white matter were observed in all patients. Predominated edematous changes of vasogenic origin appearing as perivascular lacunae in white matter and pale myelin accompanied by GFAP-positive fibrous gliosis perivascularly, at the cortico-subcortical border and submeningeal gliosis most intensive at the bottom of sulci. Submeningeal gliosis in sclerosis of Ammon's horn has been well established before (Cavanagh, Meyer 1956). The localization of astrocytic reaction points to the involvement of borderline zones of terminal vascularization. S-100 protein-positive gliosis overlapped the range of GFAP reaction in particular in the white matter, but sometimes appeared separately. This observation endorses the opinion that white matter contains more S-100 protein than gray matter (Moore, Perez 1968). In our material the GFAP-positive perivascular reaction occurred most frequently associated with S-100 protein-labeled astrocytes which extended over a wider zone than the GFAP reaction and this phenomenon was reported around the neoplasms by other authors who suspected production of both proteins as being evoked by

different stimuli (Kimura et al. 1986). The enhanced production of protein S-100 in astrocytes takes place during their hyperplasia and proliferation in response to removal of breakdown products in experimental conditions, its peak between week 2-6 of the process, its resolution together with cessation of an early reaction (Cicero et al. 1970). The intense reaction in our material can indicate a recurrent process. Besides, in an intense glial response in the white matter one can not exclude participation of oligodendroglia, which in normal conditions also contains protein S-100 (Kahn et al. 1983). Some authors express the opinion that intracellular GFAP is attributed mainly to the processes, whereas S-100 to the perikarya and possibly — nuclei (Boyes et al. 1986).

Cortical changes are restricted to irregular neuronal loss in various cortical layers, appearance of dark neurons and neurons with chronic changes intermingled with normal ones. Apart from doubts as to the character of dark neurons (Mouritzen Dam 1979), some authors report that in experimental conditions after 1 h of status epilepticus the majority of dark neurons become normal and only some survive in such a state or degenerate during the next few hours in the cortex and in the hippocampal sectors CA1 and CA3, without glial reaction (Ingvar et al. 1988). In contrast to the moderate cortical changes in the temporal lobe, the cellular changes and loss of neurons in the *nucleus amygdalae* and hippocampus were striking in spite of the difficulties in evaluation of fragmented structures. They consisted of diminished neuronal density and chronic neuronal changes of pyramidal neurons in the H1 sector, loss of hilar neurons and segmental loss of granular cells. These lesions of various intensity occurred in all examined cases. It was reported that neuronal loss in the hippocampus correlates with low density of neurons in particular sectors in the order: H3, H1, H1-2 and H2 (Mouritzen Dam 1979, 1980). The neuronal loss in each sector of the pyramidal cell layer can reach in temporal epilepsy up to 50% of neurons in control human material (Kim et al. 1990).

In our material the lesions in the pyramidal cell layer were accompanied by gliosis in *s. lacunosum-moleculare* and associated with neuronal loss in the hilus with GFAP-positive fibrous gliosis, as already observed in the Mongolian gerbil after short experimental ischemia (Gadamski, Kroh 1992). The sensibility of H1 sector and resistance of H2 sector neurons to the injury is generally accepted (Mouritzen Dam 1990). Other sectors reveal irregular loss of neurons up to 50% in the H3 sector (end-folium) in which cellular density is lowest. If sector H1 is affected there are always changes in other sectors of this layer (Mouritzen Dam 1980, 1988).

The most striking observation in our material is the lack of glial reaction in the impaired H1 sector. We have observed a similar phenomenon in experimental ischemia in the Mongolian gerbil (Gadamski, Kroh 1991, 1992). We believe that the hippocampal sector H1 contains very few astrocytes, this being an explanation for the ready vulnerability of this field to all kinds of injury.

On the basis of hippocampal changes a lack of relationship was established between the rate of neuronal loss and the duration of the illness (Kim et al. 1990). However, there exists a correlation between the loss of neurons in H1 and H1-2 sectors and the duration of illness characterized by frequent clonic-tonic seizures, contrary to the lack of any pattern of changes with

partial seizures (Mouritzen Dam 1980, 1988). Of some significance is the age of the patient, because there exists a relation between neuronal loss in H1, in the end-folium and granular cell layer and seizures in children who suffer of convulsions before the 3rd year of life (Sager, Oxbury 1988). The pattern of changes in our patients suffering of partial seizures evolving to tonic-clonic convulsions does not allow such conclusions.

Many authors found Ammon's horn sclerosis in autopsy material in psychiatric patients without epileptic seizures, and that the changes in Ammon's horn are more frequent in non-epileptic (41%) than in epileptic patients with grand-mal (20.5%), (Morel, Wildi 1954; Cavanagh, Meyer 1956). In our material Ammon's horn was not spared in cases with focal lesions in the temporal lobe, as reported by Cavanagh and Meyer (1956). Gastaut et al. (1959) concluded from their autopsy material that damage to Ammon's horn in temporal epilepsy patients is not a constant lesion but rather "not obligatory" and unfrequent and the mechanism of the damage to Ammon's horn is the same as for other parts of the temporal lobe in psychomotor epilepsy. The authors consider injury of the temporal lobe including Ammon's horn, as being most probably of ischemic origin, and as the cause and not the consequence of the seizures.

Experimental studies on brief ischemia with various survival time in gerbils (Gadamski, Kroh 1991, 1992) point to uni- or bilateral injury of the hippocampus, in particular of the CA1 sector, hilus and *gyrus dentatus*, accompanied by fibrous gliosis analogical to that found in patients with temporal psychomotor epilepsy. Albeit comparison of both conditions: human epileptogenic and experimental ischemic is doubtful, we are inclined to favor the fundamental theory of Spielmeyer (1927) concerning a vasogenic origin of hippocampal changes evoked by epileptic seizures triggered by temporal foci (malformations, ectopias), by perinatal injures (Earle et at. 1953), or by the other processes like febrile convulsions in children. The exact pathogenesis of neuronal death and hippocampal gliosis is not clear and all theories of delayed neuronal death (Kirino 1982), excitotoxic stimulation of receptors (Olney et al. 1983; Rothman, Olney 1987) or excessive intracellular influx of Ca^{2+} with membrane depolarization (Meldrum 1987) can only indicate particular stages of superimposed events of a long-lasting process in the brain, conditioned additionally by tissue maturity and medical treatment.

ZMIANY NEUROPATOLOGICZNE W RESEKOWANYM PŁACIE SKRONIOWYM PACJENTÓW Z SAMOISTNĄ PADACZKĄ SKRONIOWĄ

Streszczenie

Badania oparto na materiale pobranym w trakcie lobektomii skroniowej wykonanej w celu terapeutycznym u 16 pacjentów, u których wieloletnie napady skroniowe i uogólnione nie poddawały się leczeniu zachowawczemu. U pacjentów tych wykluczono uprzednio urazy, choroby zapalne lub nowotworowe mózgu. Badaniem neuropatologicznym stwierdzono w 7 przypadkach mikronaczyniaki i malformacje naczyniowe w oponach miękkich i w tkance mózgu nie wykrywalne makroskopowo. Heterotopie neuronalne w istocie białej i istoty białej w korze obserwowano w 3 przypadkach. Główne zmiany korowe to ubytki neuronalne i schorzenia typu przewlekłego, satelitoza perineuronalna i GFAP-dodatnia glejoza podoponowa zwłaszcza na dnie rowków,

okołonaczyniowa, warstwowa lub rozlana. W hipokampie zmiany te były wybitnie nasilone szczególnie w płytce końcowej i polu H3. W istocie białej występowała glejoza astrocytarna z żywym odczynem immunohistochemicznym GFAP i odczynem S-100, który w pewnych przypadkach był bardziej rozległy niż odczyn GFAP. Przedstawione zmiany przeanalizowano pod kątem przypuszczalnych przyczyn padaczki i uszkodzeń ponapadowych mózgu.

REFERENCES

1. Alzheimer A, Vogt H: Die Gruppierung der Epilepsie. Allg Z Psychiat, 1907, 418–448.
2. Boyes BE, Kim SV, Lee V, Sung SC: Immunohistochemical co-localization of S100b and the glial fibrillary acidic protein in rat brain. Neuroscience, 1986, 17, 857–865.
3. Cavanagh JB, Meyer A: Aetiological aspects of Ammon's horn sclerosis associated with temporal lobe epilepsy. Brit Med J, 1956, 2, 1403–1407.
4. Cicero TJ, Cowan WM, Moore BW, Suntzeff V: The cellular localization of the two brain specific proteins S-100 and 14-3-2. Brain Res, 1970, 18, 25–34.
5. Earle KM, Baldwin M, Penfield W: Incisural sclerosis and temporal lobe seizures produced by hippocampal herniation at birth. Arch Neurol Psychiat, 1953, 69, 27–42.
6. Gadamski R, Kroh H: Astrocytic reaction in dorsal hippocampus after 5 min ischemia in gerbil. Clin Neuropathol, 1991, 10, 204 (Abstr).
7. Gadamski R, Kroh H: Immunoreactivity of astroglia after brief ischemia resulting in asymmetrical damage to CA1 hippocampal sector in Mongolian gerbil. Neuropatol Pol, 1992, subjected.
8. Gastaut H, Toga M, Roger J, Gibson W: A correlation of clinical, electroencephalographic and anatomical findings in nine autopsied cases of temporal lobe epilepsy. Epilepsia, 1959, 1, 56–85.
9. Ingvar M, Morgan PF, Auer RN: The nature and timing of excitotoxic neuronal necrosis in the cerebral cortex, hippocampus and thalamus due to flurothyl-induced status epilepticus. Acta Neuropathol (Berl), 1988, 75, 362–369.
10. Kahn H, Marks A, Thom H, Baumal R: Role of antibody to S-100 protein in diagnostic pathology. Am J Clin Pathol, 1983, 79, 341–347.
11. Kim JH, Guimaraes PO, Ihen MY, Masukowa ML, Spencer DD: Hippocampal neuronal density in temporal lobe epilepsy with and without gliomas. Acta Neuropathol, 1990, 80, 41–45.
12. Kimura T, Budka H, Soler-Federsppiel S: An immunocytochemical comparison of the glia-associated proteins: glial fibrillary acidic protein (GFAP) and S-100 protein (S100P) in human brain tumors. Clin Neuropathol, 1986, 5, 21–27.
13. Kirino T: Delayed neuronal death in the gerbil hippocampus following ischemia. Brain Res, 1982, 239, 57–69.
14. Meldrum B: Physiological and biochemical mechanisms leading to nerve cell loss in status epilepticus. In: Advances in epileptology. XVI Epi Int Symp. Eds: P Wolf, M Dam, D Jouz, F Dreifuss. Raven Press, New York, 1987, 21–25.
15. Moore BW, Perez VJ: Specific acidic proteins of the nervous system. In: Physiological and biochemical aspects of nervous integration. Ed: FD Carlsson. Prentice-Hall, Engelwood Cliffs, New York, 1968, 343-359.
16. Morel F, Wildi W: Sclérose Ammonienne et épilepsie. Acta Neurol Psychiat Belg, 1956, 56, 61–74.
17. Mouritzen Dam A: The density of neurons in the human hippocampus. Neuropathol Appl Neurobiol, 1979, 249–264.
18. Mouritzen Dam A: Epilepsy and neuron loss in the hippocampus. Epilepsia, 1980, 21, 617–629.
19. Mouritzen Dam A: Consequences of severe epilepsy. Neuropathological aspects. Acta Neurol Scand, Suppl 117, 1988, 78, 24–26.
20. Mouritzen Dam A: Neuropathology of epilepsy. Acta Neurochir, Suppl 50, 1990, 20–25.
21. Olney JW, de Gulareff T, Sloviter RS: Epileptic brain damage in rats induced by sustained electrical stimulation of the perforant path. II Ultrastructural analysis of acute hippocampal pathology. Brain Res Bull, 1983, 10, 669–712.
22. Penfield W: Epileptogenic lesions. Acta Neurol Psychiat Belg, 1956, 56, 75–88.

23. Plate KH, Wieser HG, Yasargil MG, Wiestler OD: Neuropathologische Läsionen in selectiven Temporallappen-Resektionen bei complex-partieller Epilepsie: Analyse von 150 Fällen. 35 Jahrestagung der Deutschen Gesellschaft für Neuropathologie und Neuroanatomie, München, 25–28 April, 1990, p 8, (Abstr).
24. Rothman SM, Olney JW: Excitotoxicity and the NMDA receptor. Trends Neurosci, 1987, 10, 299–302.
25. Sager HJ, Oxbury JM: Hippocampal neuron loss in temporal lobe epilepsy: correlation with early childhood convulsions. Ann Neurol, 1987, 334–340.
26. Spielmeyer W: Die Pathogenesis des epileptischen Krampfes. Z Dtsch Ges Neurol Psychiat, 1927, 109, 501–520.

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