Original Article

Pattern and etiology of early childhood epilepsy: An Experience at a tertiary care University Center

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ABSTRACT

الأهداف: التحقيق في خصائص النوبات وأنواعها وتحديد مسببات الصرع لدى الأطفال الذين تقل أعمارهم عن سنتين.

المنهجية: أجريت مراجعة الرسم البياني بأثر رجعي أجريت في مستشفى الملك خالد الجامعي، المدينة الطبية، جامعة الملك سعود ، الرياض، المملكة العربية السعودية للأطفال دون سن الثانية، الذين تم تشخيص إصابتهم بالصرع، وعلى الأدوية المضادة لنوبات الصرع خلال الفترة من يناير 2017م إلى ديسمبر 2018م. تضمنت البيانات التي تم جمعها معلومات مفصلة عن نوبات المرض، والكهرباء السريرية، والتصوير العصبي، والتقييمات المختبرية والمسببات الأساسية.

النتائج: تم تضمين 150 مريضاً في الدراسة وتم تصنيفهم حسب المسببات إلى: وراثي (43، 28.7%)، بنيوي هيكلي (41، 27.3%)، استقلابي (10، 6.7%) ، معدي (8، 5.3%) ومجموعات مناعية (1، 0.7%) ومجموعات غير معروفة (47، 31.3%).وقد كانت أكثر أنواع النوبات شيوعًا هي الصرع المعمم، ومن بينها النوبات التوترية الارتجاجية المعممة التي حدثت في 56 (37%) مريضًا، تليها نوبات الصرع التوتري في 31 (21%)، وتشنج طفلي في 19 (13%)، والنوبات الرمعية العضلية في 4 (2.7%)، نوبات ونائية في 6 (4%)، ونوبات بؤرية في 33 (22%) مريض. وكان التأخر في النمو العام، و شذوذات في كل من الفحص العصبي والتصوير العصبي أكثر شيوعًا في المجموعات الهيكلية والوراثية. كان تخطيط كهربية الدماغ غير طبيعي في 82 (55%) مريضاً ، بما في ذلك غالبية المجموعة الهيكلية (26, 63.4%).

الخلاصة: تظل مسببات الصرع في هذه المجموعة غير محددة (غير معروفة) في نسبة كبيرة من الحالات، تليها الأسباب الوراثية و الهيكلية. وتعتبر هذه النتيجة إضافة علمية إلى البيانات الدولية المنشورة حول الصرع في أول عامين من العمر.

Objectives: To investigate seizure characteristics, types, and define the etiology of epilepsy in children aged ≤2 years using the 2017 ILAE classification.

Methods: A retrospective chart review was conducted at King Khalid University Hospital, King Saud University Medical City, Riyadh, Kingdom of Saudi Arabia for children below 2 years of age diagnosed with epilepsy, and on anti-seizure medications from January 2017 – December 2018. The collected data involved detailed information on the patients' seizure, electroclinical, neuroimaging, laboratory evaluations, and underlying etiology.

Results: One- hundred and fifty patients were included in the study and classified according to etiology into: genetic (43, 28.7%), structural (41, 27.3%), metabolic (10, 6.7%), infectious (8, 5.3%), immune-mediated (1, 0.7%) and unknown (47, 31.3%) groups. The most common seizure types were generalized epilepsy, among which generalized tonic-clonic seizures occurred in 56 (37%) patients, followed by tonic seizures in 31 (21%), infantile spasm in 19 (13%), myoclonic seizures in 4 (2.7%), atonic seizures in 6 (4%), and focal seizures in 33 (22%) patients. Global developmental delay and abnormalities in both neurologic exam and neuroimaging were more common in the structural and genetic groups. Electroencephalography was abnormal in 82 (55%) patients, including the majority of the structural group (26, 63.4%).

Conclusion: The etiology of epilepsy in this cohort remains undetermined (unknown) in a large proportion of cases, followed by genetic and structural causes. This result added to the published international data about epilepsy in the first 2-years of life.

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Seizures are the most common neurological disorder in children, with an incidence of 50–70 cases per 100,000 children. The prevalence is higher in neonates, with a decreasing incidence in older children.[1] Neonatal seizures occur in approximately 1.5% of neonates, febrile seizures in 2-4%, and epilepsy in up to 1% of children.[2] The occurrence of different types of childhood epilepsies is highly dependent on the age at onset of a seizure.[3] Therefore, it is necessary to determine the etiology and carefully diagnose epileptic seizures in early life to optimize management and outcomes.[4]

Structural/metabolic causes are the most common etiologies in infants with seizure.[5] Birth asphyxia is also a common prevalent etiology in infants younger than 2 years which can be preventable through better perinatal care;[6] neonatal seizures usually show an underlying severe disorder; they are unsuccessfully classified, under-diagnosed, and often challenging to manage.[7]

Advances in seizure and epilepsy classification over the years (1960,1981,1989, 2005-2009, 2010, 2017) have been accompanied with advances in the field of neuroimaging, neurophysiology, genomic technology and molecular biology, which play an important role in the management of patients, education, and epilepsy research.

The International League Against Epilepsy (ILAE) classification of epilepsy was revised in 2017 to review and recognize seizures, epilepsies, and their causes.[8] It provides an update on the original 1981 and 1989 publications and provides a modern descriptive template. Multiple studies have tested its usefulness and validity of its contents,[9-15] which offers 3 levels of terminology, starting with seizure type, epilepsy type, and epilepsy syndrome. In addition, the new classification included the etiology at each stage. The etiology is classified into structural, genetic, infectious, metabolic, immune, and unknown types, and is used as an important tool for clinicians to evaluate patients with epilepsy.[8] This study aimed to report the pattern and recognize the etiology of epilepsy in children in the first 2 years of life using the 2017 ILAE classification.

Methods. This is a retrospective study that involved a chart review of all children with seizures or epilepsy disorders who were followed up in the pediatric neurology clinic at the King Khalid University Hospital, King Saud University Medical City, Riyadh, Saudi Arabia between January 2017 and December 2018.

Data collection. The definition and classification of seizure and epilepsy proposed by the ILAE in 2017 were adopted in this study.[8] Approval from the institutional review board (IRB) was obtained at our institution. The study included all children with epilepsy who were on anti- seizure medications between the ages of 2-month and 2- years, registered with regular visits to 4 different pediatric neurology clinics and covered by 3 consultants pediatric neurologists. Data collected based on the first visit, and the details of the second seizure were used to apply the new ILAE 2017 seizure classification. Seizures were classified as recurrent unprovoked seizures based on the criteria proposed by the ILAE.[16] The epilepsy diagnosis was based on the new ILAE 2014 definition.[17] Seizures type was determined using the new ILEA 2017 seizure classification.[18] Seizure classification was based on the mode of onset; focal, generalized, and unknown onset. The etiological classification was as proposed by the ILAE.[8,19] Patients with neonatal seizures, febrile seizures, and non-epileptic events with a semiology similar to seizures were excluded. A well-structured data collection sheet was used to document clinical, laboratory and neuroimaging profiles, final diagnosis, and possible etiology of seizures. The clinical profiles recorded included; demographic data, age at presentation (onset of the first seizure), seizure type (eye witness for seizure semiology), perinatal history, developmental milestones (gross motor, fine motor, cognition, language and social), history of febrile convulsion, family history of epilepsy, and neurological findings on examination that included changes in head size, dysmorphic features, and abnormal tone and signs of upper motor neuron lesions (diplegia, hemiplegia, and quadriplegia). Laboratory profiles based on clinical presentation included; basic hemogram and metabolic (blood glucose, calcium, magnesium, urea, electrolytes, liver enzymes, and blood gases) work-up. Other advanced investigations include; metabolic markers (serum ammonia, lactate, uric acid, amino acids, biotinidase, and urinary organic acids), screening for congenital infections (toxoplasma, rubella, cytomegalovirus, and herpes simplex), and cerebrospinal fluid (CSF) analysis (glucose, lactate, protein and cell counts) were performed when indicated. Genetic tests including chromosome and mutation studies (epilepsy panel, and Whole exome sequencing test), were performed as indicated. Immune workup including serum immunoglobulin and a special autoimmune panel (CSF autoimmune antibodies screen for those well known to be associated with

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Table 1 - Demographic parameters and clinical characteristics of the patients (n=150).

Characteristics	Structural	Genetic	Infectious	Metabolic	Immune	Unknown	Total number
Total number	41 (27.3)	43 (28.7)	8 (5.3)	10 (6.7)	1 (0.7)	47 (31.3)	150
Gender distribution							
Male	23 (56.1)	17 (39.5)	4 (50.0)	6 (60.0)	0	18 (38.3)	68 (45.3)
Female	18 (43.9)	26 (60.5)	4 (50.0)	4 (40.0)	1 (100.0)	29 (61.7)	82 (54.7)
Age at onset (first seizure)							
0-7 days	4 (9.8)	8 (18.6)	0	1 (10.0)	0	4 (8.5)	17 (11.3)
8-30 days	14 (34.1)	6 (14.0)	2 (25.0)	0	0	4 (8.5)	26 (17.3)
1-24 months	23 (56.1)	29 (67.4)	6 (75.0)	9 (90.0)	1 (100.0)	39 (83.0)	107 (71.3)
Seizure type							
Focal	13 (31.7)	7 (16.3)	3 (37.5)	2 (20.0)	1 (100.0)	7 (14.9)	33 (22.0)
Generalized	28 (68.3)	36 (83.7)	5 (62.5)	8 (80.0)	0	40 (85.1)	117 (78.0)
Generalized type							
Atonic	0	1 (2.3)	0	1 (10.0)	0	4 (8.5)	6 (4)
Clonic	1 (2.4)	0	0	0	0	0	1 (0.67)
Infantile spasm	3 (7.3)	9 (20.9)	0	1 (10.0)	0	6 (12.8)	19 (13)
Myoclonic	1 (2.4)	1 (2.3)	0	0	0	2 (4.3)	4 (2.7)
Tonic	11 (26.8)	8 (18.6)	1 (12.5)	2 (20.0)	0	9 (19.1)	31(21)
Tonic clonic	12 (29.3)	17 (39.5)	4 (50.0)	4 (40.0)	0	19 (40.4)	56 (37)
History of febrile convulsion	2 (4.9)	0	0	0	0	4 (8.5)	6 (4.0)
Family history							
Epilepsy	6 (14.6)	15 (34.9)	0	4 (40.0)	0	13 (27.7)	38 (25.3)
Global developmental delay	31 (75.6)	33 (76.7)	5 (62.5)	8 (80.0)	0	18 (38.3)	95 (63.3)
Pyramidal signs	19 (46.3)	8 (18.6)	2 (25.0)	3 (30.0)	0	3 (6.3)	35 (23.3)
Hypotonia	13 (31.7)	22 (51.2)	1 (14.3)	4 (40.0)	0	11 (23.4)	51(34.0)
Dysmorphic features	4 (9.8)	10 (23.3)	0	1 (10.0)	0	4 (8.5)	19 (12.6)
abnormal head circumference	10 (24.3)	5 (11.6)	0	2 (20.0)	0	1 (2.1)	18 (12)
Abnormal Neuroimaging							
CT scan	4 (9.8)	1 (2.3)	2 (25.0)	1 (10.0)	0	1 (2.1)	96 (64)
MRI scan	36 (87.8)	23 (53.5)	6 (75.0)	7 (70.0)	1 (100.0)	14 (29.8)	
Abnormal EEG finding	26 (63.4)	21(49)	6 (75)	6 (60)	1 (100.0)	22 (47)	82 (54.7)

EEG -Electroencephalography, CT - computed tomography, MRI - Magnetic resonance imaging

seizures or status epilepticus) were performed when indicated. Neuroimaging was performed for all patients and included computed tomography (CT), magnetic resonance imaging (MRI), or a combination of both depending on the mode of seizure onset and the available imaging. The results were reviewed by a neuroradiologist. Electroencephalography (EEG), mainly interictal, was performed for all patients (for at least 20- 30 minutes). Awake and a sleep EEGs were obtained using various activation procedures. The EEG abnormalities included; focal, generalized, multifocal epileptiform discharges, and hypsarrhythmia, reviewed by an epileptologist. The data were reviewed by the first and second authors, and the final result of the classification of seizure type was based on the clinical presentation and evidence from investigations, mainly EEG and neuroimaging, and the classification of etiology based on additional information extracted from neuroimaging, genetic and metabolic investigations. According to the 2017 ILAE guidelines, the classification divided subjects into those with structural, genetic, infectious, metabolic, immune, and unknown etiologies. Patient consents were waived as the data were collected anonymously from medical records.

Statistical analysis. Data were analyzed using IBM Statistical Package for Social Sciences (SPSS) for Windows, version 23.0 (IBM Corp, Armonk, N.Y., USA). Categorical variables are presented as numbers and percentages and continuous variables as means, standard deviations, and ranges.

Ethical considerations. This study was retrospective in nature. No intervention was performed. Institutional Review Board approval for this study was obtained from the IRB of the College of Medicine, King Saud University, Riyadh, Saudi Arabia (IRB: No. E-20-4680). The study was conducted following the Declaration of Helsinki for human studies. Confidentiality of the data was ensured for all participants.

Results. A total of 150 children diagnosed with epilepsy in their first 2 years of life were included in

Table 2 - Metabolic and genetic causes among 150 children with epilepsy below 2 years of age.

Metabolic causes (total No. 10 (6.7%))
• Aminoacylase deficiency (ACY1)
• Congenital Methemoglobinemia (CYB5R3), G6PD Deficiency
• Malonic acidemia (MAL)
• Hemizygous pathogenic variant in G6PD gene
• Succinic semialdehyde dehydrogenase (SSADH) deficiency (ALDH5A1)
• Pyridoxal 5 phosphate dependent epilepsy (PNPO)
• Biotinidase deficiency
• Rhizomelic chondrodysplasia punctate type 2 (GNPAT)
• Sanfilippo A (MPS3A)
• Sulfite Oxidase deficiency (SUOX)
Genetic causes (total No. 43 (28.7%))
• SCN1A-related seizure disorder
• Dravet syndrome (SCN1A)
• Benign familial Neonatal convulsion (KCNQ2)
• Early Infantile Epileptic Encephalopathy (SCN2A)
• Early Infantile Epileptic Encephalopathy type 7 (KCNQ2)
• Early Infantile Epileptic Encephalopathy type 9 (PCDH19)
• Early Infantile Epileptic Encephalopathy type 11 (SCN2A)
• Early infantile Epileptic Encephalopathy Type 14 (KCNT1)
• Early Infantile Epileptic Encephalopathy type 18 (SZT2)
• Early infantile Epileptic Encephalopathy type 25 (SLC13A5)
• Early Infantile Epileptic Encephalopathy type 35 (ITPA)
• Earli Infantile Epileptic Encephalopathy type 49 (DENND5A)
• Early Infantile Epileptic Encephalopathy type 66 (PACS2)
• GLUT1 deficiency (SLC2A1)
• Infantile spasm (CACNB4)
• Epileptic encephalopathy, brain malformation (EML1)
• Autosomal Recessive Neurodevelopmental disorder with microcephaly, cataract and renal abnormalities (GEMIN4)
• GEMIN4- related phenotype with global developmental delay and congenital cataract
• Pseudo-TORCH syndrome (USP18)
• Epilepsy, progressive myoclonic (NHLRC1)
• Autosomal dominant Wiedemann-Steiner syndrome (KMT2A)
• X-linked epilepsy with variable learning disabilities and behavior disorders (SYN1)
• Autosomal recessive microcephaly, seizers, and developmental delay (MCSZ) (PNKP)
• Autosomal recessive spinocerebellar ataxia type 20 (SNX14)
• Ischemic stroke secondary to heterozygous G20210A factor II prothrombin mutation in F2 gene
• Tuberous Sclerosis Complex (TSC2)
• Sturge-Weber syndrome.
• Rett syndrome (FOXG1)
• Down Syndrome and Epileptic Encephalopathy (Infantile spasm)
• Galloway-Mowat syndrome (WDR73)
• Joubert syndrome (CC2D2A)
• Aicardi Goutieres syndrome (type AGS- 3

this cohort study after applying the exclusion criteria. It included a total of 68 (45.3%) boys, and 82 (54.7%) girls. The peak for the onset of the presentation was after the neonatal period, at 1 and 24 months in 107 (71.3%) children. **Table 1** showed the demographic data, and the clinical characteristics of the patients.

Based on etiology, patients were classified into genetic (43, 28.7%), structural (41,27.3%), metabolic (10, 6.7%), infectious (8, 5.3%), immune (1,0.7%) and unknown (47, 31.3%) types (**Table 1**). Tonic-clonic seizures were observed in 56 (37%) patients, followed by tonic seizures in 31 (21%) patients, infantile spasm in 19 (13%) patients, myoclonic seizures in 4 (2.7%) patients, atonic seizures in 6 (4%) patients, clonic seizures in 1 (0.67%) patient and focal seizures in 33 (22%) patients (**Tables 1**).

Six (4.0%) patients had a previous history of febrile convulsions, while 38 (25.3%) had a family history of epilepsy. Global developmental delay was found in 95 (63.3%) patients, mainly in the genetics (33, 76.7%) and structural groups (31, 75.6%). The most common neurological findings were hypotonia (51, 34.0%), followed by pyramidal signs (35, 23.3%), and dysmorphic features in (19, 12.6%).

Table 3 - Etiology of structural seizures in 41 patients.

Cause	n (%)
Perinatal insult	25 /41 (60.9%)
Congenital	11/41 (26.8%)
. Chiari malformation II (2 patients)	
. Chiari II malformation with bilateral subependymal gray matter heterotopia.	
. Dandy walker variants.	
. Arteriovenous malformation (AVM) (2 patients)	
. Large cisterna magna communicating with the 4th ventricle.	
. Left frontal insular cortical dysplasia	
. Extensive cerebral white matter cystic changes.	
. Severe cerebral malformation with pachygyria.	
. Extensive polymicrogyria.	
Traumatic	4/41 (9.8%)
. Massive parenchymal, subarachnoid, and intraventricular hemorrhage with small subdural hematoma.	
. Bilateral subdural hematoma.	
. Concussion / fracture (2 patients)	
Brain tumor	1 /41 (2.4%)
. Pilocytic astrocytoma	

Electroencephalography was abnormal in 82 (55%) patients, mainly in the structural group patients (26, 63.4%), while abnormal neuroimaging was detected in 96 (64%) patients, mainly in patients with structural and genetic etiologies, with 40 (97%) and 24 (56%) patients, respectively (**Table 1**). Epilepsy syndrome was documented in six patients with West syndrome who had hypsarrhythmia on EEG.

Genetic and metabolic causes include various disorders of amino acids, organic acids, peroxisomal disorders, lysosomal storage, and various neurogenetic disorders (**Table 2**). Perinatal insults (hypoxic-ischemic encephalopathy) were the most common cause of structural epilepsy in this cohort; (25, 60.9%), followed by congenital causes (11, 26.8%), and traumatic causes (4, 9.8%) (**Table 3**).

Discussion. This study evaluated 150 children with epilepsy who had their first seizure in the first 2 years of life between January 2017 and December 2018. We classified them according to the seizure types and etiology of epilepsy using the 2017 ILAE classification.[8,20] which provides a modern descriptive template for seizures and epilepsies.

Several studies have tested the validity of the latest 2017 ILAE classification and guidelines for older children.[9-15] These studies are not exactly comparable to the current study, as the age groups studied were different. There is little data regarding the use of the 2017 ILEA classification for children in the first 2 years of life, therefore the comparability of our data will be based on studies published using the previous versions of the ILAE classification in children.[1,15,21-24] Four of them were hospital-based studies, and 3 used the 2010 ILAE report.[1,15,24]

The majority of our cases had seizure onset beyond the neonatal period, mainly in the first year, consistent with what was previously reported in the literature .[1,5,25] Generalized seizures, mainly tonic-clonic seizures, were the most common type compared to focal seizures, and presented mainly in patients with genetics and unknown causes. This was in partial agreement to the results reported by Khreisat et al[25] and Alonazi NA et al[1] who showed that generalized tonic-clonic seizures were the majority of patients who presented with seizures in structural/metabolic epilepsy, while unknown epilepsy occurred in 20% and 44% of patients, respectively. In contrast, another study reported that focal epileptic seizures were the most common, followed by the generalized type.[15]

The most common causes of epilepsy in our cohort study in children aged <2 years were unknown (47, 31.3%), genetic (43, 28.7%), and structural causes (41, 27.3%). In comparison Alonazi et al[1] reported a ratio of unknown causes at 44%, followed by structural / metabolic causes at 43%. Al-Qudah et al[15] reported a high number of structural metabolic causes, followed by unknown causes. Both studies reported a low percentage of genetic causes, which might be attributed to the recent advances in molecular mutational studies that have allowed further diagnosis of rare neurogenetic disorders in children below 2 years of age. Abnormalities in developmental milestones, neurological examination findings, and EEG recordings were mainly observed

in children with genetic and structural causes, which reflect an underlying organic disease.[3,5] It also reflects the severity and nature of genetic causes diagnosed below 2 years of age and the type of referral cases accepted in our tertiary care center.

In our cohort, the most common cause of structural epilepsy was perinatal insults (predominantly caused by hypoxic-ischemic encephalopathy), followed by congenital, traumatic, and brain tumor causes. Advanced supportive neonatal measures for early brain protection especially during delivery, can help improve the outcome, thus reducing this type of epilepsy.

An important factor that may contribute to the high percentage of genetic causes in our study was the high rate of consanguinity among our populations which may be responsible for the occurrence of various autosomal recessive neurogenetic and metabolic disorders.[26] Genetic causes include early infantile epileptic encephalopathy (with various mutations), neurocutaneous syndrome (tuberous sclerosis complex and Sturge -Weber syndrome), and neurogenetic syndromes (Rett syndrome, Joubert syndrome, Aicardi Goutieres syndrome, and galloway syndrome), while the metabolic disorders in our country, which constitute many genetic and metabolic causes in our study, include various aminoacidopathies, organic acidemias, peroxisomal disorders, storage disease, and different types of metabolic treatable epilepsy (**Table 2**). Recent advances in genetic analysis especially in epilepsy at younger age group help in early diagnosis and facilitate the delivery of a specific target therapy to those with certain treatable causes, thus reducing the associated seizure morbidity and mortality. In our cohort 2 patients were diagnosed with treatable epilepsy, pyridoxal 5 phosphate dependent epilepsy, and biotindase deficiency, while in the majority of patients under the genetic and metabolic groups, the treatment was directed towards the epilepsy type

Unknown causes accounted for 31.3% of all patients in our study. Previous studies reported 40.4%-44% of patients as being considered to have unknown causes.[1,15] Advance in genetic technology and molecular biology may help to decrease the proportion allocated to this group.[15]

Abnormalities in neuroimaging (CT and/or MRI brain) findings were reported in 96 (64%) patients in our cohort, mainly in patients with structural (40, 97.5%), genetic (24, 55.8%), and metabolic (8, 80%) etiologies. Brain imaging helps to recognize the etiology of symptomatic epilepsy and its associated pathology.

Compared to neuroimaging, EEG is a more useful and cost-effective investigative technique performed in most patients with epilepsy.[4,19] The EEG can support the classification of seizure type, recognition of a specific syndrome, and as a result, prediction of long-term outcomes. Our study showed abnormal EEG findings in 82 (54.7%) patients, mainly in the structural group, where 26/41 (63.4%) patients presented with abnormal EEG, similar to what was reported in other studies.[3,5]

Our study is unique in being a hospital-based study in a teaching hospital using the latest classification specifically for those below 2- years of age.

Limitation of the study. The availability of hospital-based retrospective studies using the revised terminology proposed by the ILAE in 2017 in the first 2 years of life was limited in the literature to compare with our findings. However, we considered that the new categories of genetic, structural, metabolic, and unknown in the 2017 report corresponds to the previous genetic, structural/metabolic, and unknown terminology in 2010.[1] In addition, optimal epidemiological data cannot be extracted from this study due to the small sample size, and the nature of a hospital-based, retrospective, single-center study. Limitations in specific advanced molecular mutational studies may contribute partially to the high percentage of unknown causes among our population with a high rate of consanguinity and neurogenetic disorders.[26]

Conclusion. This study suggests that the etiology of epilepsy in most patients aged <2 years was mainly unknown or secondary to genetic causes probably due to the high rate of consanguinity in our country. This result adds to published international data about epilepsy in the first 2-years of life. Using the ILAE etiological classification of epilepsy (2017) helps to recognize, diagnose and appropriately manage children with epilepsy.

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