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Original article

Epileptic spasm and other forms of epilepsy in presumed perinatal arterial ischemic stroke in Turkey after more than 10 years follow-up: A single centre study

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Abstract

Purpose: To identify the frequency of epilepsy and whether the association of epilepsy with clinical and neuroimaging findings in children with presumed perinatal arterial ischemic stroke (PPAIS).

Methods: We performed a retrospective analysis of 37 children with PPAIS followed-up at a tertiary referral center between January 1, 2000, and October 31, 2016. Clinical data including demographic features, age at onset of symptoms and seizures, initial clinical presentation, epilepsy features, used antiepileptic drugs, and thrombophilia screening results were abstracted from medical records. Brain magnetic resonance imaging scans were assessed for infarct laterality, location and affected brain regions.

Results: The median age of the patients was 12 years (range 2–17.9 years) at last assessment. The initial symptom of PPAIS was early hand preference in 33 children (89%) and seizure in 4 children (11%). A total of 20 children (54%) developed epilepsy at a median age of 0.9 years. There were two peaks of epilepsy onset in infancy and adolescence. Fifteen children (41%) had focal epilepsy and 5 children (14%) had epileptic spasms. Twelve out of 20 children (60%) with epilepsy had drug resistant epilepsy. Cortical involvement was a statistically significant predictor of epilepsy ($p = 0.021$, relative risk 4.4, 95% confidence interval 0.7–27.7).

Conclusion: More than half of the children with PPAIS suffered from epilepsy during childhood, of whom developed drug resistant epilepsy in majority. Children with cortical lesion may have a higher risk to develop epilepsy.

Keywords: Child; Epilepsy; Stroke

1. Introduction

Children with presumed perinatal arterial ischemic stroke (PPAIS) frequently develop epilepsy in childhood. Most of the studies evaluating epilepsy after perinatal stroke, in which the frequency of epilepsy is highly variable ranging from 27% to 54%, were consisted of children with PPAIS, neonatal arterial ischemic stroke and periventricular venous infarction. There are a few studies focusing on PPAIS, however, these studies have relatively short follow-up periods [1–6]. Initial symptom of stroke and affected brain area have been suggested to be predictive of epilepsy outcome in children with presumed perinatal stroke [3,5].

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In this study, we aimed to identify the frequency of epilepsy in long-term and whether there is an association of epilepsy with clinical and neuroimaging findings in children with PPAIS.

2. Methods

This was a single centre retrospective cohort study of the patients with PPAIS followed-up at a tertiary referral center, Istanbul Faculty of Medicine, Department of Pediatric Neurology, in Turkey between January 1, 2000, and October 31, 2016.

2.1. Participants

Children with presumed perinatal ischemic stroke were selected for the study from the database of the Istanbul Faculty of Medicine, Department of Pediatric Neurology. Presumed perinatal ischemic stroke defines a child with no neonatal neurologic history presenting with newly recognized neurological deficit or seizure attributable to remote stroke on neuroimaging [3,7]. Children with limiting lesions to arterial territories on brain magnetic resonance imaging (MRI) and at least 2 years-of-age at the last assessment were included. The exclusion criteria were the presence of periventricular venous infarction or perinatal hemorrhagic stroke on neuroimaging, and other diseases affecting central nervous system.

The study protocol was approved by the Ethics Committees of the Istanbul Faculty of Medicine. All participants agreed to participate in the study and the guardian of each subject signed a written informed consent.

2.2. Clinical data

Clinical data including (1) demographic features, (2) initial symptom of PPAIS, (3) age at onset of symptoms and seizures, (4) epilepsy features, (5) used antiepileptic drugs, and (6) thrombophilia screening results were abstracted from medical records.

Epilepsy was defined as either at least two unprovoked seizures occurring more than 24 h apart or 1 unprovoked seizure with a high probability for further seizures [8]. Children with epilepsy were categorized as having drug resistant epilepsy in case of failure of two tolerated appropriate antiepileptic drug use [9].

Screening for thrombophilia was comprised of activity of antithrombin III, protein C and protein S, fibrinogen, factor VIII, factor IX, activated protein C resistance, plasminogen, anticardiolipin antibodies, lupus anticoagulant, lipoprotein a and homocysteine levels, genotyping of methylenetetrahydrofolate reductase (MTHFR) (677C > T, A1298C), prothrombin c.20210G > A, factor V Leiden and plasminogen activator inhibitor-1 (PAI-1).

2.3. Neuroimaging data

The required brain MRI protocol for inclusion was 1.5 Tesla MRI including T2-weighted/FLAIR, T1-weighted sequences in the sagittal and axial planes. MRI scans were assessed for infarct laterality, location and affected brain regions (basal ganglia, cortex, cerebellum, or brainstem) by an experienced neuroradiologist, blinded to the clinical data findings (S.S.).

2.4. Statistical analysis

All statistical analyses were performed by SPSS Statistics for Windows version 21.0 (IBM Corp., Armonk, NY, USA) and R version 3.4.2. Descriptive statistics for quantitative and qualitative variables were defined as median and frequency, respectively. The ages at onset of symptoms and seizures were analyzed by Shapiro-Wilk test for their normality of distribution. Statistical comparison of the ages at onset of symptoms and seizures was performed between the patients with or without epilepsy using Mann-Whitney U test. The initial symptom of PPAIS, the presence of thrombophilia risk factor, and neuroimaging findings including infarct laterality, location and affected brain regions were analyzed by Fisher exact test to determine their association to epilepsy, and relative risk was calculated in case of any significant difference. A value of $p < 0.05$ was considered statistically significant. The Kaplan–Meier estimate of epilepsy-free survival was calculated. In case of epilepsy occurrence, the censor time was identified as the time between birth and the age at epilepsy onset, otherwise the time between birth and the age at last follow-up.

3. Results

3.1. Participants' characteristics

A total of 37 patients (22 male, 15 female) with PPAIS were analyzed (Fig. 1). At last assessment, the median age of the patients was 12 years (range 2–17.9 years). The demographic and clinical features of patients are presented in Table 1.

All participants were born appropriate for gestational age at term without any history of neonatal asphyxia. The initial symptom of PPAIS was early hand preference in 33 children (89%) and seizure in 4 children (11%) at a median age of 7 months (range 2–19 months). Seizure types were epileptic spasms, myoclonic and focal seizures in 4 children initially presenting with seizure.

Thirty-one out of 37 children underwent prothrombotic risk factors screening and 9 children (29%) had at least 1 prothrombotic risk factor. None of them had stroke recurrence.

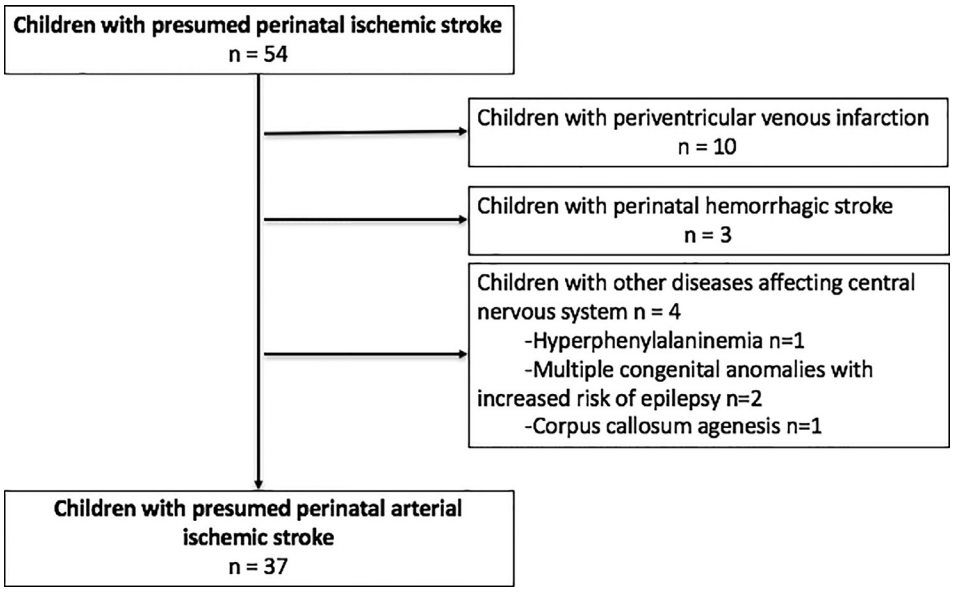

Fig. 1. Flow chart of participation.

Table 1
Demographic and clinical features of patients.

	Patients with presumed perinatal arterial ischemic stroke
N	37
Male, *n* (%)	22 (59)
The median age at last assessment, year (range)	12 (2–17.9)
The median age at onset of symptom, month (range)	7 (2–19)
Initial clinical presentation, neurological deficit/seizure, *n* (%)	33/4 (89/11)
The median age at onset of seizures, month (range)	11 (4–192)
Epilepsy, *n* (%)	20 (54)
Drug resistant epilepsy, *n* (%)	12 (32)
Epileptic spams, *n* (%)	5 (14)

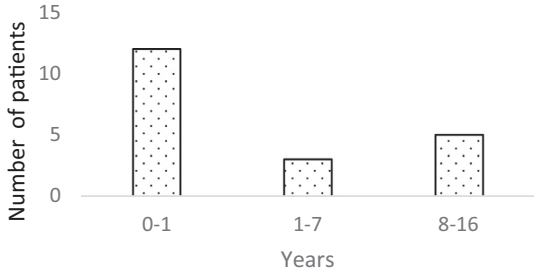

Fig. 2. Distribution of patients based on the age at epilepsy onset.

3.2. Epilepsy characteristics

Twenty children (54%) developed epilepsy and 12 children (32%) had drug resistant epilepsy. Median age at onset of seizure was 11 months (range 4–192 months). Twelve out of 20 children (60%) developed epilepsy before 1-year-old, 3 children (15%) between 1 and 7 years, 5 children (25%) between 8 and 16 years. There were two peaks of epilepsy onset in infancy and adolescence (Fig. 2). Kaplan-Meier epilepsy-free survival curves are shown in Fig. 3. Estimated cumulative incidence of epilepsy was 35% (95% confidence interval [CI] 18–49%) by 2 years of age, 53% by 10 years of age (95% CI 32–68%), and 74% (95% CI 33–90%) by 16 years of age.

Among children with epilepsy, 15 children (75%) had focal epilepsy and 5 children (25%) had epileptic spasms. Epileptic spams began between 4 and 7.5 months of age in 4 children. In one child routine electroencephalography (EEG) revealed hypsarrhythmia pattern at 8 months of age, after which subtle spasms subsequently appeared. The ictal EEG and electromyography recordings revealed a typical pattern of epileptic spasms in all 5 children. The age at onset of epilepsy was earlier in children with epileptic spasms compared to children with other forms of epilepsy (4.5 months vs. 12.5 months, $p = 0.09$).

3.3. Neuroimaging findings

On brain MRI scans, all participants had unifocal infarction. One out of 37 children had infarction in the anterior cerebral artery territory, 1 in the posterior cerebral artery territory, the others (95%) in the middle cerebral artery territory. Infarct lateralized to the left hemisphere of the brain in 24 patients (65%) and right hemisphere of the brain in 13 patients (35%).

Cortex, basal ganglia and brain stem, which was a remote lesion, were the stroke-affected areas (81%,

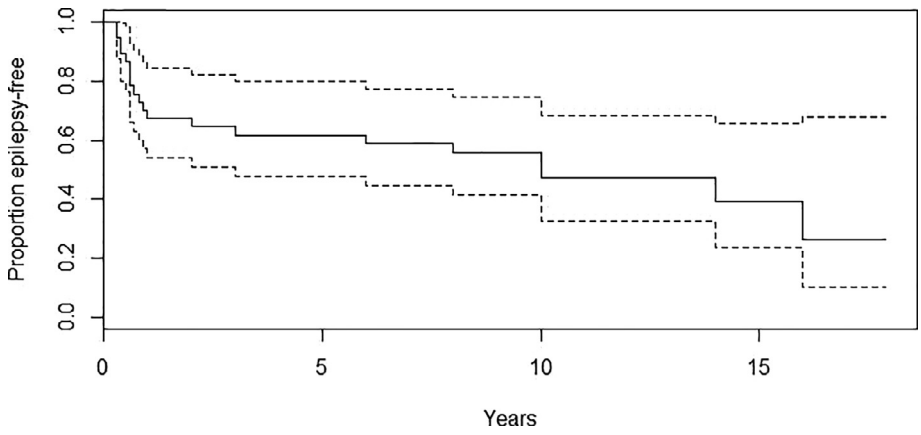

Fig. 3. Kaplan-Meier analysis showing epilepsy-free survival.

78%, 3%, respectively). None of the patients had cerebellar stroke. Neuroimaging features are provided in Table 2 and Fig. 4.

3.4. Medications

The antiepileptic drugs used were levetiracetam (9), valproic acid (8), clonazepam (5), oxcarbazepine (5), carbamazepine (4), and topiramate (4). None were treated with antiepileptic drug prior to epilepsy diagnosis. Four out of 5 patients with epileptic spasms were treated with adrenocorticotropic hormone, one received vigabatrin. Their spasms ceased, but 4 of them had drug resistant epilepsy at a median age of 4 years (range 2.5–6 years). One with epileptic spasms had no seizure after 2 years-of-age and have remained seizure-free for the last 15 years. At last assessment, among patients with epilepsy only one was seizure free off medication for more than 6 months, the remaining 19 patients had been on antiepileptic drug(s).

3.5. Association of epilepsy with other variables

There was no significant difference in the mode of initial symptom, the age at symptom onset of PPAIS, and thrombophilia screening results between patients with epilepsy and those without epilepsy ($p = 0.11$, $p = 0.08$, and $p = 1.00$ respectively).

Statistical analysis did not reveal any significant differences in infarct lateralization between patients with or without epilepsy ($p = 0.48$). Cortical involvement was a statistically significant predictor of epilepsy ($p = 0.021$, relative risk 4.4, 95% confidence interval 0.7–27.7) (Fig. 5). Basal ganglia and brainstem involvement were not statistically different between patients with or without epilepsy ($p = 0.29$, $p = 0.27$, respectively). There was no difference observed between patients with or without epileptic spasms in terms of infarct lateralization, location and affected brain regions ($p > 0.05$).

4. Discussion

Our study assessed the frequency and associated factors of epilepsy in children with PPAIS followed-up over a median of 12 years. More than half of children with PPAIS (54%) developed epilepsy, which is relatively higher than most of the previous results (27–50%) [1–5]. In a previous study with a long follow-up duration, the frequency of epilepsy was 55% in children

Table 2
Clinical and neuroimaging features in patients with or without epilepsy.

	Patients with epilepsy $n = 20$	Patients without epilepsy $n = 17$	p
The median age at onset of symptoms (month)	6	6	0.08
range	1.5–18	3.5–20	
Male/female, *n*	11/9	11/6	0.55
Initial clinical presentation with neurological deficit/seizure, *n* (%)	16 (80)/4 (20)	17 (1 0 0)/0 (0)	0.11
Infarct laterality, *n* (%)			0.48
Left	14 (70)	10 (59)	
Right	6 (30)	7 (41)	
Infarct location, *n* (%)			
Basal ganglia	17 (85)	12 (70)	0.29
Cortex	19 (95)	11 (65)	0.021
Brainstem	0	1 (6)	0.27
Cerebellum	0	0	1.00
The presence of prothrombotic risk factor, *n* (%)	5/17 (29)	4/14 (28)	1.00

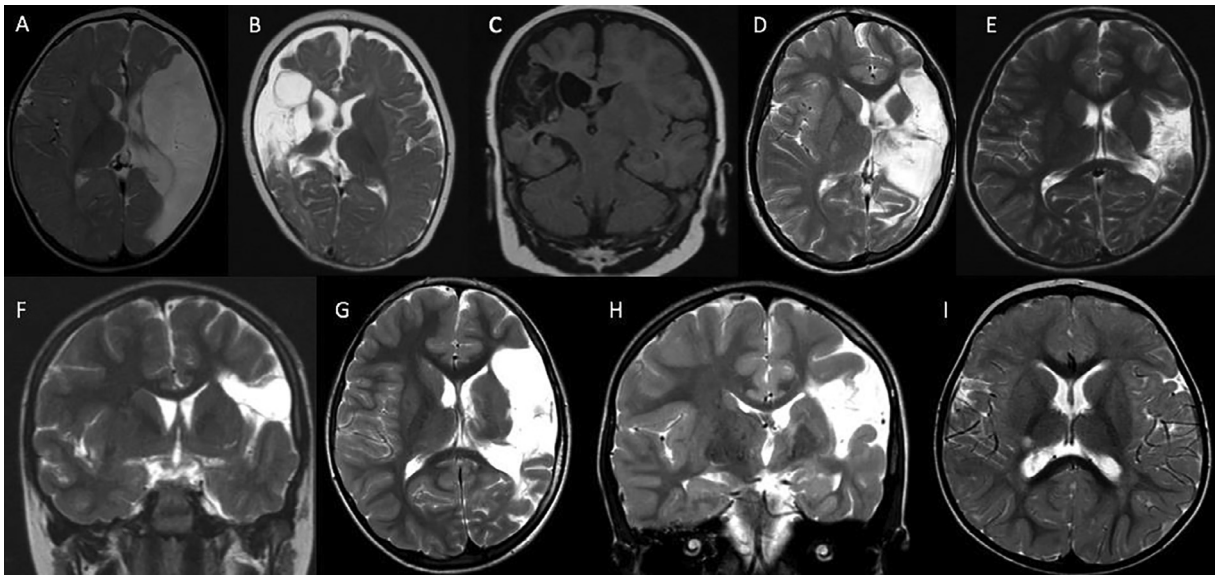

Fig. 4. The findings of brain magnetic resonance imaging. (A) Axial T2-weighted magnetic resonance imaging (MRI) shows a large left-sided medial cerebral artery stroke at the age of 9 months in a patient with epileptic spasms. (B, C) Axial fluid-attenuated inversion recovery, axial T2-weighted MRI image reveal a right-sided medial cerebral artery stroke with damage in the thalamus, basal ganglia, and frontotemporal lobes without any gliosis at the age of 6 months. (D) Axial T2-weighted MRI image shows left-sided hemiatrophy and cystic encephalomalasic area at the age of 14 years. (E, F) At the age of 10 years, axial and coronal T2-weighted MRI images show a left-sided medial cerebral artery stroke restricted to the frontotemporal lobes without basal ganglia damage. (G, H) At the age of 7 years, axial and coronal T2-weighted MRI shows cystic encephalomalasic area in the frontotemporal lobes with enlarged left ventricle. (I) Axial T2-weighted MRI images shows lacunar stroke involving the right genu of the internal capsule at the age of 9 months.

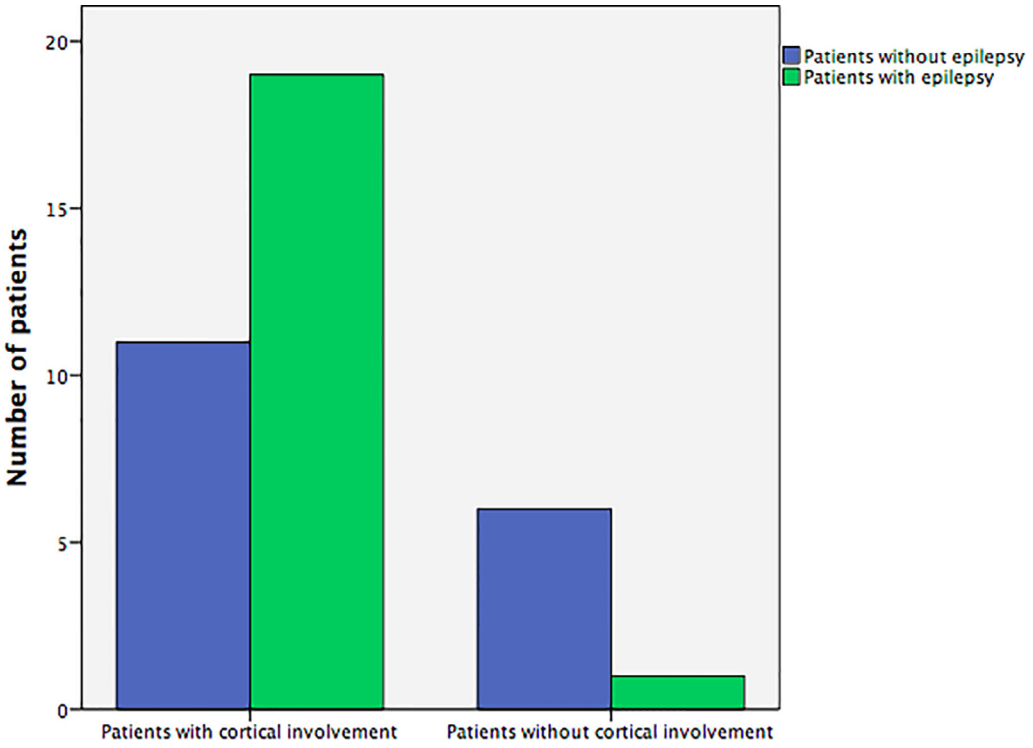

Fig. 5. Distribution of patients with or without cortical involvement based on the occurrence of epilepsy.

with perinatal arterial ischemic stroke, in which a quarter of them developed epilepsy between 8 and 13 years [6]. There were two peaks of epilepsy onset, one in infancy and one in adolescence. It is reasonable that long term follow-up, which is sufficient to capture second peak, directly influences the cumulative frequency of epilepsy.

The developing brain is characterized by an increase in neuronal excitability and seizure susceptibility. The incidence of epilepsy was greatest in the first year of life, followed by adolescence and early childhood. It has been suggested that particular brain structures at a certain level of maturity may be more susceptible to develop epilepsy than others [10]. Also, an age-dependent mechanism has been considered that responsible for the secondary generalization of focal cortical epileptic discharges to emerge epileptic spasms. In our study, the age at onset of epilepsy was earlier in children with epileptic spasms than children with other forms of epilepsy. It was shown that epileptiform discharges generated by a cortical lesion interact with brainstem and basal ganglia structures that have projections throughout the brain at a certain stage of functional maturation [11,12]. These abnormal functional interactions including neurotransmitter pathways may be responsible for the generation of epileptic spasms [13]. These suggestions may elucidate why not every child with PPAIS develops epilepsy or epileptic spasms.

The initial presentation of PPAIS was neurologic deficit in the majority of patients. Seizure was the initial symptom in a small group of patients (11%) in line with previous studies (9–25%) [1,3,5,14,15]. The age at onset of symptoms was earlier in children presenting with seizure, of whom seizure types were epileptic spasms, myoclonic and focal seizures, than children with neurologic deficit. Initial presentation with seizure and the age of symptom onset were not predictive of epilepsy or drug resistant epilepsy in contrast to previous finding [5].

PPAIS mainly affected the middle cerebral artery territory in keeping with results from previous studies [1,3–5,14,16]. Stroke more commonly involved the cortex and basal ganglia than brain stem and cerebellum, which could be attributed to the arterial territory affected [2,4]. Coexistence of cortex and basal ganglia lesions had been defined as a predictor for epilepsy in patients with PPAIS by comparing with different subtypes of arterial strokes, such as neonatal or childhood arterial ischemic stroke [2]. We found that cortical involvement was a significant predictor of epilepsy rather than basal ganglia involvement. This concurs with studies of PPAIS, in which development of epilepsy has been linked to cortical involvement [3,4]. However, there was no association between infarct lateralization, location and affected brain regions with the occurrence of epileptic spasms in consistence with previous finding [17].

The stroke-associated damage in the developing brain may result in severe forms of epilepsy [4,5]. Drug resistant epilepsy emerged in 60% of patients with epilepsy, similar to prior results (43%) [4]. Epileptic spasms constitute a subgroup of epilepsy that may lead to worsen the neurodevelopmental outcome. In our cohort, the frequency of children with epileptic spasms was 14%, which is relatively higher than the previous results (5–9%) [1,2,5]. It is noteworthy that routine EEG revealed hypsarrhythmia pattern in one patient, which subsequently he developed subtle spasms. The International Collaborative Infantile Spasms Study trial results show an association between earlier intervention and better outcomes in children with epileptic spasms [18]. Therefore, it should be considered to evaluate the patients with PPAIS in terms of epilepsy even in the absence of overt seizure to allow earlier intervention.

Strengths of our study include its long-term follow-up, and study design allowing to evaluate the PPAIS and epilepsy relationship directly, instead of comparing with other types of perinatal strokes. Some of the limitations were the retrospective design of the study, small sample size, selection bias associated with being a tertiary referral center, and the lack of baseline EEG findings. To compare the baseline EEG findings between patients with or without epilepsy may provide additional information on predictors of epilepsy. Also, it may be better to analyze the neuroimaging data in a more detailed aspect based on the suggestion that particular brain structures may be more susceptible to develop epilepsy [10]. Lastly, due to the fact that some children with PPAIS may remain asymptomatic and finish their life without being diagnosed, the frequency of epilepsy in children with PPAIS may be lower than the frequency reported.

5. Conclusion

In conclusion, more than half of the children with PPAIS suffered from epilepsy during childhood, of whom developed drug resistant epilepsy in majority. Children with cortical lesion may have a higher risk to develop epilepsy. EEG should be monitored closely in patients with PPAIS even in the absence of seizure to avoid delay in treatment.

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