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The Relationship Between Clinico-Pathological Properties and p-Glycoprotein Expression in Hippocampal Sclerosis Among Patients with Mesial Temporal Lobe Epilepsy Who Undergo Selective Amygdalohippocampectomy Operation

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ABSTRACT

Introduction: The overproduction of the efflux transporters in the blood-brain barrier is considered to play a role in the development of drug resistance in mesial temporal lobe epilepsy (MTLE) patients. The aim of the present study was to investigate the relationship of clinical features of patients with MTLE accompanied by hippocampal sclerosis (HS) and the p-glycoprotein (p-gp) expression and neuronal loss in the hippocampus.

Methods: This study included a total of 33 patients who underwent selective amygdala-hippocampectomy operation. A detailed medical history of each patient, including age, side of HS, sex, age of habitual seizure onset, duration of habitual seizures, type and age of initial precipitating injury, presence and duration of latent period, presence and duration of silent period, monthly seizure frequency within 1 year prior to operation, mean age at the time of operation was evaluated retrospectively.

Results: The p-gp expression was significantly higher in the patient group with a seizure frequency of more than 15 days per month and a disease duration of more than 20 years. There was no significant difference between the p-gp expression and the clinical features of the MTLE-HS patients.

Conclusion: These results suggest that p-gp expression is affected by disease duration and seizure frequency rather than a patient's clinical and pathological properties. In patients with HS-MTLE, potential use of the p-gp inhibitors as additional therapy and developing novel drugs not carried by multidrug carriers expressed in blood-brain barrier should be regarded as the new treatment targets.

Keywords: P-glycoprotein, hippocampal sclerosis, mesial temporal lobe epilepsy, drug resistance

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INTRODUCTION

Mesial temporal lobe epilepsy accompanied by hippocampal sclerosis (MTLE-HS) is the most common drug-resistant epilepsy type (1). Its definitive therapy is surgery. Seventy to eighty percent of patients remain seizure-free after surgery (2, 3). Although HS has been described in the pathophysiology of MTLE, events that trigger this process remain unknown. Retrospective studies involving surgical series an "Initial Precipitating Injury" (IPI) including febrile convulsions (FC), trauma, hypoxia, and intracranial infections has been reported at a high rate (4).

While IPI cannot be determined in some patients, habitual seizures can be observed immediately after IPI in some others. There is usually a latent period when seizures are absent between IPI and habitual seizures. In some patients, there is a period called the "silent period" when seizure activity can be easily controlled before it becomes resistant to medical therapy at the beginning of the seizures (4, 5). It has been reported that IPI's type and age at the time of IPI may affect the pathophysiological process in HS-MTLE, and that in patients with MTLE who have IPI before the age of 5 have a greater likelihood of having unilateral hippocampal atrophy and abnormal mossy fibers in the inner molecular layer than other MTLE patients (6).

In addition to diffusion, the drugs may be passed into brain by the carrier-bound transport system (7). Multidrug carriers belonging to the "adenosine triphosphate (ATP) binding cassette" (ABC), such as p-glycoprotein (p-gp), which is the product of multi-drug resistance gene (MDR1) gen found in endothelial cells of the blood-brain barrier (BBB), and "multi-drug resistance proteins" (MRPs), are governed by active efflux mechanism and limit the entry of any drugs into the brain (7, 8).

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Recent studies have shown that p-gp and MRPs play important role in the efflux of antiepileptic drugs (AEDs) and lower concentrations of AEDs in the intracellular area in the epileptic brains, and that p-gp has a wide distribution in epileptogenic lesions (9, 10). The overproduction of the efflux transporters in the BBB is considered to play a role in the development of drug resistance in MTLE patients (9).

The aim of the present study was to determine the relationship between clinico-pathological properties and p-glycoprotein expression in hippocampal sclerosis among patients with mesial temporal lobe epilepsy.

METHODS

This study included a total of 33 patients who were under follow-up of Bakırköy Psychiatric Diseases Training and Research Hospital Third Neurology Clinic, Epilepsy Outpatient Clinic with a diagnosis of drug-resistant HS-MTLE who underwent selective amygdala-hippocampectomy operation between 2001 and 2006. All patients' clinical histories were re-assessed retrospectively. The clinical history obtained from medical records and family members included information about age, side of HS, sex, age of habitual seizure onset, duration of habitual seizures, type and age of IPI, presence and duration of latent period, presence and duration of silent period, monthly seizure frequency within 1 year prior to operation, mean age at the time of operation, and family history of seizure.

The patients were grouped as IPI with seizures, IPI without seizures, and non-IPI groups.

IPI with seizures: included patients with seizures or FC accompanied by an important medical disorder.

Seizure-free IPI group: included patients without a history of seizures who had important medical conditions such as head and birth trauma, hypoxia and central nervous system infection. In our patient group there were patients with head trauma and birth trauma.

Non-IPI: Included Patients Without a History of IPI.

The patients' paraffin-embedded brain tissues were studied from the pathology archive. A pathologist experienced in this subject assessed the blocks with respect to the degree neuronal injury in the hippocampus and immunohistochemical p-gp expression. All procedures performed in the study was in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Histopathological Features

The severity of neuronal loss and gliosis was graded into three categories on the basis of Wyler's (11) grading system: Low (Grade 1), moderate (Grade 2), and high grade (Grade 3–4).

Grade 1: contains a slight injury in the hippocampal pyramidal cell layer CA1, CA3, and/or CA4 regions (>10% neuron loss or involvement absent).

Grade 2: contains a moderate amount of injury in the hippocampal pyramidal cell layer CA1, CA3, and/or CA4 regions (gliosis with 10%-50% neuron loss).

Grade 3: contains a severe injury in the hippocampal pyramidal cell layer CA1, CA3, and/or CA4 regions; CA2 is relatively preserved (gliosis with >50% neuron loss).

Grade 4: Severe injury in all regions of hippocampal pyramidal cell layers (gliosis with >50% neuron loss) Dentate fascia, subiculum, and parahippocampal gyrus may also be affected.

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Antibodies and Materials Used for Immunohistochemistry

In order to detect p-gp protein with the immunohistochemical method, mouse monoclonal antibodies clone 494 (C494) (1:100 dilution: NeoMarkers, LabVision, cat. #AP-9003, USA) was used as the primary antibody and clone 5B12 (C5B12) (1:10 dilution: NEoMarkers, LabVision, USA, Cat. # AP-9003) as the secondary antibody.

Immunohistochemical Method

One paraffin block reflecting the general features of each case was selected for immunohistochemical studies from the the pathology archive. From formalin-fixated, paraffin-embedded blocks, sections prepared 3–5 micrometer thick were taken to poly-I-lysine coated glass slides. The sections were waited to dry overnight in a 56-centigrade stove to make the sections adhere to glass. The sections were passed through five separate xylene baths for 5 minutes each to complete the deparaffinization process. The sections were then passed through five separate ethyl alcohol series of decreasing concentrations for five minutes each to hydrate the sections. Then, using the standard high-pressure temperature method an "antigen retrieval" procedure was applied. The preparations were cooled at room temperature in a buffer solution for at least 20 minutes and poured into distilled water, and then into ph 7.6 tris buffer saline (PBS). The preparations were then treated with 3% (v/v) H2O2 for 15 minutes to eliminate endogenous peroxide activity, and they were then washed with PBS for 2x5 minutes. In order to prevent nonspecific binding with primary antibody, a 15-minute blockage was applied, which was followed by rapid passage through 4 separate PBS baths. Primary antibody was applied. After 1-hour incubation period, pressure was applied with antigen retrieval whistle. The second antibody was applied after 2 hours of incubation. As a positive control in the immunohistochemical studies, surrenal tissue was used for C494 and liver tissue for C5B12.

Assessment of Immunoreactivity

Immunoreactivity staining was graded as weak, moderate, and strong. Immunoreactivity index considered the percentage of stained cells to the area of examination. Accordingly, less than 25% was considered weak staining, 25–50% moderate, and >50% intense and were classified as mild-moderate and strong according to the severity of the staining.

Statistical Analysis

The statistical analysis was conducted using the Statistical Package for the Social Sciences for Windows, version 20.0 (SPSS Inc., Chicago, IL, USA) software program. The metadata were represented with averages ± standard deviations, numbers and percentages. The comparison of categorical variables was performed using Chi-square test or Fisher's exact test, depending on the appropriateness of theoretic condition. In the normally distributed constant data comparison, the Student's t-test was used, and in the non-normally distributed group, the Mann-Whitney U test was used. A p value of less than 0.05 was considered significant for all statistical analyses.

RESULTS

This study included 33 patients. Eighteen (54.4%) patients were male and 15 (45.4%) were female. The mean age at operation was 27.24±5.64. The women had a mean age at operation of 27.5±11.2) and men 26.8±6.45. There was no significant correlation between age at operation and sex as well as between age at IPI and IPI groups (with versus without seizures).

Thirty of 33 (90.9%) patients had IPI. Twenty-two (66.7%) had IPI with seizures; 8 (26.7%) seizure-free IPI; 3 (9.1%) were non-IPI. Twenty-two

(73.3%) of 29 patients in the IPI group had FC; 7 (23.3%) had head trauma; and 1 (3.3%) had birth trauma. No significant difference was found between operation side, presence and duration of latent period, presence and duration of silent period and the mean duration of habitual seizures in the IPI groups with versus without seizures. The clinical findings of the patients are shown in Table 1.

According to the histopathological features, 2 (6.1%) patients had low grade, 9 (% 27.3) moderate grade and 22 (66.7%) high grade neuronal loss (Figure 1A-1B). We found no significant difference between the hippocampal neuronal injury and IPI groups, mean duration of habitual seizures, and p-gp staining (Table 1).

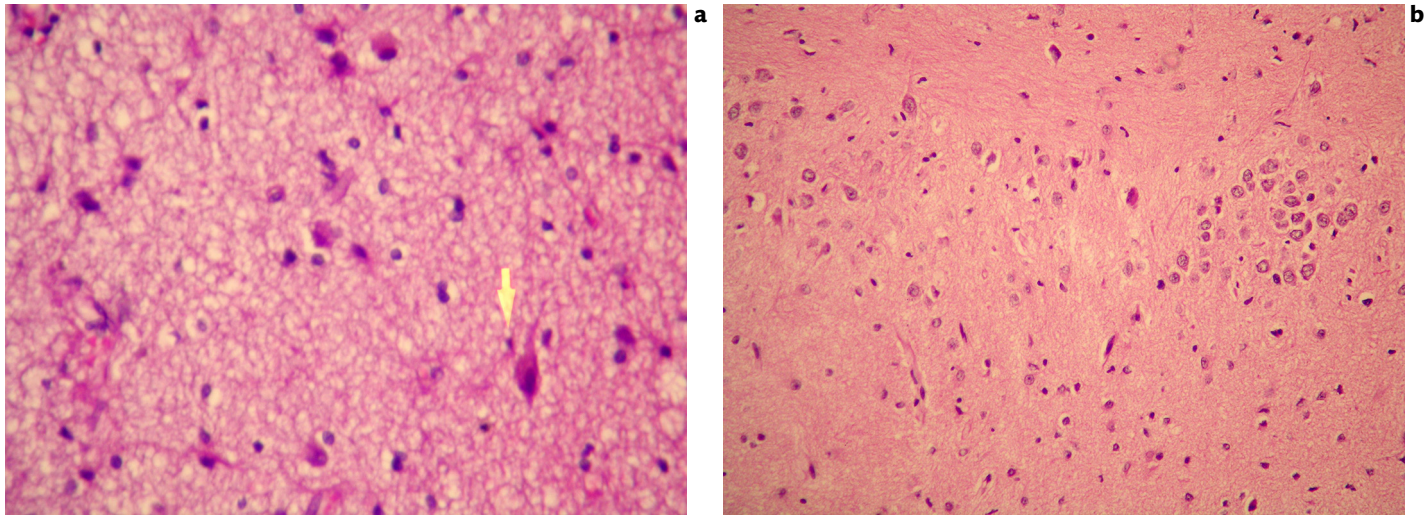

Figure 1. a, b. CA1 sector showing high grade neuronal loss, rare neuronal cell (yellow arrow) and gliosis (a). Dentate gyrus showing neuronal loss in the middle area (b).

Table 1. Clinical and histopathological parameters of the epilepsy patients

	Non-IPI (n=3)	IPI with seizures (n=22)	Seizure-free IPI (n=8)	*P* value
Onset of epilepsy (age-year ± SD)	13.33±3.21	9.3±5.76	12.75±10.53	0.409
Duration of epilepsy (year ± SD)	17±7.94	16±9.40	17±7.00	0.617
Side of operation Right Left		 11 (84.6%) 11 (64.7%)	 2 (15.4%) 6 (35.3%)	0.212
IPI <5 IPI >5		20 (80%) 3 (60%)	5 (20%) 2 (40%)	0.329
Neuronal loss low-moderate high grade		 7 (70%) 15 (75%)	 3 (30%) 5 (25%)	0.548

IPI, initial precipitating injury; *P* value, significance between IPI with seizures group and seizure-free IPI group.

Table 2. Comparison of clinical parameters with the p-gp expression in the hippocampus

	C494 capillary endothelial cells		C5B12 capillary endothelial cells			
	Mild-moderate	strong	Mild-moderate	Strong	P	*p*1
Disease duration >20 years <20 years	 4 (40%) 18 (78.3%)	 6 (60%) 5 (21.7%)	 9 (90%) 17 (77.3%)	 (10%) 5 (22.%)	0.049	0.636
seizure frequency >15 days (per month) <15 days (per month)	 3 (25%) 19 (90.5%)	 9 (75%) 2 (9.5%)	 7 (58.3%) 19 (95.0%)	 5 (41.7%) 1 (5.0%)	0.000	0.018
Neuronal loss low-moderate high	 9 (81.8%) 13 (59.1%)	 2 (18.2%) 9 (40.9%)	 9 (18.8%) 17 (81.0%)	 2 (18.2%) 4 (19.0%)	0.258	0.670
LP with without	 4 (66.7%) 17 (65.4%)	 2 (33.3%) 9 (34.6%)	 3 (75%) 20 (76.9%)	 1 (25%) 6 (23.1%)	0.601	0.677
SP with without	 15 (60%) 7 8 (7.5%)	 10 (40%) 1 (12.5%)	 20 (83.3%) 6 (75%)	 4 (16.7%) 2 (25.0% 9	0.217	0.624

LP, latent period; SP, silent period; *p*, significance between mild-moderate and high protein expression in the capillary endothelial cells with the antibody C494; *p*1, significance between mild-moderate and high protein expression in the capillary endothelial cells with the antibody C5B12.

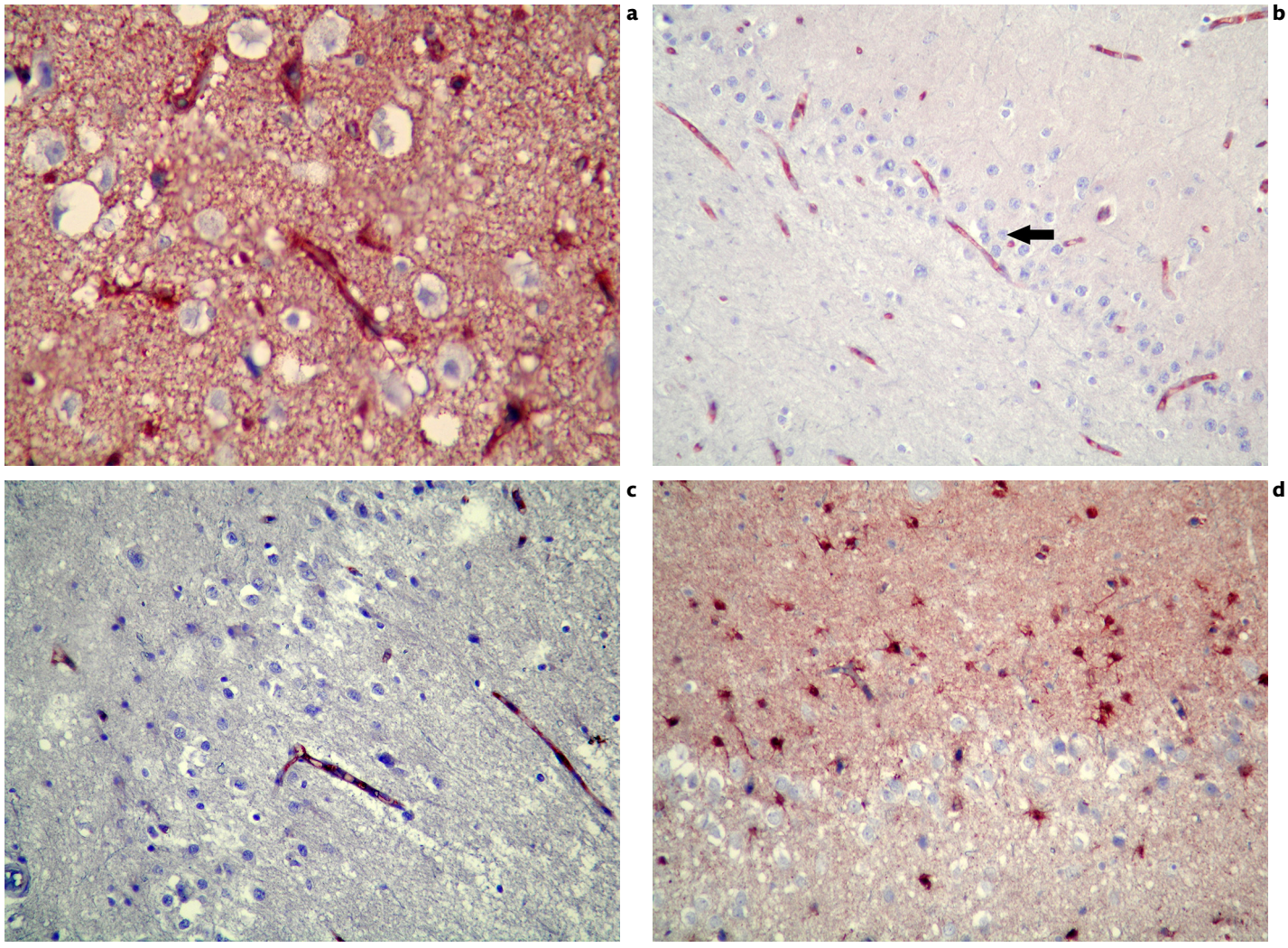

Figure 2. a-d. Intensive positive staining towards the hilus in dentate gyrus with C494 (a). Intense staining in capillaries with C494 (b). Brown staining in capillaries with C5B12 (c). Dentate gyrus capillaries endothelial cells showing moderate immuno-positivity with C5B12 (d).

All patients had protein expression with C494 in the capillary endothelial cells. C494 protein expression was mild in 3 (9.1%) patients; moderate in 19 (57.6%) patients, and high in 11 (33.3%). Expression with the antibody C494 in the astrocytic cells was mild in 9 (27.3%) patients, moderate in 8 (24.2%), and high in 2 (6.1%). No expression was evident in 14 patients. Expression in the endothelial cells with the C5B12 was mild in 6 (18.2%) patients, moderate in 20 (60.6%), and high in 6 (18.2%). One patient did not exhibit any expression. Expression in the astrocytic cells with the antibody C5B12 was mild in 1 patient and moderate in another; 31 patients did not show any expression (Figure 2A-D). The comparison of the protein expression in the capillary endothelial cells with C494 with the duration of habitual seizures revealed that when the disease duration exceeded 20 years, there was an intense staining. A comparison of protein expression in the capillary endothelial cells with C494 and C5B12 with monthly seizure frequency revealed a significantly more intense staining in the patient group with more than 15 days of seizures. There were no significant differences between C494 and C5B12 and IPI groups, degree of neuronal injury, and LP presence and duration, SP presence and duration (Table 2).

DISCUSSION

HS-MTLE is the group that most commonly undergo epilepsy surgery at adolescence and adulthood, and that shows the most resistance against medical therapy. HS-MTLE typically starts at late childhood and early adolescence, mostly between 4 and 16 years of age. In HS-MTLE patients, seizures start earlier than the other forms (4). IPI was reported at a rate of 90% among HS-MTLE patients (6). In our study we also observed an age of onset of 10.53 (±7.05) for habitual seizures; additionally, 90.9% of patients had IPI.

Prior studies have reported that patients develop IPI including FC, trauma, hypoxia, and intracranial infections, usually before the age of 5 or before non-febrile habitual seizures start (4, 6, 12). Berg et al. reported that 81% of patients had a history of seizures at infancy or childhood (13). Our study also showed that IPI emerged before 5 years of age in 78.7% of patients and after 5 years in 12.1%. Among the patients of the IPI group, 73.3% had FC; 23.3% had head trauma; and 3.3% had birth trauma.

Mathern et al. reported that IPI with seizures was frequently seen among HS-MTLE patients younger than 4 years of age whereas seizure-free IPI was seen in patients older than 4 years; they also reported that mean duration of habitual seizures was longer in the IPI group compared to the non-IPI group (6, 12). Our study did not reveal any significant difference between the IPI groups with and without seizure with respect to age of IPI, mean duration of habitual seizures and lesion side

There are characteristically a silent period and a latent period in HS-MTLE patients (4, 5). Our study similarly revealed a latent period (LP) in 78.22% of patients and a silent period in 24.22% (SP). No significant difference

was seen between IPI groups with regard to the presence of LP and SP. Berg et al. reported that SP is seen more frequently among epileptics with an early seizure onset (<5 years) as well as FC and HS (13). In our study, 6 (87.5%) out of 9 patients with SP had FC, and FC was observed below the age of 5 years in 87.5% of them. These findings support the view that there is a latent period and a silent period in the HS-MTLE patients, and that the patients with a silent period usually belong to the IPI with seizure group. IPI appearing below the age of 5 years in the majority of patients with a latent and a silent period suggests that the presence of LP and SP could be possibly affected by the age of onset of IPI. We are of the opinion that this subject should be further investigated in large patient series.

Mathern et al. reported severe neuronal loss in almost all hippocampus preparations among patients with HS-MTLE and IPI as well as a habitual seizure duration exceeding 20 years whereas they observed variable, albeit severe, degrees of neuronal loss among those who had a shorter duration, and a lesser degree of neuronal loss in the seizure-free group compared to the IPI group with seizures while other studies did not show any correlation between epilepsy duration and HS (12–14). In our study, no significant difference was observed between habitual seizure duration and between IPI groups with versus without seizure with respect to neuronal injury in hippocampus. The lack of statistical significance may have resulted from a small sample volume. In the non-IPI group, an assessment could not be made, again due to a small patient number. Former studies have reported that IP during early childhood is associated with more severe neuronal loss (13, 15). On the contrary, it has been reported that age of IPI did not affect the degree of neuronal loss (6, 12, 16). In our study, there was no significant relationship between the degree of neuronal injury between IPI onset >5 years and IPI onset <5 years.

Under physiological conditions p-gp is expressed predominantly in endothelial cells, and to a lesser degree in parenchymal and perivascular astrocytes (10, 17). However, seizures increase p-gp expression in various cell types (17–20). Sisodiya showed the overexpression of multi drug resistance gene-1 P-glycoprotein (MDR1) and multidrug resistance-associated protein 1 (MRP1) only lesionally (19).

Overproduction of p-gp in the endothelial cells of BBB prevents the entry of some drugs into the central nervous system. Löschler et al. showed that many antiepileptic drugs including phenytoin, phenobarbital, carbamazepine, lamotrigine, and felbamate are substrates for p-gp, MRPs, or both (21). Prior studies have shown that excessive p-gp production in the brain is related to the development of pharmaco-resistance against phenytoin in patients with resistant epilepsy (22, 23). Furthermore, a 46% increase was observed in hippocampal phenytoin level compared to controls as a result of p-gp deficiency at BBB of MDR1 knockout mice (24). Moreover, cerebral concentrations of many drugs were significantly increased following p-gp blockage at BBB by cerebral administration of p-gp inhibitors (21).

It has been shown that cerebral concentration of p-gp was increased in with drug-resistant epilepsy patients compared to drug-responsive epilepsy patients and healthy controls (25, 26). Similarly, an increase in p-gp expression was shown in endothelial cells as a major feature of HS-TLE (10, 18, 19). In a study on normal hippocampi that were obtained from the operations in which mesial temporal structures were removed for therapeutic purposes among patients with brain tumors resistant to medical therapy, no change was observed in both glial and endothelial cells with respect to p-gp expression (27). In the Kubata's study no correlation could be found between the degree of gliosis in hippocampus and parahippocampus and the carriers' expression (10). Although a small number of patients were studied in the present study, p-gp expression in parenchymal cells in the hippocampus was relatively higher in patients with a greater seizure duration.

In our study C494 was used as the primary antibody. C494 was more sensitive than C5B12. In line with the literature, no significant difference was found between neuronal injury in the hippocampus and p-glycoprotein staining. The comparison of protein expression of C494 in capillary endothelial cells with habitual seizure duration showed a significantly more intense staining in the group with a disease duration of more than 20 years. These findings were in support of those reported in Kubata's study and suggest that p-gp expression is also affected during disease progression (10).

A comparison of protein expression determined by C494 and C5B12 in the capillary endothelial cells with mean monthly seizure frequency revealed a significantly more intense staining in patients with a seizure frequency of more than 15 days per month. A strong p-gp expression in patients with increased seizure frequency supports the view that p-gp is effective for developing resistance against medical treatment. In an animal model with TLE it was shown that seizures caused a short-lived excessive p-gp expression in cerebral capillary endothelial cells, astroglias, and neurons, which supports the notion that, rather than epilepsy, seizures themselves cause overexpression of drug transporters. Prior studies have reported an increase in the gene coding p-gp and MDRs proteins induced by seizures (20, 28).

The limitations of our study are the small sample size and the lack of a comparison with brain tissues of patients with non-resistant epilepsy. As no surgical treatment was performed in that patient group, using their brain tissue for the study was not possible.

In conclusion, no statistically significant correlation was observed between p-gp expression and the IPI groups with and without seizures, age at the start of IPI, age at the start of habitual seizures, presence and duration of a latent period, presence of a silent period, and degree of neuronal injury at the hippocampus. These results suggest that p-gp expression is affected by disease duration and seizure frequency rather than a patient's clinical and pathological properties. Considering that the p-gp expression was greater in the patient group with a higher monthly seizure frequency, one may speculate that starting an appropriate antiepileptic drug therapy and controlling seizures at an early period after seizure onset may slow p-gp expression and delay drug resistance. Furthermore, p-gp expression was significantly higher in the resected temporal lobe in patients with HS-TLE who had postoperative seizure recurrence (29). We are of the opinion that this subject should be investigated retrospectively in larger patient volumes. Many p-gp and MRPs inhibitors are used in human cancers (23). Inhibition of ABC carriers may be used to enhance passage of many drugs into the brain (30). In patients with HS-MTLE, potential use of the inhibitors as additional therapy and developing novel drugs not carried by multidrug carriers expressed in BBB should be regarded as the new treatment targets.

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