

The role of cranial magnetic resonance imaging findings in pediatric epilepsy: A single-center experience

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ABSTRACT

OBJECTIVE: The aim of this study was to investigate cranial magnetic resonance imaging (MRI) findings in different age groups and genders in pediatric epilepsy, to determine the percentages of etiologic factors, and to evaluate the association between MRI positivity and treatment resistance.

METHODS: Cranial MRIs of 359 patients with epilepsy aged 1 month to 18 years were retrospectively evaluated. Etiologic factors as an underlying cause of epilepsy were classified as previous parenchymal damage, hippocampal sclerosis, malformations of cortical development, tumor, neurocutaneous syndrome, myelination disorder, vascular anomaly, metabolic/genetic/neurodegenerative diseases, encephalitis, and an uncategorized "other" group. Data were transferred to IBM SPSS Statistics 25.0 (SPSS Inc., Chicago, IL, USA), and descriptive statistics, correlation analyses, chi-square, and t-tests were performed.

RESULTS: Among the patients included in the study, 141 (39.3%) had pathological findings on MRI related to the etiology. Previous parenchymal damage (39.7%) was the most common etiologic cause in all age groups. Regarding the relationship between drug resistance and MRI positivity, MRI positivity was observed in 72% of drug-resistant cases, while a complete response to therapy was found in 67.6% of MRI-negative cases.

CONCLUSION: MRI guides clinicians to determine the presence of an etiologic factor as the underlying cause of childhood epilepsy before treatment planning. MRI positivity is a remarkable indicator of response to antiseizure drug treatment and drug resistance.

Keywords: Drug resistance; epilepsy; etiology; magnetic resonance imaging; polytherapy.

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Epilepsy is defined as a brain disorder characterized by recurrent and unpredictable interruptions of normal brain function, called epileptic seizures [1]. Neuroimaging plays an important role in the evaluation, referral, and treatment of a child with epilepsy. In the evaluation of epilepsy cases, magnetic resonance imaging (MRI) is the most specific and sensitive of all structural imaging modalities for

detecting subtle abnormalities. The primary role of MRI in epilepsy cases is to identify and establish the underlying structural abnormalities such as tumors, malformations of cortical development, hippocampal sclerosis, neurocutaneous diseases, vascular malformations, sequelae changes, etc. Thus, it could assist in the etiologic diagnosis and classification of different epilepsies and epileptic syndromes,

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and contribute to the planning of treatment strategies and assessment of prognosis [2]. Over the years, advances in the use of MR (high-field MRI, functional MRI, diffusion tensor imaging, MR spectroscopy, and positron emission tomography-MRI) have contributed to the identification of epileptogenic foci and treatment planning [3]. However, especially in developing countries, these advanced neuroimaging techniques are not preferred in most centers due to their cost, and the diagnosis and treatment of patients are carried out based on the evaluation of traditional anatomical MRI. In the last two decades, with the advances in diagnostic imaging, the detection rate of cortical dysplasia by MRI has increased, and therefore fewer cases have been classified as “cryptogenic” (“unknown” in the new classification) [3]. Pathology is observed in approximately half of the imaging studies in children with new-onset focal epilepsy, and 15–20% of these studies provide useful information for the detection of an epileptogenic focus [4–6]. However, it has been reported that MRI has little benefit in cases of idiopathic generalized epilepsy and benign rolandic epilepsy cases [7, 8]. In addition, it was found that the surgical success rate in MRI-positive patients was twice that of MRI-negative patients [9].

The aim of the present study was to emphasize the role of cranial MRI in determining the etiology of pediatric epilepsy, as well as to determine the lesion detection rates in epilepsy cases referred to MRI in our clinic, to compare these rates with the literature, to evaluate the age and gender distribution of MRI findings, to determine the distribution percentage of underlying etiologic causes, and to evaluate the associations of the MRI findings with epilepsy types and treatment response.

MATERIALS AND METHODS

Ethical committee approval for this retrospective study was obtained on May 15, 2020, with decision number 48670771-514.10. Our study was conducted in accordance with the Declaration of Helsinki. The present study included 359 pediatric patients aged 1 month to 18 years who were referred to the Pediatric Neurology Clinic during January 2017–May 2020 with new-onset nonfebrile seizure complaints, who were diagnosed with epilepsy, and whose cranial MRI was performed at the radiology clinic of the city hospital. Cases with a history of psychogenic non-epileptic seizures, febrile seizures, acute metabolic seizures (e.g., hyponatremia, etc.), trauma-related seizures, and status epilepticus within the 10 days prior to MRI (because MRI findings may be confusing

Highlight key points

- There is an association between MRI positivity and treatment success, drug resistance, and epilepsy type.
- Cranial MRI plays a crucial role in the treatment planning of pediatric epilepsy cases.
- Performing control MRIs with dedicated epilepsy protocols and ≥ 3 Tesla MRI machines will facilitate the detection of subtle epileptogenic foci in MRI-negative patients who are resistant to treatment or require polytherapy.

in the acute period) were not included. Benign findings unrelated to the etiology of epilepsy but that could be detected incidentally on a cranial MRI, such as partial empty sella, megacisterna magna, perivascular spaces, benign intracranial cysts (choroidal fissure cyst, pineal cyst, arachnoid cyst), and benign intracranial calcifications (e.g., choroid plexus cysts, falx calcifications), were not recorded. The patients' cranial MRI images were retrospectively evaluated. An MRI examination of the patients was performed with a 1.5 Tesla magnet MRI machine (Achieva, Philips Medical Systems, Best, The Netherlands) according to the epilepsy protocol. Gadolinium contrast material (dose: 0.1 mg/kg) was used when there was concern for tumor, vascular malformation, infection, or inflammation. The standardized MRI sequences in the pediatric epilepsy protocol are listed in Table 1.

Patients were grouped according to age, gender, type of epilepsy, number of anti-seizure medications if any, etiology, drug response, and drug resistance. Drug resistance was defined as the inability to achieve complete seizure freedom despite two appropriately selected anti-seizure drugs (monotherapy or combination), and drug response was defined as having a seizure-free period of at least three times the seizure interval before treatment or a seizure-free period of 12 months, whichever is longer [10]. Etiologic causes of the disease were classified as previous parenchymal damage, malformations of cortical development, space-occupying lesion in the parenchyma, metabolic/neurodegenerative diseases, myelination disorder, hippocampal sclerosis, neurocutaneous syndrome, encephalitis/encephalopathy, vascular anomaly, and the other group whose cause is unknown or cannot be categorized.

The types of epilepsy were classified as focal, generalized, combined focal, generalized, and unknown. Patients with MRI findings that would explain the etiology of the epilepsy were considered MRI-positive. Demographic data were analyzed based on age and gender. The relationship between MRI positivity and

TABLE 1. The standardized 1.5 Tesla MRI protocol for pediatric epilepsy patients

MRI sequences	Slice thickness/interslice gap (mm)	Matrix	Field of view (mm)	TR (ms)	Flip angle
T1W 3D gradient isovolumetric sagittal	1/0	240×200	240×240	25	30
T2W TSE axial	3/0–0.5	304×238	230×230	9272	90
T2W SE coronal	3/0–0.5	304×238	230×230	7850	90
FLAIR axial	3/0–0.5	256×173	230×230	6000	90
FLAIR coronal	3/0.5	256×173	210×210	7850	90
T1W IR axial	3/0–0.5	288×202	211×211	2250	90
DWI axial	5/1	128×128	230×230	4305	-
SWI	3/0.5	256×205	220×220	1491	18
Post-contrast T1W 3D isovolumetric sagittal	1/0	240×183	240×240	25	30

T1W 3D: T1-weighted 3-dimensional; TSE: Turbo spin echo; SE: Spin echo; FLAIR: Fluid attenuated inversion recovery; IR: Inversion recovery; DWI: Diffusion weighted imaging; SWI: Susceptibility weighted imaging; TR: Time to repetition. In DWI, b-values were 800–1000 s/mm².

epilepsy types and their rates was evaluated. The association of MRI positivity with drug resistance and complete response, the use of monotherapy or polytherapy in treatment, and their rates were evaluated.

Statistical Analysis

Statistical analysis of the data was performed using IBM SPSS Statistics 25.0 (SPSS Inc., Chicago, IL, USA). The differences between the frequencies of categorical variables were examined using the Chi-square test and Fisher's exact test. The independent Student's t-test was used for the normally distributed parameters. A p-value less than 0.001 was considered statistically significant. The Mann–Whitney test was used for the comparisons between two independent groups for data not normally distributed. Descriptive statistics for non-normally distributed data were presented as mean with \pm standard deviation.

RESULTS

Regarding the gender distribution of the 359 epilepsy cases participating in the study, 53.2% (n=191) were male and 46.8% (n=168) were female. The mean age of the patients was 90.6 ± 55.7 months. Among the patients who participated in the study, the number of those who had pathological findings related to the etiology on MRI was 141 (39.3%), and the number of those who did not have pathological findings was 218 (60.7%). The demographics and some clinical data of the patients (including MRI positivity, type of epilepsy, number of medications used, and status of drug resistance) are shown in Table 2.

TABLE 2. Number (N) and percentage (%) of all patients according to gender, MRI positivity, MRI positivity of different age groups, epilepsy types, patients with monotherapy, polytherapy, seizure freedom or drug resistance

Parameters	n=359 (%)
Male	53.2
Female	46.8
MRI positive	39.3
MRI negative	60.7
MRI positive male	51.1
MRI positive female	49
MRI positive	
0–1 years	17
1–6 years	31.9
6–12 years	32.6
>12 years	18.4
Types of epilepsy	
Focal	59.9
Generalized	24.2
Focal and generalized	4.5
Unknown	11.4
Monotherapy	66.9
Polytherapy	30.4
No medication	2.8
Seizure freedom	80.2
Drug-resistant epilepsy	13.9
Other conditions	5.9

MRI: Magnetic resonance imaging.

TABLE 3. Number and percentage distribution of epilepsy cases (n=141) with findings on MRI according to the aetiological causes

MRI findings	%
Previous parenchymal injury	39.7
Malformations of cortical development	7.1
Space-occupying lesion in the parenchyma	6.3
Metabolic-degenerative disease	5.7
Myelination disorder	5.7
Hippocampal sclerosis	3.6
Neurocutaneous syndrome	3.6
Encephalitis/encephalopathy	2.8
Vascular anomaly	1.4
Unknown cause/not categorized	24.1

MRI: Magnetic resonance imaging.

The distribution of the 141 cases with MRI findings and their detailed etiologies are shown in Table 3. Previous parenchymal injury (39.7%) (Fig. 1), malformations of cortical development (Fig. 2), and space-occupying lesions in the parenchyma (6.3%) were the most common pathologies, while vascular anomaly (1.4%) (Fig. 3) was the rarest pathology. Metabolic abnormality was present in the etiology of 5.7% of the MRI-positive cases (Fig. 4). Thirty-four cases (24.1%) that had pathological findings on MRI but could not be included in these etiological

groups were classified as having an unknown or uncategorized cause. The pathologies in the group of patients with unknown or uncategorized causes were: pathological signal changes in the centrum semiovale; hyperintensity in the periventricular white matter; hypoplastic corpus callosum; restricted diffusion in the basal ganglia, and prominent appearance in the lateral ventricles. Among MRI-positive cases, cerebral atrophy was present in 66 patients (46.8%), while cerebellar pathology (atrophy, hypoplasia, encephalomalacia) was found in 14 patients (9.9%).

The relationship between epilepsy type and presence of MRI findings is shown in Table 4. Pathological findings on MRI were most frequent in the combined focal and generalized epilepsy groups (68.8%) ($p < 0.001$).

The frequencies of epilepsy types and their associations with drug resistance are shown in Table 4. It was found that 93.2% of the cases with combined focal and generalized epilepsy were in the drug-resistant group ($p < 0.001$).

The association of pathological findings on MRI with drug resistance and complete response is shown in Table 5. Thirty-six of the 50 patients with drug-resistant epilepsy (72%) had findings on MRI, while the majority of patients (67.6%) who had a complete response to drugs had no MRI findings ($p < 0.001$).

Regarding the relationship between MRI positivity and patients receiving of monotherapy and polytherapy, pathology was detected on MRI in 29.1% of patients in

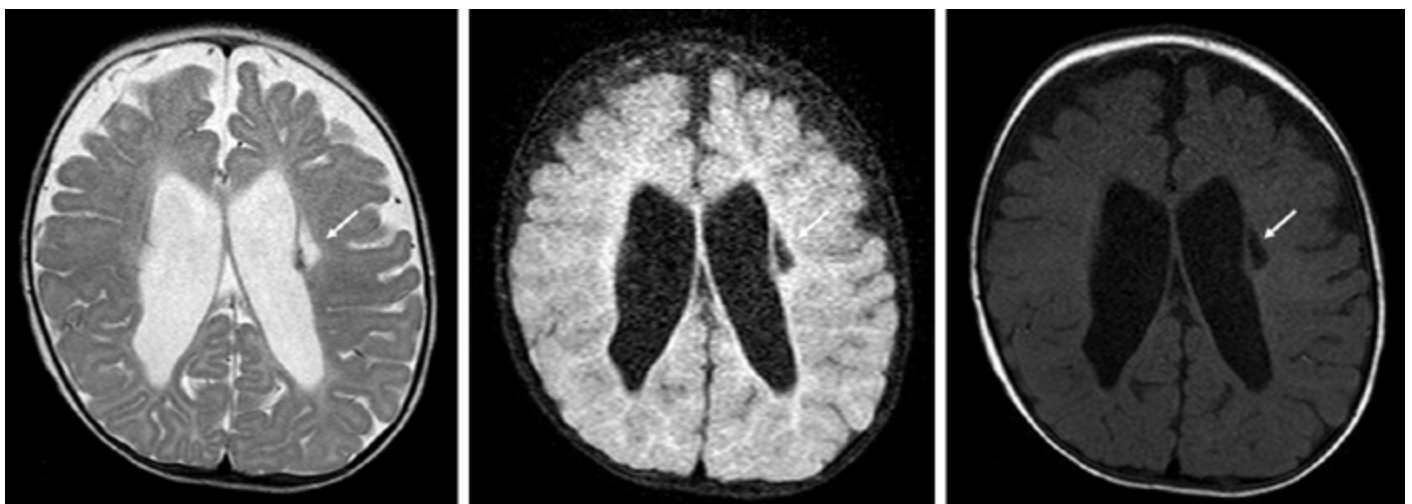


FIGURE 1. MRI of an 8-month-old female patient with cerebral palsy and a history of perinatal hypoxia and prematurity. Axial T2-weighted image (T2-WI), fluid attenuated inversion recovery (FLAIR), and T1-weighted images (T1-WI) are shown from left to right. Atrophic volume loss in the periventricular white matter, ex vacuo dilatation and contour lobulation of the lateral ventricles, and periventricular cystic encephalomalacia adjacent to the body of the left lateral ventricle (arrow) are shown.

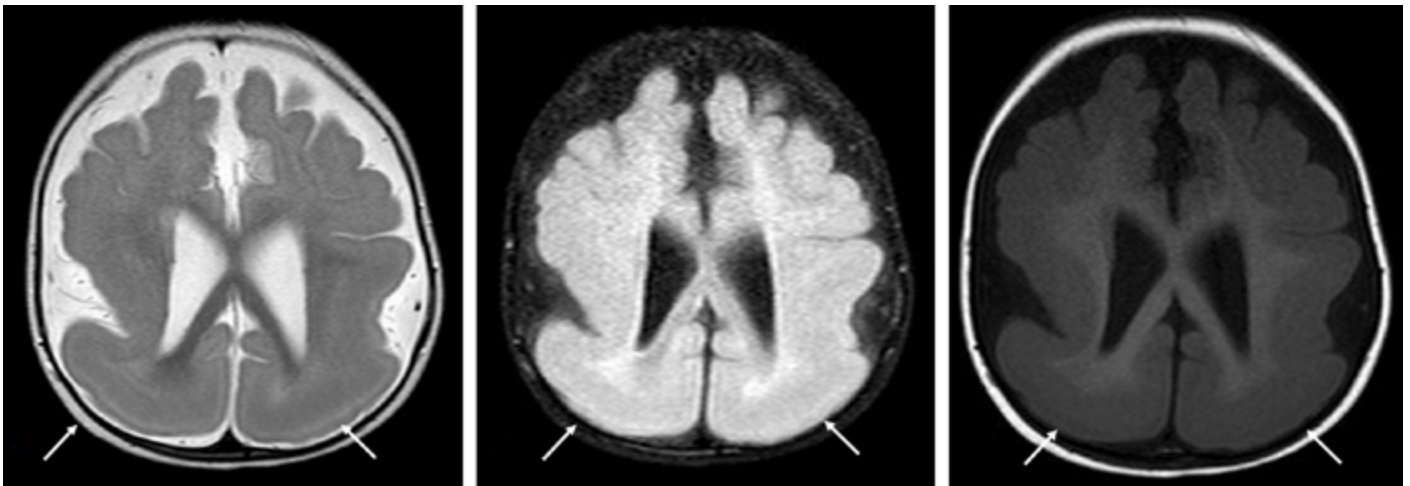


FIGURE 2. MRI of a seven-month-old female patient with epilepsy. Axial T2-WI, FLAIR and T1-WI are shown from left to right. Findings of type I lissencephaly characterized by thick cortex, shallow and sparse sulci (arrows) in both cerebral hemispheres are most prominent in the biparietal regions.

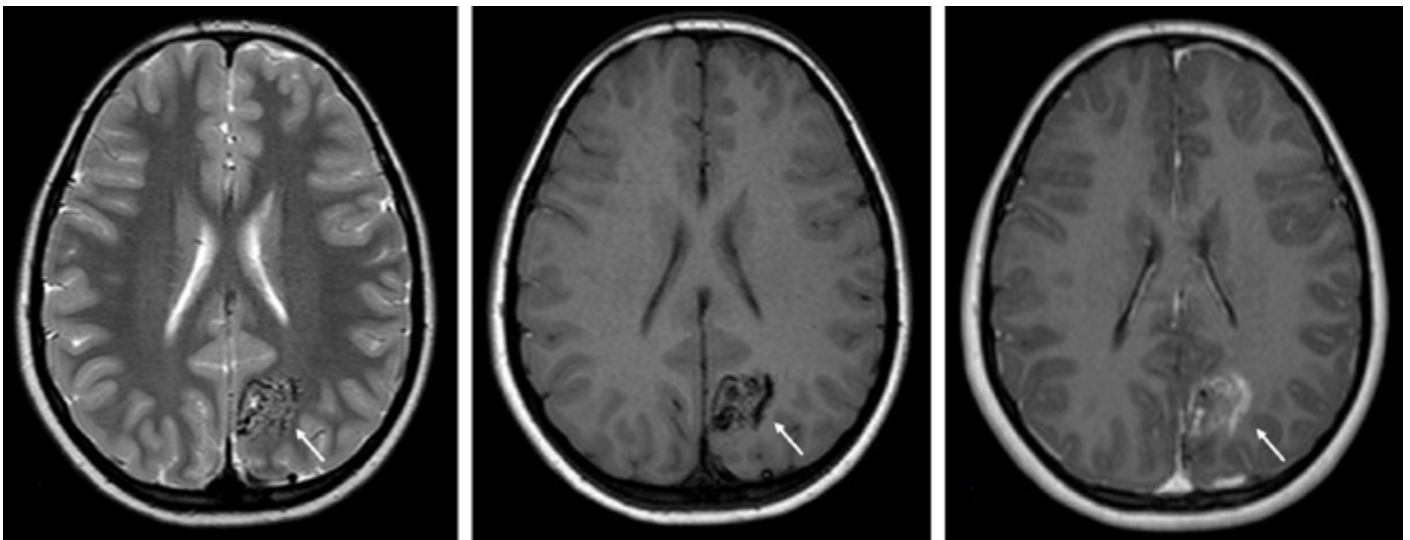


FIGURE 3. MRI of an eight-year-old female patient with epilepsy. The nidus of an arteriovenous malformation in the medial parafalcine region of the left posterior parietal lobe is seen in the cortico-subcortical area, consisting of enlarged and clustered signal-void vascular structures in axial T2-WI (on the left side), T1-WI (in the middle), which showed contrast enhancement after intravenous Gadolinium injection (on the right side).

the monotherapy group (a total of 240 patients) and in 62.9% of patients in the polytherapy group (a total of 109 patients) ($p < 0.001$). MRI positivity was seen in 3 out of 10 patients (30%) who were not receiving medication.

When the relationship between the pathologies in the etiology of epilepsy detected by MRI and the types of epilepsy was examined, it was found that of the 56 cases with previous parenchymal damage, the majority of the patients (80.4%, $n=45$) had focal epilepsy, 5.4% ($n=3$) had generalized epilepsy, and 10.7% ($n=6$) had combined

focal and generalized type epilepsy ($p < 0.001$). Among cases with cerebral parenchymal atrophy, 65.2% ($n=43$) had focal, 12.1% ($n=8$) had generalized, and 13.6% ($n=9$) had combined focal and generalized type epilepsy ($p < 0.001$). There was no significant association between other pathological MRI findings and the type of epilepsy.

Type of epilepsy was not significantly associated with side of MRI pathology (right or left hemisphere, or both), location in the cerebral parenchyma (gray or white matter, or both), or presence of cerebellar involvement.

TABLE 4. Association between epilepsy types and MRI positivity/negativity

Epilepsy type	MRI (-)		MRI (+)	
	n	%	n	%
Focal epilepsy	109	50.7	106	49.3
Generalized epilepsy	73	83.9	14	16.1
Combined focal and generalized	5	31.2	11	68.8
Unknown	31	75.6	10	24.4

MRI: Magnetic resonance imaging.

TABLE 5. Association of pathologic findings on magnetic resonance imaging with drug resistance and complete response

Epilepsy type	MRI (-)		MRI (+)	
	n	%	n	%
Drug-resistant epilepsy	14	28	36	72
Epilepsy with complete response to the drug	188	67.6	90	32.4

MRI: Magnetic resonance imaging. Patients with partial response to drug or patients without drug treatment were not included in the table.

DISCUSSION

The present study is one of the few to examine the role of brain MRI findings in determining the underlying etiologic cause of childhood epilepsy, the association of MRI positivity with epilepsy types, and the impact of these factors on treatment success (such as the presence of drug resistance and the number of drugs used). Cranial MRI plays a key role in predicting polytherapy or monotherapy candidates in epilepsy patients, as well as in identifying drug-resistant surgery candidates and thus providing rapid and effective seizure control.

In 39.3% of our case population (141/359), pathological findings were detected on MRI. The majority of these were previous parenchymal damage (39.7%) and malformations of cortical development (7.1%). In a study conducted by Kalnin et al. [11] on 281 pediatric patients who had unprovoked seizures for the first time, MRI positivity was reported to be 31% (87/281), and gray matter lesions such as ventricular enlargement (51%), leukomalacia/gliosis (23%), heterotopy, or cortical dysplasia (12%) were also the most frequently detected pathologies. In another study conducted by Durá-Travé et al. [12] on 457 pediatric epilepsy patients, the

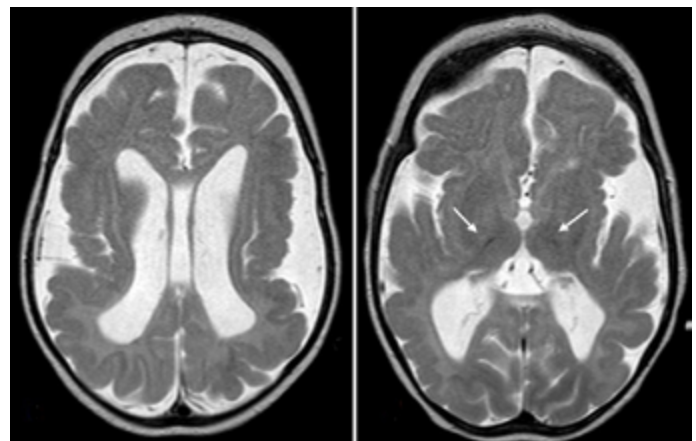


FIGURE 4. MRI images of a 6-month-old male patient with a homozygous mutation in the *OCNL* gene (pseudo-TORCH syndrome 1). It shows diffuse atrophic volume loss which is more prominent in the cerebral white matter and thalami. Bithalamic calcifications are visible as hypointense foci on axial T2-weighted images (arrows).

lesion detection rate on MRI was 29.4% (134/457), the detection rate of significant lesions (which were considered to be potentially related to the epilepsy) was 21.9% (100/457), and the most common abnormalities were

white matter lesions (27.6%). As observed in the present study, the most common pathology in MRI-positive cases in many studies was previous parenchymal injury. Perinatal asphyxia could be observed at a rate of 1–10/1000 live births, depending on the developmental level of countries [13]. Therefore, it is something expected that previous parenchymal injuries, especially those associated with hypoxic-ischemic encephalopathy, are the most common etiological factors detected by MRI.

Cerebral cortical malformations may occur after an interruption of normal developmental processes that may be associated with neuronal proliferation, migration, or organization. Malformations of cortical development are the second most common pathological condition, with a frequency of 7.1% (11/141) in the present study. Although this rate has been reported in a range of 9–30% in different studies, this variation is due to differences in inclusion/exclusion criteria, study objectives, and sample sizes [11, 12, 14].

Brain tumors account for 2–4% of epileptogenic lesions in the general epilepsy population, and the formation of abnormal discharges in normal neurons irritated by the mass has been suggested as the main mechanism in the development of epilepsy [8, 15]. The brain tumors detected in our study were hypothalamic hamartoma, pilocytic astrocytoma, diffuse midline glioma, and glioblastoma. Their frequency was 1.4% (9/359) among all epilepsy cases and 5.7% (9/141) among MRI-positive cases. It was the third most common pathology. In the literature, this rate varied between 0.6 and 4%, and thus our findings seemed to support the literature [2, 5, 12, 16].

In 18.4% of our cases (66/359), we found unilateral or bilateral cerebral atrophy in the cerebral hemispheres at the level of the gray and/or white matter. Cerebral atrophy is characterized by parenchymal volume loss and enlargement of intra- and extra-axial cerebrospinal fluid spaces and can have many causes, such as metabolic, demyelinating, neurodegenerative, infectious, inflammatory, cerebrovascular, and post-traumatic processes. It is a finding that may accompany the pathologies in the etiology of epilepsy or may be seen on MRI as a complication of neuronal damage caused by a disease independent of the etiology or as a complication of chronic antiseizure medication use [17–19]. The frequency of cerebral atrophy in studies of childhood epilepsy ranged from 10 to 19%, and these findings were supported by our study [2, 12, 20].

Age classification of MRI-positive cases showed that the pathology was most commonly detected in school-aged children (32.6%). However, in the literature, infants had the highest frequency of pathology in the literature

[12]. The reason for this difference in our study may be related to the socioeconomic status and awareness level of the families, as well as to the fact that most of the included cases were school-aged children. Since late admission to the hospital or a late visit to a physician may be another reason for the difference in the distribution of the groups, we suggest that the assessment of socioeconomic level may be related to the age of diagnosis.

Regarding the gender distribution of epilepsy and MRI-positive cases in the present study, the frequency was higher in males. In a prevalence study of approximately 46,000 children with epilepsy in Türkiye, the frequency of epilepsy was found to be significantly higher in males ($p < 0.05$) [21]. There are other studies in the literature indicating that the male-to-female ratio in children with epilepsy is high in favor of the male gender [22]. It has been speculated that steroid hormones and a higher susceptibility of men to injury-related seizures than females may play a role in the gender difference [23, 24]. However, there are also studies suggesting that some specific epilepsy subtypes (e.g., idiopathic generalized epilepsy, cryptogenic location-associated epilepsy) are more common in women [25].

In the management of newly diagnosed epilepsy patients, monotherapy is preferred to polytherapy because it has similar efficacy but better tolerability in most patients [26]. There are studies reporting that the cases who responded well to monotherapy had no or minor abnormalities on MRI [27]. In the present study, MRI pathology was detected in 29.1% of the monotherapy group and 62.9% of the polytherapy group, and the differences between these two groups were significant ($p < 0.001$). In another study evaluating the differences between epilepsy patients receiving polytherapy and those receiving monotherapy, MRI positivity was found in 34.6% of those receiving monotherapy and 69% of those receiving polytherapy [28]. In this respect, the results of the study were consistent with the literature and supported the thesis that MRI positivity is one of the factors to be considered in treatment planning and in the evaluation of treatment outcomes.

Drug-resistant epilepsy is associated not only with a significant decrease in quality of life, but also with psychiatric problems such as depression and behavioral disturbances [29]. It has been reported in the literature that seizure control cannot be achieved in 10–30% of cases despite appropriate and effective medical treatment, and these cases fall into the drug-resistant group [2, 30, 31]. In our study, drug resistance was found in 13.9% ($n=50$) of the patients. MRI positivity was present in 36 (72%)

of the treatment-resistant cases in the present study, and this rate was highly significant compared to the drug-responsive cases ($p < 0.001$). In the study by Gururaj et al. [32], 78% of the patients in the resistant group and 8% of patients in the control group had pathology on MRI. Although our results were generally consistent with those in the literature, it should be noted that the range in the present study was wider. It is difficult to control seizures if the underlying pathology is not removed during the development of resistance [33]. Identification of an epileptogenic lesion on MRI in drug-resistant epilepsy is a strong predictor of successful epilepsy surgery. However, a normal MRI should not preclude surgical evaluation, as favorable outcomes in this group are still possible in this group [34].

When the epilepsy types were classified into four main groups: focal, generalized, combined focal/generalized, and unknown, the highest frequency of MRI positivity was found in the combined focal/generalized group (68.8%) (Table 4). In the study conducted by Amirsalari et al. [2] on 200 pediatric patients, abnormal MRI findings were detected in 57 cases (28.5%), but there was no significant relationship between epilepsy type and abnormal MRI findings. In the study conducted by Kalnin et al. [11], in children with symptomatic or cryptogenic seizures, at least one MRI abnormality was found in 42.9% of patients with generalized seizures and in 39.2% of patients with focal seizures. At least one MRI abnormality was found in 23–30% of patients with generalized idiopathic epilepsy. Betting et al. [35] studied 134 patients with idiopathic generalized epilepsy between the ages of 9 and 50 years and found abnormal MRI findings in 24% of the patients. The differences between our findings and those in the literature can be attributed to the differences in the patient populations and to the fact that the types of epilepsy were classified differently in these studies.

The present study had several limitations [1]. This was a retrospective study based on clinical and radiological records. The first MRIs of the patients' were evaluated in the study. There are studies in the literature reporting that repeat MRI showed positive findings in patients with focal epilepsy [4, 36, 37]. The study was performed with a 1.5 Tesla MR machine, and it is known that the sensitivity for detecting focal epileptogenic foci is higher with high-resolution MRI devices (≥ 3 Tesla) [38, 39]. We did not include EEG findings because some patients had their EEGs performed at different institutions, so we could not analyze the relationship between EEG and MRI findings. Drug resistance may be caused by patients' lack of adherence to therapy, but we did not investigate patients' adherence to therapy.

Conclusion

This single-center retrospective study of 359 pediatric epilepsy cases in search of etiologic causes (with an MRI positivity rate of 39.3%, in which previous paraneoplastic injury was the most common) may contribute to the national data pool. In addition, we have shown that there is an association between MRI positivity and treatment success (monotherapy vs. polytherapy), drug resistance, and epilepsy type. Thus, cranial MRI plays a crucial role in the treatment planning of pediatric epilepsy cases. MRI helps predict prognosis, determine long-term resistance to antiseizure drugs, and identify potential surgical candidates. Performing control MRIs with dedicated epilepsy protocols and ≥ 3 Tesla MRI machines will facilitate the detection of subtle epileptogenic foci in MRI-negative patients who are resistant to treatment or require polytherapy.

Ethics Committee Approval: The Istanbul Prof. Dr. Cemil Tascioglu City Hospital Clinical Research Ethics Committee granted approval for this study (date: 05.15.2020, number: 48670771-514.10).

Authorship Contributions: Concept – OY, TAU; Design – OY; Supervision – OY; Materials – OY, TAU; Data collection and/or processing – OY, TAU; Analysis and/or interpretation – OY, TAU; Literature review – OY, TAU; Writing – OY, TAU; Critical review – OY.

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