Relationship between Epileptogenesis and Morphological Changes in the Cerebral Cortex

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The relationship between disorders in the cytoarchitectonics (microdysgenesis) and formation of epileptogenic zones was studied on clinical material. Results of surgical treatment of 29 patients with drug-resistant temporal epilepsy are presented. Intraoperative electrocorticography was carried out in all patients. Histological studies of the cortex from the zone of regular epileptic activity registration were carried out in 23 cases. A relationship between completeness of radical removal of the zone of regular epileptic activity and treatment results was detected. Histological studies of resected cortex revealed signs of microdysgenesis in all cases. The presence of similar changes in the zone of regular epileptic activity registration, resection of which is essential for attack control, suggests a pathogenetic relationship between microdysgenesis and generation of epileptic activity.

Key Words: *temporal epilepsy; epileptogenic zone; microdysgenesis*

Disorders of the cortical cytoarchitectonics (microdysgenesis; MDG) are often detected in epilepsy associated with local lesions [4,10]. They were described for focal cortical dysplasia [8,9] and intracerebral tumors [6], hippocampal sclerosis [1], in patients without pathological changes detected by MRT [2]. Pathogenetic significance of histological changes remains little studied [4]. We evaluated the relationship between pathomorphological changes and formation of the epileptogenic zone on clinical material.

MATERIALS AND METHODS

Results of surgical treatment of 29 patients with drug-resistant temporal epilepsy, data of intraoperative neurophysiological studies, and histological changes in the resected cortex are analyzed. The distribution of patients by sex, age, and duration of the disease (from the first attack) is presented in Table 1. The duration of postoperative observation varied from 1 to 10 years (more than 2 years in 24 cases).

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The study included patients with small (<3 cm in diameter) intracerebral tumors of extrahippocampal location without progressive growth (n=14), focal cortical dysplasia (n=8), and hippocampal sclerosis (n=4). In 3 cases, no structural abnormalities were detected by high-resolution MRT. Combined pathology (combination of extrahippocampal involvement with hippocampal sclerosis) was observed in 5 cases.

The MRT protocol included scanning in the T1, T2, and FLAIR modes. The studies were carried out on devices with magnetic field intensity of 0.5 T (10 patients) and 1.5 T (19 patients). Neurophysiological study included intraoperative electrocorticography and monitoring of the scalp EEG from the parietal, frontoposterior, temporal, and parasagittal areas. The potentials were registered directly from the brain tissue using flat 8-contact electrodes and a probe electrode. Bioelectrical activity was recorded on a Voyageur multichannel digital electroencephalograph (Nicolet).

Intraoperative studies revealed zones of regular epileptiform activity (ZREA) in all cases (Fig. 1). The patients were divided into 2 groups by the ZREA size. Group 1 included patients with ZREA exceeding the damaged zone by more than 5 mm (21 patients).

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Group 2 consisted of 8 patients with ZREA located inside the apparent lesion (Table 1).

Anteromedial temporal resections, adapted to electrocorticogram, were carried out in 16 patients (14 in group 1 and 2 in group 2), resection of the damaged site in 4 cases (1 in group 1 and 3 in group 2), resection of the lesion with the marginal zone in 6 cases (4 in group 1 and 2 in group 2), selective resections of the hippocampus in 3 cases (2 in group 1 and 1 in group 2). Left-side resections were carried out in 15 cases, right-side in 14.

Histological studies of the ZREA cortex were carried out in 23 cases. The cortex of visually intact zones was examined in 19 cases, sites of the cortex adjacent

TABLE 1. Characteristics of Patients

Case No.	Sex, age (years)	Disease duration, years	Etiology	Side	Surgery
Group 1					
1	m, 13	2	PA	left	Resection “with edges”
2	f, 22	6	FA	right	Resection
3	m, 26	20	PA	right	Resection “with edges”
4	m, 21	3	PA+HS	right	AMTP
5	m, 29	17	ODG+HS	left	Resection “with edges”
6	m, 18	5	PA	left	AMTP
7	m, 24	14	PXA	left	AMTP
8	f, 17	6	FA	left	AMTP
9	f, 35	24	OA	left	AMTP
10	m, 18	16	FCD	right	AMTP
11	m, 25	13	FCD+HS	left	Resection “with edges”
12	m, 24	13	FCD	left	AMTP
13	m, 21	6	FCD	right	AMTP
14	f, 23	18	FCD+HS	right	AMTP
15	m, 33	32	FCD+HS	right	AMTP
16	m, 20	18	HS	right	AMTP
17	m, 42	22	HS	right	AMTP
18	f, 26	24	HS	right	AMTP
19	f, 43	23	Normal MRT	right	RH
20	f, 28	11	Normal MRT	left	RH
21	f, 21	7	Normal MRT	left	AMTP
Group 2					
22	f, 19	7	ODG	right	Resection
23	m, 25	5	FA	left	Resection
24	f, 25	9	OA	left	Resection
25	m, 16	2	FA	right	Resection “with edges”
26	f, 20	3	GG	left	AMTP
27	m, 18	2	FCD (I b)	right	Resection “with edges”
28	m, 34	13	FCD (I b)	left	AMTP

Note. PA: pyloid astrocytoma; FA: fibrillar astrocytoma; PXA: polymorphic xanthoastrocytoma; ODG: oligodendroglioma; OA: oligoastrocytoma; GG: ganglioglioma; FCD: focal cortical dysplasia; HS: hippocampal sclerosis; AMTR: anteromedial temporal resection; RH: resection of the hippocampus.

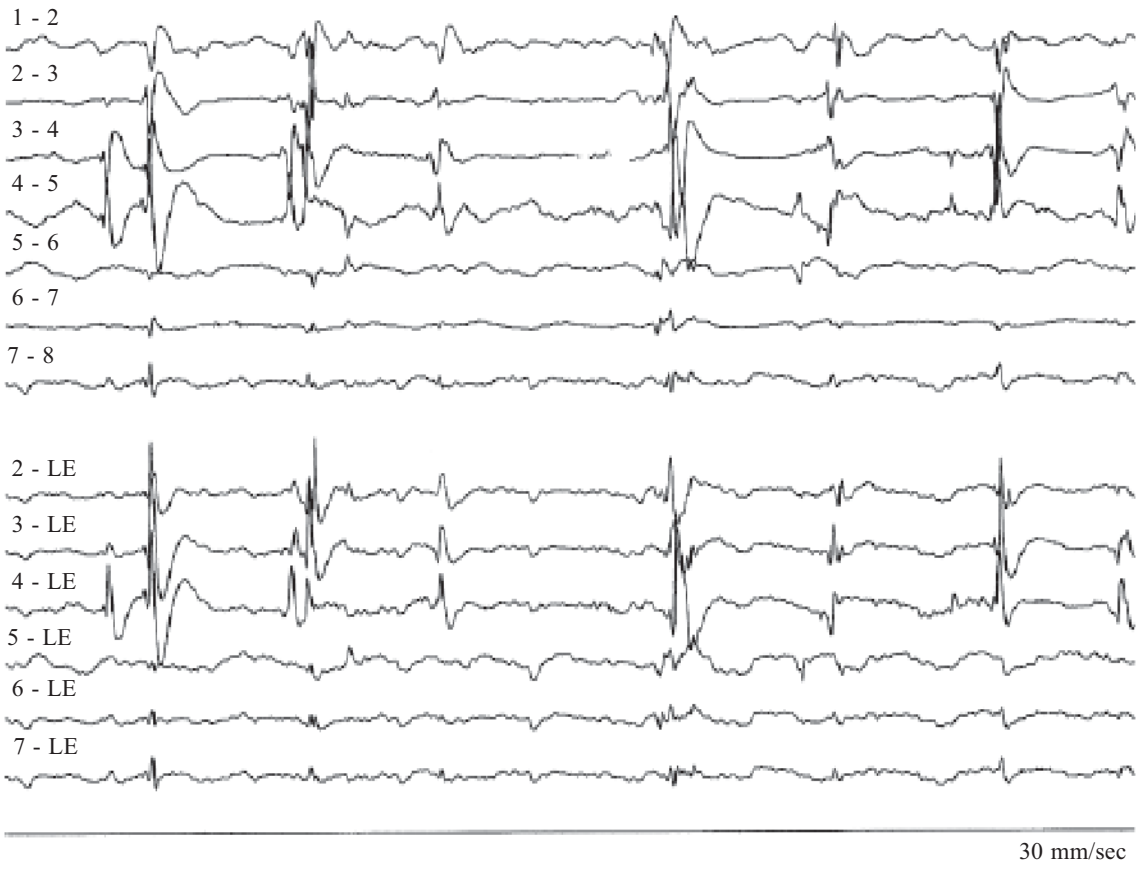

Fig. 1. Neurophysiological signs of ZREA. Case No. 6. Intraoperative electrocorticogram. LE: united reference electrode. Regularly emerging high-amplitude epileptiform complexes under electrodes Nos. 2, 3, 4. Episodic epileptiform complexes under the rest electrodes.

to the damaged zone in 4. Biopsy specimens were fixed in 10% neutral formalin with subsequent embedding in paraffin (the fragments were oriented by the cortical pattern), sections (3-5 μ) were stained with hematoxylin and eosin and by Niessle's method for evaluating the degree of neuronal changes.

The outcomes were evaluated by a modified classification [3]: class I: no dysadapting attacks (Ia: complete absence; Ib: auras); class II: rare dysadapting attacks (up to 2 per year); class III: reduction of the incidence of attacks by more than 90% (but more often than 2 per year); and class IV: no effect.

Statistical analysis was carried out using precise Fisher's test. The differences between the groups were evaluated using Mann—Whitney test.

RESULTS

In group 1, class I outcomes were attained in 11 patients (Ia in 6 cases), class II outcomes in 5 patients, classes III-IV outcomes in 5 cases. In group 2, class I outcomes were attained (Ia in 7 cases; Table 1). The groups differed significantly by the incidence of classes I and Ia outcomes (Table 2).

The results were better after complete resection of ZREA than in cases when permanent epileptiform activity was retained in the remaining cortical areas. The differences were statistically significant for class I (p=0.03 in group 1; p=0.009 for both groups). The presence of episodic epileptic activity in the remaining sites was inessential for the results of treatment (Table 3).

Both groups included patients with different duration of manifest disease: 2-24 years in group 1 and 2-13 years in group 2 (Table 1). Patients with longer disease duration predominated in group 1, the differ-

TABLE 2. Relationship between Outcomes and ZREA Size

Classification	Group 1	Group 2	P (Fisher's test)
Class Ia	6	7	0.01
Classes Ib-IV	15	1	
Class I	11	8	0.027
Classes II-IV	10	0	

TABLE 3. Relationship between Outcome and Completeness of ZREA Resection

Classification		Regular EA in remaining cortex	Episodic or zero EA in remaining cortex	P (Fisher's test)
Group 1				
	class I	9	11	0.03
	classes II-IV	4	6	
All patients				
	class I	0	19	0.009
	classes II-IV	4	6	

Note. EA: epileptiform activity.

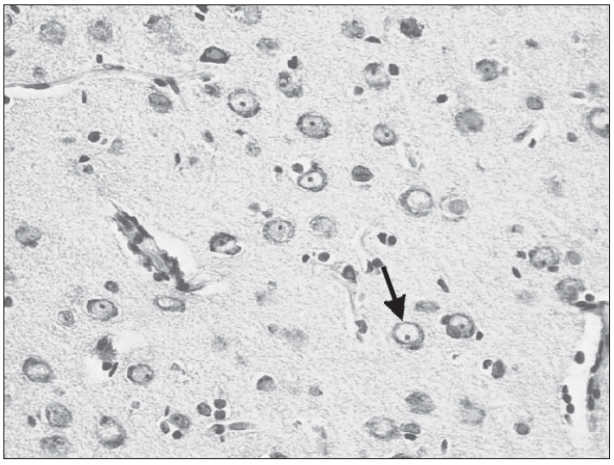

Fig. 2. Histology of the cortex in ZREA. Case No. 21 (normal MRT). The cortex of the basal compartments of the temporal lobe. Disorders in the cytoarchitectonics with immature neurons (arrow), ×400.

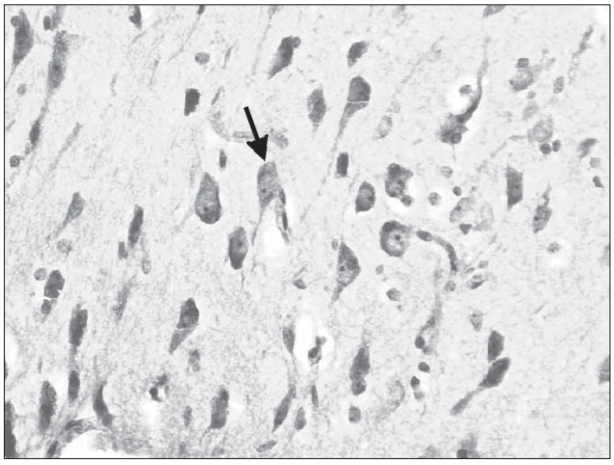

Fig. 3. Histology of the cortex in ZREA. Case No. 12 (MRT showed focal cortical dysplasia of the right temporal lobe pole). The cortex of the posterobasilar compartments of the temporal lobe. Disorders in the cytoarchitectonics with giant pyramidal neurons (arrows), ×400.

ences were statistically significant (Mann—Whitney test: Z=2.373; p=0.018).

Histological studies showed similar changes of the MDG type in resected cortex in all 23 cases. Cortical architectonics disorders of different severity (from slight violation of the laminar interface to their complete disorganization) were detected in all patients. Immature neurons were detected in 14 cases (Fig. 2), in 9 of these degenerative neurons were detected (Fig. 3). Pronounced disorders in the architectonics in patients with normal MRT picture were paralleled by moderately pronounced dysmorphic changes in neurons: accumulation of small groups of large pyramidal neurons, glial hyperplasia of different severity in the adjacent white matter. Diffuse angiomatosis and fibrosis of vascular walls were detected in the pia mater in some cases.

Hence, cessation of attacks after resection of the epileptogenic zone is the main property of this zone [5]. The ZREA can be regarded as a neurophysiological equivalent of the epileptogenic zone [7]. We detected MDG type changes in epileptogenic zones in all cases when histological study of resected tissue was carried out. Similar type of lesions of the epileptogenic zones in different conditions suggests that, on the one hand, MDG can be one of the causes of epileptic activity generation and that, on the other hand, it is a morphological sign of epileptogenic involvement. The relationship between the duration of manifest period of the disease and size of the epileptogenic zone suggests the possibility of a progressive course of symptomatic epilepsy at the expense of extension of the zone of epileptogenic involvement.

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