



Comparison of ILAE 2010 and semiological seizure classification in children with epilepsy



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ABSTRACT

Objective: The aim of this study was to compare both ILAE 2010 and semiological seizure classification (SSC) in terms of their applicability and utility and to predict epileptogenic zone in children with epilepsy. **Methods:** Both ILAE 2010 classification and SSC which is a part of five dimensional classification were applied for a total 138 children by dividing into younger (≤ 6 y/o) and older (> 6 y/o) age groups over the last two years as retrospectively. After the assessment of the seizures types, epilepsy syndromes, and etiologies; the data were also compared to evaluate if having correlation between epileptogenic zone and seizure subtypes in both ILAE 2010 and SSC.

Results: ILAE 2010 indicated that 66.7% of the patients had focal seizures, 15.9% had generalized seizures, and 14.4% had seizures of unknown origin. The SSC revealed that the most frequent seizure type was simple seizures (56.5%), second frequent one was complex motor seizures (46.4%) and dialeptic seizures (39.9%). To predict epileptogenic zone, SSC was found to be more specific than ILAE in terms of the more subgroups of SSC were related to the more subgroups of epileptogenic zone ($p < 0.05$). Furthermore, there was a clear correlation between focal foci and specific seizure types in older ages, while many foci caused to same seizure types and tend to no clear focal foci with generalized onset in younger ages. On the other hand, the relationship between epileptogenic zone and etiology was more remarkable in the five dimensional classification.

Significance: Preference of seizure classification system is unique for each patient and depends on requirements. Therefore, one dimension cannot be sufficient for evaluation the nature of the seizures in some patients. Furthermore, age related evolution of the seizure types should not be ignored due to ongoing maturation state of the brain. ILAE 2010 and SSC have weak and strong points compared to each other. Semiological seizure classification is more informative in terms of identifying the epileptogenic zone which may be important in specific occasions like pre-surgical work up, while ILAE is simple and easier method which can be applied for seizure description and their characteristics in daily practice.

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Abbreviations: ILAE, International League Against Epilepsy; SSC, semiological seizure classification; MRI, magnetic resonance imaging; EEG, electroencephalography; HIE, hypoxic ischemic encephalopathy; ADHD, attention deficit & hyperactivity disorders; GTC, generalized tonic-clonic seizures; SMS, simple motor seizures; CMS, complex motor seizures; CSWS, continuous spike-wave complexes during sleep; ESES, electrical status epilepticus in sleep; CAE, childhood absence epilepsy; JAE, juvenile absence epilepsy; LGS, Lennox Gastaut syndrome; HS, hippocampal sclerosis; MCD, malformation of cortical development; FCD, focal cortical dysplasia; ≤ 6 y/o, younger than 6-year-old, represents younger age groups; > 6 y/o, older than 6-year-old, represents older age groups.

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1. Introduction

Classification of seizures and epilepsies are still conflicting topic in terms of their applicability into individual perspective and contribution to the management of the disease (Bancaud et al., 1981, 1989; Lüders et al., 1998; Engel and ILAE, 2001; Engel, 2006; Berg et al., 2010; Berg and Millichap, 2013). Many factors should be taken into account when choosing a classification method, as there are some different approaches with various consensuses (Bancaud et al., 1981, 1989; Lüders et al., 1998; Engel and ILAE, 2001; Engel, 2006; Berg et al., 2010; Berg and Millichap, 2013). The International League Against Epilepsy “ILAE” is a common classification system that was first used in 1969s which basically depends on a combina-

tion of “electro-clinical” findings (Bancaud et al., 1981, 1989; Engel and ILAE, 2001; Engel, 2006). Since then, it has been periodically revised (Berg et al., 2010; Berg and Millichap, 2013; Lüders et al., 2012; Berg and Scheffer, 2011; Korff and Scheffer, 2013; French, 2014; Panayiotopoulos, 2011; Berg and Cross, 2012; Camfield, 2012), and the last version was updated in 2010 which basically composes as generalized, focal including auras, autonomic, motor, dyscognitive; and unknown seizures (Berg et al., 2010; Berg and Millichap, 2013; Korff and Scheffer, 2013). A different approach, Lüders et al. (1998) proposed a new classification option so called “Semiological Seizure Classification” (SSC) which is independent of EEG and additional supplementary tests; it depends on sole clinical manifestations (Lüders et al., 1998; Bautista and Luders, 2000; Loddenkemper et al., 2005; Jan and Girvin, 2008; Tufenkjian and Lüders, 2012). Related to SSC, Loddenkemper et al. put forward a five dimensional epilepsy classification that utilizes a combination of epileptogenic zone, seizure semiology, seizure frequency, etiology, and co-morbidities (Loddenkemper et al., 2005; Lüders et al., 2012).

Although seizure and epilepsy classifications have been changed over time with new technological advances (Berg and Scheffer 2011; Lüders et al., 2012), there are limited and conflicting studies regarding ILAE and SSC classifications which compare to each other in terms of daily clinical use or applicability to the scientific settings, like epilepsy surgery in children with epilepsy (Benbadis et al., 2001; Kim et al., 2002; Hirfanoglu et al., 2007; Vendrame et al., 2011; van Campen et al., 2013). Furthermore, immature features and rich connections of the brain, same focus can be presented as different seizure semiologies with tendency of being generalized seizures in younger age group in children (Källén et al., 2002; Fogarasi et al., 2007a,b; Gupta et al., 2007; Kakisaka et al., 2011; de la Vaissière et al., 2014; Gataullina et al., 2015). Therefore, seizure classifications are rather complex and hard to simplify in the pediatric age group. As much as comprehensive, but also easy classifications are important to understanding the nature of the events (Bautista and Luders, 2000; Kim et al., 2002; Hirfanoglu et al., 2007; Udani and Desai et al., 2014). However, there is no comprehensive studies which discuss advantages and disadvantages of both new ILAE 2010 and SSC.

The aim of this study was to evaluate ILAE 2010 and SSC in terms of both utility, applicability, and contribution to estimate to the epileptogenic zone in children with epilepsy by comparing younger (≤ 6 y/o) and older (> 6 y/o) age groups.

2. Materials and methods

2.1. Patients and demographics

We analyzed 173 consecutive patients aged between 2 and 17 years (11.33 ± 4.3 years) gathered from the Pediatric Video EEG Monitoring Unit at Gazi University School of Medicine between January 2012 and January 2014 as retrospectively. After excluding patients having no seizures, subclinical seizures, and non-epileptic paroxysmal events, a total 138 patients (41.3% girl, 58.7% boys) were included to the study. Twenty four patients (17.3%) was younger than 6 year old (≤ 6 y/o), while 114 (82.6%) patients were older than 6 year old (> 6 y/o). The patients were admitted for the purposes of presurgical workup, clinical seizure definition, or to differentiate between epileptic and non-epileptic paroxysmal events including pseudoseizures. History of the patients, seizure onset age, use of antiepileptic drugs (AED), and seizure frequency, risk factors for epilepsy, detailed physical-neurological examinations, and co-morbidities were collected from the chart reviews and summarized in Table 1.

Table 1
Demographics and etiology of the patients.

Variables	Number of the patients (n: 138, %, means $\pm$)
Age (year)	11.33 $\pm$ 4.37
Gender	
Girl	57 (41.3)
Boy	81 (58.7)
Seizure onset age (month)	139.52 $\pm$ 922.65
Number of the AEDs	2.5 $\pm$ 1.17
Seizure frequency	
Daily	68 (49.3)
Persistent (at least once a week)	38 (27.5)
Rare or undefined	32 (23.2)
Risk factors	
Infection, febrile seizures, trauma, hypoxia, hemorrhage	66 (47.8)
Family history for epilepsy	16 (11.6)
None	53 (38.4)
Co-morbidities	
Mental-motor retardation	38 (27.5)
Hemiparesis or other motor deficiencies	21 (15.2)
ADHD or psychiatric disorders	5 (3.6)
None	74 (53.6)
Etiology-ILAE 2010 classification	
Structural-metabolic	88 (63.7)
Genetic	6 (4.3)
Unknown	44 (31.9)
Etiology-Five dimensional classification	
MCD-FCD-Hamartoma	29 (21)
Trauma-HIE-vascular-infarct-encephalomalasia	23 (16.7)
Hippocampal sclerosis	14 (10.1)
Tumors	13 (9.4)
Infection-Rasmussen Syndrome	8 (5.7)
Unknown-idiopathic-cryptogenic	23 (16.7)
ESES-LGS	20 (14.5)
CAE-JAE	5 (3.6)

2.2. Video EEG monitoring

Scalp electrodes were placed according to the International 10–20 system with extra electrodes for anterior temporal regions recorded by Nihon-Kohden Neurofax EEG 1200. If needed, antiepileptic drugs were tapered by considering seizure frequency, history of status epilepticus, and other specific conditions for each patient. The video and EEG records were synchronized with a closed circuits system. The duration of video-EEG recording ranged between 1 and 7 days depending on the number of seizures and their quality. Trained EEG technicians and nurses examined the patients to evaluate their level of consciousness or motor responses throughout the seizures. Eventually, all video-EEG records were mainly re-evaluated by two experienced pediatric neurologists (TH and AS) as retrospectively. Final decisions were based on the agreement of findings by both physicians.

2.3. Seizure classification and epileptogenic zone

Each seizure for each patients was classified by according to both the ILAE 2010 (Berg et al., 2010) and the SSC (Lüders et al., 1998) as below:

The ILAE 2010 seizure&epilepsy classification was performed in order to evaluate etiology, seizure types, and the electro-clinical syndrome of epilepsy (Berg et al., 2010). Therefore, etiology was divided into three main groups as genetic, structural-metabolic, and unknown origin (Berg et al., 2010). Seizure types were classified into 4 main groups (1) Generalized seizures: Tonic, clonic, tonic-clonic, absence, atonic, and myoclonic seizures. (2) Focal seizures: Aura, autonomic, motor, and dyscognitive seizures. The term of dyscognitive seizures represents primarily as only impaired consciousness or cognition with or without automatisms arising from focal foci which basically matches to complex partial seizures

of ILAE 1981. (3) Seizures that evolved into bilateral convulsive seizures. (4) Unknown-unclassified seizures including epileptic spasms (Berg et al., 2010). As a third step for ILAE 2010, epilepsy syndromes were classified as age-dependent epilepsy syndromes, surgical syndromes, or non-syndromic epilepsies (Berg et al., 2010).

For second part of the study, seizure classification was also carried out with five-dimensional classification as proposed by Loddenkemper et al. (2005) including epileptogenic zone, SSC, seizure frequency, etiology, and contributed co-morbidities (Loddenkemper et al., 2005). The semiologic seizure classification represents 5 main groups: (1) Aura (2) Autonomic seizure (3) Dialeptic seizures: Either only impaired consciousness, i.e. typical dialeptic which matches the absence seizures or initial part of dyscognitive seizures of ILAE 2010 or followed by those with the other groups of seizures confining automotor seizures. (4) Motor seizures are either simple motor seizures (SMS), i.e., tonic, clonic, tonic-clonic, myoclonic, versive seizures, and epileptic spasms; or complex motor seizures (CMS), i.e., hypermotor, automotor, and gelastic seizures (5) Special seizures, i.e., hypomotor, akinetic, and atonic seizures (Lüders et al., 1998). Overall, SSC was assessed by the evolution of seizures which propagates to the sequential occurrence of one seizure component to another (e.g., Seizure 1: Dialeptic seizure → right hand automotor seizure → left versive seizure) (Lüders et al., 1998). Detailed etiology was also assessed by a part of five-dimensional classification with the subgroups of tumors, malformations of cortical developments (MCD-FCD), hippocampal sclerosis (HS), vascular malformations, and encephalomalasia (Lüders et al., 1998; Loddenkemper et al., 2005).

Overall “**Epileptogenic zone**” has been defined as “The area of cortex that is indispensable for the generation of epileptic seizures;” it has been referred to as the minimum brain region that should be removed for seizure freedom (Loddenkemper et al., 2005). Therefore, final epileptogenic zone was mainly based on a combination of seizure semiology, ictal and interictal EEG, and MRI findings. In the presence of discordant data, additional diagnostic methods including functional tests (PET, fMRI), structural imaging (tractography, DTI), and neurophysiologic testing was used. Hence, the epileptogenic zone was assessed within 4 main groups as follows: (1) Focal epileptogenic zone comprising frontal, temporal, and parieto-occipital (Posterior cortex), (2) Multilobar/multifocal (two-or more adjacent or independent focus), (3) Generalized and (4) Unclassified epileptogenic zone that is obscured with muscle artifacts or no clear focal or generalized onset (Loddenkemper et al., 2005).

As a last part of study, the patients were also divided into a big two group as younger than 6-year-old (≤ 6 y/o, represents younger age group) or older than 6-year-old (> 6 y/o, represents older age group) for the purpose of evaluating the differences between younger and older age group in terms of seizure semiology and their relationship to epileptogenic zone.

2.4. Statistical analysis

Statistical Package for Social Sciences (SPSS) software, Version 22.0 (SPSS Inc., Chicago, Ill, USA) was used for data analysis. Data were presented as sums, means $\pm$ standard deviations (SD), or percentages. Chi square was applied to evaluate if there were some differences between the seizure types of ILAE 2010 and SSC according to the age groups. Correlation coefficients (r and p values) assessed the relationship between epileptogenic zone and ILAE 2010 seizure subtypes, SSC, etiology, by both in total patients and also dividing to younger (≤ 6 y/o) and older age (> 6 y/o) groups. Values of p less than 0.05 were considered statistically significant. This study was approved by the Gazi University School of Medicine Ethical Committee (Approval number: 76869).

3. Results

3.1. Etiology

According to ILAE 2010 classification, the most common etiological factor was structural-metabolic (63.7%) causes. However, 31.9% of patients had still unknown origin which was almost half time less frequent (16.7%) in the five dimensional classification. Remaining reasons were MCD (Malformation of cortical development) (21%), hippocampal sclerosis (HS) (10.1%), tumors (9.4%), and age-dependent epilepsies (18.1%) (Table 1).

3.2. Seizure types and frequencies

Seizure frequency was between 1 and 75 per patient during their stay at video EEG monitoring unit. Therefore, of the 138 patients, 115 (83.3%) had only one seizure type, 18 (13%) had two different seizure types, and 6 (4.3%) had three different seizure types. Based on these data, 169 different seizure types were recorded from the 138 patients. Aura was recorded in at the onset of 43 seizures (25.4%) in both ILAE 2010 and SSC.

Overall, a total of 1677 seizures were recorded from 169 different seizure types according to the ILAE 2010 seizure classification. The most common seizure type was focal seizures (66.7%) with subgroup of motor (35.5%), dyscognitive (27.5%), autonomic (6.5%), and evolved to bilateral convulsive seizures (13%). While generalized seizures were seen 15.9% of the patients, less frequent seizure type was unclassified seizures (14.5%) with classified as epileptic spasms (Table 2). On the other hand, the frequency of auras and focal seizures was rather higher in the older ages (> 6 y/o), whereas generalized and atonic seizures were more frequent in younger age groups (≤ 6 y/o) ($p < 0.05$) (Table 2).

When the patients were classified according to electro-clinical syndromes of ILAE 2010, most of them ($n: 62, 45\%$) were categorized by nonsyndromic epilepsies due to structural-metabolic causes like MCD, tumors, infection, perinatal insult; 18% ($n: 25$) were age dependent electro-clinical syndrome including Lennox-Gastaut Syndrome, CSWS, CAE; 16.7% ($n: 23$) were surgical syndromes including mesial temporal lobe epilepsy with HS, and hypothalamic hamartomas. Epilepsies of unknown origin were still observed in 20.2% of the patients.

According to the SSC, 61 (36.3%) seizures had only one semiology, 49 (29.1%) had two sequential semiologies, and 58 (34.5%) of those proceeded with three sequential semiologies. Therefore, a total of 2569 seizures obtained from 169 different seizure types. Most patients had SMS (56.5%) with subtypes of versive (15.9%), tonic (21.7%), clonic (18.1%), GTC (13%), myoclonic seizures (5.8%), and epileptic spasm (15.2%). A second common seizure types were CMS (46.4%) including automotor (29.7%), hypermotor (7.2%), and gelastic seizures (2.2%). Dialeptic (39.9%), autonomic (6.5%), and special seizures (9.4%) were the remaining frequent seizure types (Table 3). In different point of view, when dyscognitive seizures ($n: 45$ in ILAE 2010) were matched to the equivalent seizure types in SSC, 8 (17.7%) patients were found to have dialeptic seizures, 12 (26.6%) had automotor seizures, 21 (46.6%) had dialeptic seizures followed by automotor seizures, and 4 (8.8%) had hypomotor seizures (Table 3). According to age groups, non specific dialeptic seizures, CMS and its subgroup automotor seizures were seen higher in older than 6 year ($p < 0.05$), while special seizures like atonic and hypomotor seizures were seen predominantly in the younger age group ($p < 0.05$) (Table 3).

3.3. Epileptogenic zone

The most common epileptogenic zone was multifocal/multilobar ($n: 51, 37\%$) and focal epileptogenic zones ($n:$

Table 2
Distribution and frequency of ILAE 2010 seizure classification and epilepsy syndromes.

ILAE 2010 Seizure Classification	Total number of the patients (n: 138, %)	Total number of different seizure type (n: 169, %)	Total number of the seizures (n: 1677, %)	Number of the patients ≤6 y/o (n: 24, %)	Number of the patients >6 y/o (n:114, %)	p [*]
Auras	43 (31.2)	43 (25.4)	298 (17.7)	3 (12.5)	40 (35.1)	0.022
Focal seizures	92 (66.7)	103 (60.9)	943 (56.2)	12 (50)	80 (70.2)	0.050
Dyscognitive seizures	38 (27.5)	45 (26.6)	231 (13.7)	4 (16.7)	34 (29.8)	0.144
Motor seizures	49 (35.5)	49 (28.9)	637 (37.9)	6 (25)	43 (37.7)	0.172
Autonomic seizure	9 (6.5)	9 (5.3)	75 (4.4)	3 (12.5)	6 (5.3)	0.190
Evolved to secondary GS	18 (13)	18 (10.6)	97 (5.7)	2 (8.3)	16 (14)	0.315
Generalized seizures	22 (15.9)	28 (16.5)	350 (20.8)	9 (37.5)	13 (11.4)	0.004
Absence seizures	5 (3.6)	5 (2.9)	115 (6.8)	2 (8.3)	4 (3.5)	0.280
Atypical absence seizures	6 (4.3)	6 (3.5)	80 (4.7)	2 (8.3)	4 (3.5)	0.280
GTC	4 (2.9)	4 (2.3)	25 (1.4)	1 (4.2)	3 (2.6)	0.539
Clonic seizures	2 (1.44)	2 (1.18)	6 (0.35)	1 (4.2)	1 (0.9)	0.319
Myoclonic seizures	6 (4.3)	6 (3.5)	51 (3)	2 (8.3)	4 (3.5)	0.280
Atonic seizures	5 (3.6)	5 (2.9)	73 (4.3)	3 (12.5)	2 (1.8)	0.037
Epileptic spasm	20 (14.5)	20 (11.8)	287 (17.1)	6 (25)	15 (13.2)	0.102

* p (Chi square): Differences between younger (≤6 y/o) and older (>6 y/o) ages.

Table 3
Distribution and frequency of semiological seizure classification.

Semiological Seizure Classification	The number of the patients (n:138,%)	Total number of the seizures (n: 2569, %)	The number of the patients ≤ 6 y/o (n:24,%)	The number of the patients > 6 y/o (n:114, %)	p [*]
Auras	43 (31.2)	298 (11.5)	3 (12.5)	40 (35.1)	0.022
Autonomic seizures	9 (6.5)	103 (4)	1 (4.2)	8 (7)	0.514
Dialeptic seizures	55 (39.9)	361 (14)	7 (29.2)	46 (40.4)	0.215
Typical dialeptic seizures	5 (3.6)	110 (4.4)	2 (8.3)	3 (2.6)	0.208
Atypical dialeptic seizures	6 (4.3)	75 (2.9)	2 (8.3)	4 (3.5)	0.280
Dialeptic seizures	44 (31.8)	176 (6.8)	3 (12.5)	40 (35.1)	0.022
Simple motor seizures	78 (56.5)	1187 (46.2)	16 (66.7)	72 (63.2)	0.469
Versive seizures	22 (15.9)	159 (6.1)	2 (8.3)	21 (18.4)	0.186
Tonic seizures	30 (21.7)	362 (14)	4 (16.7)	28 (24.6)	0.294
Tonic-generalized seizures	7 (5.1)	90 (3.5)	3 (12.5)	4 (3.5)	0.101
Tonic-focal seizures	28 (20.3)	272 (10.5)	3 (12.5)	26 (22.8)	0.087
Asymmetrical tonic seizures	16 (11.6)	207 (8)	3 (12.5)	14 (12.3)	0.446
Clonic seizures	25 (18.1)	250 (9.7)	4 (16.7)	25 (21.9)	0.395
Clonic-generalized seizures	6 (4.3)	225 (8.7)	3 (12.5)	5 (4.4)	0.143
Clonic-focal seizures	25 (18.1)	25 (0.9)	2 (8.3)	23 (20.2)	0.139
GTC	18 (13)	61 (2.3)	2 (8.3)	15 (13.2)	0.399
Myoclonic seizures	8 (5.8)	67 (2.6)	2 (8.3)	6 (5.3)	0.420
Epileptic spasm	20 (15.2)	288 (11.2)	7 (29.2)	14 (12.3)	0.044
Complex motor seizures	64 (46.4)	391 (15.2)	5 (20.8)	60 (52.6)	0.004
Automotor seizures	41 (29.7)	216 (8.4)	3 (12.5)	39 (34.2)	0.027
Hypermotor seizures	10 (7.2)	142 (5.5)	–	11 (9.6)	–
Gelastic seizures	3 (2.2)	33 (1.3)	–	3 (2.6)	–
Special seizures	13 (9.4)	229 (8.9)	8 (33.3)	5 (4.4)	0.000
Atonic seizures	6 (4.3)	114 (4.4)	4 (13)	2 (1.8)	0.037
Hypomotor seizures	6 (4.3)	88 (3.4)	6 (25)	1 (0.9)	0.000
Negative myoclonic seizures	1 (0.7)	25 (0.9)	1 (4.2)	–	–
Akinetic seizures	1 (0.7)	2 (0.07)	–	1 (0.9)	–

* p (Chi square): Differences between younger (≤6 y/o) and older (>6 y/o) ages.

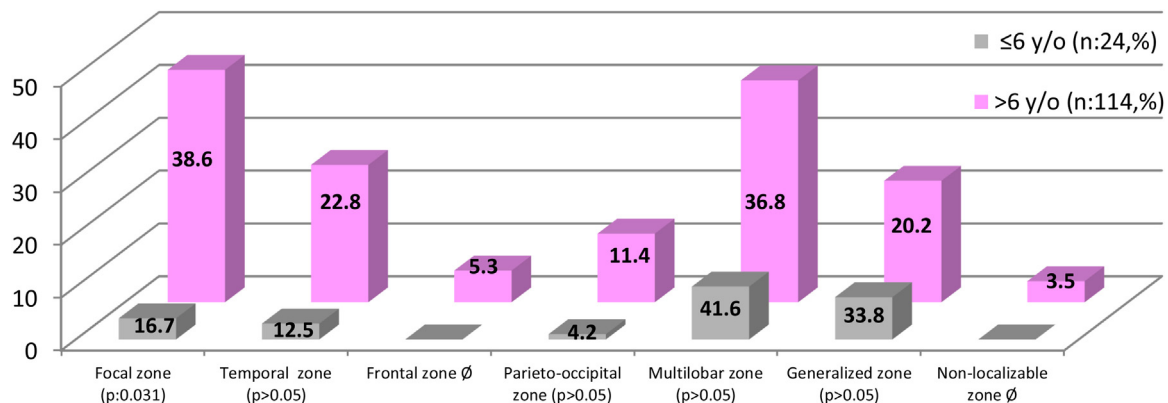


Fig. 1. The distribution of the epileptogenic zone. y coordinate shows the number of the patients. The number on the column represents the percentage of the patients according to each age group. p value (chi square) indicates the comparison of the younger and older age groups.

50, 36%) including temporal lobe (n: 29, 21%), parieto-occipital lobe (n: 14, 10%), and frontal lobe (n: 7, 5%). The second frequent epileptogenic zone was generalized zone (n: 34, 25%), and least frequent (n: 4, 2.8%) one was non-localizable epileptogenic zone. Additionally, the only differences was found in the focal epileptogenic zone with higher ratio in the older ages ($p=0.031$). No differences were recorded for remaining epileptogenic zones between the age groups ($p>0.05$) [Fig. 1](#).

3.4. Correlation between ILAE 2010 classification and epileptogenic zone

Focal seizures (n: 92) were found to be related to the focal (42/92) and parieto-occipital zones (13/92) ($p<0.05$). When subgroups of focal seizures were evaluated in details, dyscognitive seizures (n: 38) were mostly seen in focal (21/38) and temporal (13/38) epileptogenic zones, while motor seizures (n: 49) were related to multilobar (26/49) zones ($p<0.05$). Conversely, there was a negative correlation between dyscognitive and motor seizures to generalized epileptogenic zones ($p<0.05$). When those relationship were evaluated according to specific age groups, most striking point was that dyscognitive seizures were related to temporal zones in older ages, while parieto-occipital zones in younger children ($p<0.05$). ([Table 4](#)).

Generalized seizures, including typical (5/5) and atypical absence seizures (6/6), and also clonic seizures (2/2) were considerably associated with generalized focus ($p<0.05$). While in total and older age group has a negative correlation for focal or multilobar epileptogenic zones to generalized seizures, no correlation has been found for those in younger than 6 years ([Table 4](#)).

Epileptic spasms (n: 20) were relevant to both generalized (14/20) and unclassified focus ($p<0.05$) in general. Conversely, there was a negative correlation between epileptic spasms to focal and temporal zones in total ages in both ILAE 2010 and SSC and older than 6 year old in ILAE 2010 ($p<0.05$) ([Table 4](#)).

3.5. Correlation between SSC and epileptogenic zone

More seizure types of SSC were found to have more relationship with epileptogenic zones. Typical dialeptic seizures (n: 5) were strongly associated with generalized focus; interestingly, nonspecific dialeptic seizures (n: 44) were related to focal (24/44) and temporal (15/44) epileptogenic zones ($p<0.05$) with negative correlation to generalized focus ($p<0.05$) in total and older age group ([Table 4](#)).

For SMS, there was a positive correlation between versive seizures to focal (12/22) and parieto-occipital (6/22) zones with same tendency in older age groups; clonic seizures to multilobar zones (10/25) with negative correlation to generalized onset ($p<0.05$). Focal tonic and asymmetric tonic seizures were related to non-localizable zones (2/28, 2/16) ($p<0.05$), however, there was a negative correspondence with temporal foci in older age group ($p<0.05$). Generalized tonic seizures and epileptic spasms was related to generalized zones (5/7, 15/20) ([Table 4](#)).

For CMS, there was a positive relationship between automotor seizures to focal (33/64, 27/41) and temporal zones in total (23/64, 21/41) and older ages with negative correlation to generalized onset and parieto-occipital zone in younger age group ($p<0.05$). Hypermotor seizures and gelastic seizures were related to frontal zones in total (4/10, 1/3) and older age group ($p<0.05$) ([Table 4](#)).

Special seizures were showed a negative correlation with focal and temporal focus in general ($p<0.05$). Atonic seizures were correlated to multilobar zones (9/13, 5/6) while akinetic seizures were related to frontal zones (1/1) ($p<0.05$) in total of the patient. Atonic and hypomotor seizures had also significant relationship to mul-

tilobar focus in younger age groups with negative association to generalized focus as opposite to older ages ($p<0.05$) ([Table 4](#)).

3.6. Correlation between seizure classifications, epileptogenic zone and etiology

According to ILAE 2010 classification, focal seizures were related to structural-metabolic etiologies (66/92), while generalized seizures (typical and atypical absence, clonic seizures, and GTC) were related to genetic etiology (4/22) ($p<0.05$). As to epileptogenic zone, Structural-metabolic etiologies were related to focal (42/88) and temporal focus (25/88), while genetic (5/6) and unknown (17/44) etiology was correlated to generalized zone ($p<0.05$). On the other hand, there was a negative correlation between structural-metabolic etiologies and generalized zone between genetic or unknown etiology and focal and temporal focus ($p<0.05$) ([Table 5](#)).

For the five dimensional classification, CMS and its subgroup of automotor seizures were correlated with HS (12/64; 12/41) and tumor (10/64; 8/41) respectively; tonic (10/28) and gelastic seizures (2/3) were correlated with MCD and hamartomas; versive (7/22) and clonic seizures (10/25) were related to focal etiology (trauma-HIE-vascular-infarct-encephalomalasia) ($p<0.05$). When evaluated to epileptogenic zone, there was a positive association between HS and tumors to focal (14/14, 10/13) and temporal zones (12/14, 7/13); MCD and the parieto-occipital (2/29) and frontal zones (4/29); trauma-HIE-vascular-infarct-encephalomalasia and the parieto-occipital (5/23) and multilobar zones (13/23); Rasmussen syndrome and multilobar zones (7/8); unknown-idiopathic etiology to the generalized (23/23) zones ($p<0.05$). There was a negative correlation between HS, tumor and generalized or multilobar zone and also between Rasmussen and idiopathic epileptic syndromes to focal or temporal focus ($p<0.05$) ([Table 5](#)).

When the correlations were assessed by age groups for younger and older children, the more subgroup of five dimensional classification was found to be related to the more focal foci, especially in younger ages ([Table 5](#), Supplementary Table S3). The most striking point was the temporal focus was related to trauma and traumatic brain injury in younger ages, however those had a negative association in the older children ($p<0.05$) ([Table 5](#), Supplementary Table S3). Conversely, trauma and its sequela was presented in the parieto-occipital focus in the older group ([Table 5](#)).

4. Discussion

Seizure classification is still ongoing evolutionary algorithm which depends on preferred methods and new advanced supplementary tools (Bancaud et al., 1981, 1989; Lüders et al., 1998; Engel and ILAE, 2001; Loddenkemper et al., 2005; Engel, 2006; Berg et al., 2010; Berg and Millichap, 2013). This current study is one of the rare efforts in children with epilepsy regarding detailed analysis of both ILAE 2010 and SSC by comparing each other and subgroup of younger (≤ 6 y/o) and older (> 6 y/o) ages. We found both advantages and disadvantages of each other in seizure classification, epileptogenic zone, epilepsy syndrome, and etiology.

4.1. Seizure classification

Seizure classification of ILAE is a comprehensive and easy system which points to take consider only first or most impressive component of the events with combination of EEG (Bancaud et al., 1981, 1989; Engel and ILAE, 2001; Engel, 2006; Berg et al., 2010; Berg and Millichap, 2013; Berg and Scheffer, 2011; Panayiotopoulos, 2011; Korff and Scheffer, 2013; Berg and Cross, 2012; French, 2014; Udani and Desai, 2014). Recently, Campen et al. (2013) showed that ILAE 2010 is also feasible method in terms of

Table 4

Correlation between epileptogenic zone and ILAE 2010 & semiological seizure classification.

Epileptogenic zone (n:138)	Focal	Temporal	Parieto-occipital	Frontal	Multilobar	Generalized	Non localizable
<i>ILAE 2010 Seizure Classification</i>							
Focal seizures	p: 0.001, r: 0.281(*) (#)	NC	p: 0.032, r: 0.183	NC	NC	p: 0.000, r: −0.477(*) (#)	NC
Dyscognitive seizures	p: 0.005, r: 0.238 (#)	p: 0.035, r: 0.180 (#)	(*)	NC	NC	p: 0.025, r: −0.191 (#)	NC
Motor seizures	NC	NC	NC	NC	p: 0.006, r: 0.231 (#)	p: 0.010, r: −0.218(*) (#)	NC
Generalized seizures	p: 0.002, r: −0.257 (#)	NC	NC	NC	p: 0.05, r: −0.167 (#)	p: 0.000, r: 0.518 (#)	NC
Typical absence seizures	NC	NC	NC	NC	NC	p: 0.001, r: 0.277(*) (#)	NC
Atypical absence seizures	NC	NC	NC	NC	NC	p: 0.000, r: 0.360(*) (#)	NC
Clonic seizures	NC	NC	NC	NC	NC	p: 0.008, r: 0.225 (#)	NC
GTC	NC	NC	NC	NC	NC	(#)	NC
Atonic seizures	NC	NC	NC	NC	(*)	NC	NC
Epileptic spasms	p: 0.000, r: −0.301 (#)	p: 0.010, r: −0.219 (#)	NC	NC	NC	p: 0.000, r: 0.420(*) (#)	p: 0.041, r: 0.174 (#)
<i>Semiological Seizure Classification</i>							
Dialeptic seizures-total	p: 0.041, r: 0.174 (#)	NC	NC	NC	NC	NC	NC
Typical dialeptic seizures	NC	NC	NC	NC	NC	p: 0.001, r: 0.277(*) (#)	NC
Atypical dialeptic seizures	NC	NC	NC	NC	NC	p: 0.000, r: 0.360(*) (#)	NC
Dialeptic seizures-non specific	p: 0.001, r: 0.271 (#)	p: 0.013, r: 0.210 (#)	NC	NC	NC	p: 0.000, r: −0.300 (#)	NC
Simple motor seizures	NC	(−#)	NC	NC	NC	NC	NC
Versive seizures	p: 0.034, r: 0.181	NC	p: 0.003, r: 0.247 (#)	NC	NC	p: 0.028, r: −0.187	NC
Clonic seizures-total	NC	NC	NC	NC	p: 0.000, r: 0.333 (#)	p: 0.037, r: −0.178	NC
Clonic-focal seizures	NC	NC	NC	NC	p: 0.000, r: 0.333 (#)	p: 0.003, r: −0.253 (#)	NC
Tonic-total	NC	(#)	NC	NC	NC	NC	NC
Tonic-generalized seizures	p: 0.048, r: −0.169	NC	NC	NC	NC	p: 0.001, r: 0.271 (#)	NC
Tonic-focal seizures	NC	(−#)	NC	NC	NC	NC	p: 0.044, r: 0.172
Asymmetrical tonic seizures	(−#)	(−#)	NC	NC	NC	NC	p: 0.015, r: 0.207 (#)
Myoclonic seizures	NC	NC	NC	NC	NC	(#)	p: 0.008, r: 0.226
Epileptic spasms	p: 0.002, r: −0.267	p: 0.010, r: −0.219	NC	NC	NC	p: 0.000, r: 0.449 (*) (#)	NC
Complex motor seizures	p: 0.000, r: 0.297 (#)	p: 0.000, r: 0.305 (*) (#)	(*)	NC	NC	p: 0.000, r: −0.326 (#)	NC
Automotor seizures	p: 0.000, r: 0.391 (#)	p: 0.000, r: 0.443 (#)	(*)	NC	NC	p: 0.000, r: −0.350 (#)	NC
Hypermotor seizures	NC	NC	NC	p: 0.000, r: 0.489 (#)	NC	NC	NC
Gelastic seizures	NC	NC	NC	p: 0.013, r: 0.212 (#)	NC	NC	NC
Special seizures	p: 0.031, r: −0.183	p: 0.051, r: −0.166	NC	NC	p: 0.013, r: 0.210 (*)	(−*)	NC
Atonic seizures	NC	NC	NC	NC	p: 0.018, r: 0.201 (*)	NC	NC
Hypomotor	NC	NC	NC	NC	(*)	(#) (−*)	NC
Akinetic seizures	NC	NC	NC	p: 0.000, r: 0.401 (#)	NC	NC	NC

The apparent numbers in the boxes represent the correlation between all the age group and epileptogenic zones without divided to the subgroup of the age. If the box has additional * or # or both signs, those means: “*” represents the same correlation was also seen in ≤6y/o, “#” represents the same correlation was also seen >6y/o as the same way in the boxes. If the boxes contains just only * or # signs without p and r value, it means there was no correlation in total, but there was a correlation in specific age group which represented by the sign. For detailed p and r values of * and #, please look at the Supplementary Tables S1 and S2. Negative (−r) values represent negative and meaningful correlations between variables. NC: No correlation between the variables (p > 0.05).

Table 5
Correlation between epileptogenic zone and etiology according to ILAE 2010 and five dimensional classification.

Epileptogenic zone (n:138)	Focal	Temporal	Parieto-occipital	Frontal	Multilobar	Generalized	Unclassified
<i>Etiology-ILAE 2010 Etiological Classification</i>							
Structural-Metabolic	p: 0.000, r: 0.370 (#)	p: 0.003, r: 0.248 (#)	-	-	-	p: 0.000, r: -0.379 (#)(*)	p: 0.022, r: -0.195
Genetic	-	-	-	-	-	p: 0.000, r: 0.311 (#)	-
Unknown	p: 0.000, r: -0.308 (#)	p: 0.010, r: -0.219 (#)	(*)	-	-	p: 0.002, r: 0.258 (#)(*)	p: 0.045(#), r: 0.171
<i>Etiology-Five Dimensional Classification</i>							
Hippocampal sclerosis	p: 0.000, r: 0.460 (#)	p: 0.000, r: 0.534 (#)(*)	-	-	p: 0.002, r: -0.261 (#)	p: 0.034, r: -0.181	-
Tumor	p: 0.001, r: 0.285 (#)	p: 0.002, r: 0.260 (#)(*)	-	-	-	p: 0.042, r: -0.174	-
FCD-MCD-Hamartoma	-	-	p: 0.044, r: 0.172	p: 0.005, r: 0.239 (#)	-	-	-
Trauma & sequelae	(*)	(-#)(*)	p: 0.044, r: 0.172 (#)	-	p: 0.041, r: 0.174	p: 0.023, r: -0.194	-
Infection-Rasmussen syndrome	p: 0.035, r: -0.180	-	-	-	p: 0.003, r: 0.254	-	-
Unknown-idiopathic	-	p: 0.000, r: -0.308	-	-	-	p: 0.000, r: 0.409	p: 0.016, r: 0.204
CAE-JAE-JME	p: 0.000, r: -0.374	-	-	-	-	p: 0.002, r: 0.267	-
LGS-ESES	p: 0.002, r: -0.257	-	-	-	-	p: 0.000, r: 0.420	-

The apparent numbers in the boxes represent the correlation between all the age group and epileptogenic zones without divided to the subgroup of the age. If the box has additional * or # or both signs, those means: “*” represents the same correlation was also seen in ≤ 6 y/o, “#” represents the same correlation was also seen > 6 y/o as the same way in the boxes. If the boxes contains just only * or # signs without p and r value, it means there was no correlation in total, but there was a correlation in specific age group which represented by the sign. For detailed p and r values of * and #, please look at the Supplementary Table S3. Negative (-r) values represent negative and meaningful correlations between variables. NC: No correlation between the variables (p > 0.05).

interobserver agreement as much as ILAE 1981 and 1989 classifications. They have also found that the most frequent seizure types were focal (69%), generalized (21.2%), and epileptic spasms (3%) (Campen et al., 2013). As concordant to those findings, we showed that the most prevalent seizure types were focal (66.7%) including dyscognitive (27.5%), motor (35.5%), and autonomic seizures (6.5%). Interestingly, we also detected that auras and focal seizures were more prevalent in the older ages (> 6 y/o), while generalized and atonic seizures were more frequent in the younger ages (≤ 6 y/o). This might be explained by immature connections and ongoing complex-active myelination process may tend to have more generalized seizures in younger brains (Loddenkemper et al., 2004; Gupta et al., 2007; Kakisaka et al., 2011).

Recently, there are some proposals about certain subgroup of ILAE 2010 seizure classification to clarify their coverage and descriptions (Blumenfeld and Jackson, 2013; Lüders et al., 2014; Blumenfeld and Meador, 2014; Wilson and Baxendale, 2014). The main argument is that alteration or loss of consciousness may not be explained by only statement of “dyscognitive” (Blumenfeld and Jackson, 2013; Lüders et al., 2014; Blumenfeld and Meador, 2014; Wilson and Baxendale, 2014). Therefore, Lüders et al. (2014) proposed a new concept to categorize the consciousness and cognition which can be evaluated in five subgroups like aura, dyscognitive seizures indicated to specific cognitive deficit e.g. aphasia, apraxia, ictal delirium; dialeptic seizure indicated to disruption of consciousness; and epileptic coma. Based on this new concept, Blumenfeld and Meador (2014) was developed three categories of consciousness, so that impaired content of consciousness confining focal seizures with or without cognitive dysfunction; impaired level of consciousness like absence seizures, and impaired both content and level of consciousness like epileptic coma can be used instead of “dyscognitive”. In the light of those findings, dyscognitive seizures can be represented as single or combined seizures in a different consecutive combination of seizures in SSC. Hence, we found that dyscognitive seizures was represented as only dialeptic, automotor, and hypomotor seizures or a combination of dialeptic seizures followed by automotor seizures according to SSC system. As a similar concept with our study, there was only one investigation which matched the complex partial seizures (CPS) of ILAE 1981 to equivalent seizure types of the SSC (Benbadis et al., 2001). They found that 66 (87%) patients were classified as automotor, dialeptic, hypermotor or hypomotor seizures in SSC as closed findings to our results (Benbadis et al., 2001).

Semiological seizure classification allows us to provide better descriptions of many seizure subgroups by performing sequential analysis throughout one seizure evolution (Lüders et al., 1998, 2012; Bautista and Lüders, 2000; Benbadis et al., 2001; Loddenkemper et al., 2005; Hirfanoglu et al., 2007; Jan and Girvin, 2008; Tufenkjian and Lüders, 2012; Campen et al., 2013). Therefore, we found that only one (36.3%) or two consecutive (29.1%) or three consecutive (34.5%) semiologies were important in the evolution of the seizures. Limited and different results about the seizure subtypes of SSC were reported in different settings (Benbadis et al., 2001; Kim et al., 2002; Hirfanoglu et al., 2007). Most frequent seizure types were SMS (55.7–86.6%), then CMS (26.9–30.3%) and dialeptic seizures (21–35.5%) in different studies (Benbadis et al., 2001; Kim et al., 2002; Hirfanoglu et al., 2007). Our cohort reflected that the similar frequency and ratios of those seizure types as confirmatory to previous studies (Benbadis et al., 2001; Kim et al., 2002; Hirfanoglu et al., 2007). A remarkable point of our study, dialeptic and automotor seizures were seen much higher in older ages, while negative component seizures so called “special seizures” such as atonic and hypomotor seizures were appeared predominantly in the younger age groups. Consequently, possible age dependent seizure evolution should be taken consider when classification is applying to individual perspective and related to developmental

stage, such as automotor seizures are related to capability of fine motor movements which is matured as aged. (Källén et al., 2002; Fogarasi et al., 2007a,b; Gataullina et al., 2015; Ray and Kotagal., 2005).

4.2. Relationship between seizure types and epileptogenic zones

A recent investigation in children studied by Vendrame et al. (2011) assessed that dyscognitive seizures can be related not only temporal zone but also correlated to generalized focus as different from our results. Whereas, our study showed that dyscognitive seizures were related to temporal epileptogenic zones with a negative correlation to generalized foci. This discrepancy was arisen from between two study that different criteria were used for coverage of dyscognitive seizures which was described dyscognitive seizures as not only impaired consciousness due to focal foci but also included absence seizures in the last mentioned study. However, we described dyscognitive seizures as only impaired cognition and consciousness or combination of those with automatisms arising from focal foci (Berg et al., 2010; Panayiotopoulos, 2011; Vendrame et al., 2011; Lüders et al., 2012; Berg and Millichap, 2013; Korff and Scheffer, 2013; Blumenfeld and Jackson, 2013; Wilson and Baxendale, 2014). Consequently, seizure descriptions of ILAE 2010 should need to be revised for not to lead confusion and also to prevent over or underestimating coverage of the seizures (Berg et al., 2010; Panayiotopoulos, 2011; Vendrame et al., 2011; Lüders et al., 2012; Berg and Millichap, 2013; Korff and Scheffer, 2013; Blumenfeld and Jackson, 2013; Wilson and Baxendale, 2014).

We also detected that CMS of SSC were frequently seen in older ages with tendency of more focal origin. Furthermore, the focal foci for CMS shows some diversities with ages. So that, non specific dialeptic seizures (excluded to typical dialeptic seizures) and automotor seizures from CMS of SSC and their equivalent dyscognitive seizure from ILAE 2010 were related to temporal focus in older children while parieto-occipital zone in younger age groups. As opposed of our results, parieto-occipital zone is a rare and unexpected location for dyscognitive and automotor seizures (Fogarasi et al., 2003; Ray and Kotagal., 2005; Ristić et al., 2012; Gataullina et al., 2015). Similarly, atonic and hypomotor seizures of special seizures in SSC were presented with multifocal foci in younger age group with opposite relationship generalized focus, while older age groups had tendency of generalized focus. Depends of this result, we inferred that hypomotor seizures should be carefully examined if the presence of potential focal foci in younger ages. (Källén et al., 2002; Fogarasi et al., 2003; Ray and Kotagal., 2005; Ristić et al., 2012; Gataullina et al., 2015). Eventually, age dependent diverse foci were suggested us that one type of clinical presentation can be originated from different foci in younger age groups due to ongoing developmental process of certain brain regions and wide distributed connections (Källén et al., 2002; Fogarasi et al., 2003; Loddenkemper et al., 2004; Ray and Kotagal., 2005; Gupta et al., 2007; Jan and Girvin, 2008; Kakisaka et al., 2011; Ristić et al., 2012; Gataullina et al., 2015). Therefore, it is not surprised that temporal lobe seizures can be presented as behavioral changes or motor arrest so called “hypomotor or dialeptic seizures” in younger age group, while hand automatism can be appreciated older children as supported some rare studies and our cohort. (Källén et al., 2002; Fogarasi et al., 2003; Loddenkemper et al., 2004; Ray and Kotagal., 2005; Gupta et al., 2007; Kakisaka et al., 2011; Ristić et al., 2012; Gataullina et al., 2015).

Versive seizures of SMS from SSC were indicated to different foci such as temporal, frontal, multilobar, non-localizable, and generalized zones in various studies (Shukla et al., 2002; Jan and Girvin, 2008; Vendrame et al., 2011), whereas parieto-occipital zone was shown to in our study. This discrepancy may be depended on both age factor and also being initial or evolutionary part of the seizures

(Shukla et al., 2002; Jan and Girvin, 2008; Vendrame et al., 2011). Nevertheless, versive seizures are strongly associated with the contralateral hemisphere as in our study which is a valuable lateralizing sign for surgical cases (Benbadis et al., 2001; Kim et al., 2002). From a different point of view, the impact of opposite association between seizure types and epileptogenic zones are as important as positive correlation between those when deciding to the algorithm of the evaluation. One of the noteworthy results our study, asymmetric tonic seizures was addressed to have negative possibility to originate from temporal lobe in older ages. Supplementary sensorimotor, dorsolateral, orbitofrontal, frontopolar, and cingulate gyrus of frontal lobe were reported as postulated areas for asymmetric tonic seizure in different age groups and settings (Kotagal et al., 2003; Jan and Girvin 2008; Bagla and Skidmore, 2011; Tufenkjian and Lüders, 2012; Bonini et al., 2013, 2014; Marshly et al., 2016). Similarly, a negative relationship between epileptic spasm to temporal focus in older ages whereas no such an effect in younger children were suggested us to focal origins should be carefully evaluated for not to overlook a certain foci in younger children as supported to previous studies (Kakisaka et al., 2013; Ronzano et al., 2015; de la Vaissière et al., 2014).

4.3. Relationship between epilepsy syndromes and etiology & epileptogenic zone

ILAE 2010 provides a good perspective for epilepsy classification especially in the group of age-dependent syndromes compared to previous ILAE 1981 and 1989 classifications (Campen et al., 2013; Udani and Desai, 2014). However, almost half of the patients (45%) were still classified as nonsyndromic epilepsies in our series which includes diverse spectrum of metabolic and structural etiologies, suggested us to be some possible overlaps between the groups. Campen et al. showed that the most weak point of ILAE 2010 was the unknown or unclassifiable epilepsies in when compared to previous ILAE classifications (Campen et al., 2013). This limitation can be explained by a large percentage of the patients were categorized just only according to pathological and laboratory findings; however anatomical localization which were addressed as “Localization related epilepsies” in ILAE 1989 and 2006 syndrome classification was ignored in ILAE 2010 (Bancaud et al., 1989; Engel and ILAE, 2001). As encouraged this suggestion, we found more remarkable relationship between focal epileptogenic zone and etiology in five dimensional classification due to reserving structural etiology with clear subgroups. By considering this aspect, trauma and its complications were found to be correlated to temporal focus in younger ages while opposite association with older ages which was related to parieto-occipital focus in our cohort. This point provided us to a very important contribution to realized that the affected areas to the vulnerable hypoxia may change depends of the developmental stage and ongoing evolution of watershed areas and metabolic circuits (Fogarasi et al., 2003; Bregant et al., 2013; Harteman et al., 2013; Gataullina et al., 2015).

Therefore, etiology can be assumed an indispensable dimension during evaluation of epileptogenic zone (Loddenkemper et al., 2005; Campen et al., 2013; Udani and Desai, 2014). Overall, the five dimensional classification was seemed to a comprehensive system by harboring many features such as epileptogenic zone, SSC, etiology, and co-morbidities. Consequently, ILAE 2010 needs to be revised for clarifying some overlaps between epilepsy syndromes (Lüders et al., 2012; Korff and Scheffer, 2013; Campen et al., 2013).

5. Conclusion

During classification of seizures and epilepsies, the most important stage is to take consider if some details or general information

to understand the evolution of the disease. Both ILAE 2010 and SSC have some weak and strong points in terms of seizure classification and estimation of the epileptogenic zones. ILAE 2010 provides simple and easy perspective with a single step during classification, while SSC gives us a better definition regarding anatomical localization by assessing multiple consecutive steps. Even though primary goal of the classification is not only assessment of the epileptogenic zone, nevertheless the importance of classification cannot be ignored while seeking epileptic focus e.g in candidates for epilepsy surgery. To our knowledge, this current study is the first trial which compares both SSC and ILAE 2010 seizure classification in terms of predicting to the epileptogenic zone in children with epilepsy by dividing specific age groups. The fact of the age unique different presentations of the same focus or the possibility of an identical seizure types originating from various foci should be taken consider during classification of seizure and epilepsy in younger pediatric ages. Furthermore, not only positive relationship but also negative association between seizure types and etiology to the epileptogenic zones can also be important factor for assessing the priority of the investigating steps. Our results were also implied that the more specified subgroups of seizure types lead to have a better chance of analysis to the epileptogenic zone in SSC. However, seizure classification should be applied depends on the requirement of the patients. Semiological seizure classification can be used in determination of anatomical localization and scientific purposes such as presurgical workup, while ILAE 2010 classification can be preferred in general practice for daily clinical approach.

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None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.eplepsyres.2016.11.007>.

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