ORIGINAL ARTICLE

Clinical characteristics and aetiology of early childhood epilepsy: a single centre experience in Saudi Arabia

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ABSTRACT

Seizures in children and neonatal period have variety of causes; however, most of childhood seizures are idiopathic. The aim of this study was to review the causes of epilepsy in children presenting in the first 2 years of life using the International League Against Epilepsy classification released in 2010. This was a retrospective chart review study that was conducted at a tertiary center in Saudi Arabia. Two hundred and twenty-one patients were included in the study, 31 with conditions mimic epilepsy were excluded. The remaining 190 patients were classified into: Group A, structural/metabolic, 82 (43%); Group B, genetic, 24 (13%) and Group C, unknown, 84 (44%). The commonest seizures' type was tonic–clonic in 106 (56%), followed by clonic 29 (15.3%), myoclonic 22 (11.6%) and a tonic 16 (8.4%). Pyramidal signs, global developmental delay, hypotonia, micro/macrocephaly and abnormal computed tomography and/or magnetic resonance imaging brain were more common in the structural/metabolic group ($p < 0.05$). Electroencephalography was abnormal in 136 (72%) patients, mostly in the structural/metabolic group ($p = 0.011$). In conclusion, the aetiology of epilepsy in this cohort was mainly unknown or secondary to structural/metabolic causes.

KEYWORDS:

Childhood; Epilepsy; Aetiology; Saudi Arabia; Seizures.

INTRODUCTION

Seizures are an important cause of neurological morbidity in children with an incidence of 50–70 cases per 100,000. The incidence is higher in the neonatal period, with decreasing frequency in older children [1]. This is because of the relative lack of inhibitory neurotransmitters and immature development of their pathways in early life [2]. This results in a developmental imbalance between maturation of excitatory and inhibitory circuits [3]. The primary inhibitory neurotransmitter in adults,

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γ-aminobutyric acid, is excitatory in the hippocampal neurons of young children [4]. In addition to this, there is a higher density of the excitatory receptors, N-methyl-D-aspartate, in the neocortical regions of the growing brain, resulting in enhanced excitatory activities [2–4]. All these factors result in increased susceptibility to developing brain to a variety of insults that manifest as epilepsy [5].

The aetiology of epilepsy is classified into structural/metabolic, genetic and unknown according to the 2010 report by the International League Against Epilepsy (ILAE) [6]. The ILAE classification of Epilepsy reflects more of understanding of the underlying causes of epilepsy, which is used as a critical tool for the clinician in evaluating an individual with epilepsy. Structural/metabolic seizures are caused by an identifiable brain insult such as hypoxic-ischemic encephalopathy [7,8]. In contrast, genetic epilepsy occurs in patients with a specific genetic error such as autosomal dominant nocturnal frontal lobe epilepsy [6]. It is occasionally difficult to determine the aetiology of epilepsy especially in the first year of life [9,10]. This study aimed to describe the pattern and identify the aetiology of epilepsy in children presenting in the first 2 years of life using the classification proposed by the ILAE in 2010.

MATERIALS AND METHODS

This retrospective, descriptive hospital-based study was conducted at Saad Specialist Hospital (SSH), Alkhobar, Saudi Arabia between January 2010 and December 2011. SSH is a private hospital with a total of 600 beds including 100 beds allocated to children. Children diagnosed with epilepsy from birth to 2 years of age were recruited. Subjects were identified from the medical records of patients admitted to SSH or those attending the paediatric neurology outpatient clinics, with a diagnosis of epilepsy. These clinics operate three times a week with an average of 10 patients per clinic.

The definition of epilepsy and its disorders proposed by the ILAE in 2010 was adopted in this study [6]. Patients with febrile convulsion and those with conditions mimic epilepsy were excluded.

The medical records of the identified subjects were systematically reviewed by the second and the last authors using a structured case report form to document clinical and laboratory characteristics, the final diagnosis and the possible aetiology of seizures. The clinical characteristics recorded included: chronological age, sex, age at the first seizure, seizure type, family history of epilepsy, history of febrile convulsion, perinatal history, developmental milestones and general and neurological examination findings. Developmental delay was defined as a global delay if two or more of the following developmental domains were impaired: gross motor, fine motor, cognition and language and social. Other clinical features reported were: microcephaly, macrocephaly, dysmorphic features and an abnormal tone and signs of upper motor neuron lesions (diplegia, hemiplegia and quadriplegia). Results of investigations, which were tailored to the clinical presentation of patients, were documented in the case report form. These investigations included: blood glucose, calcium, magnesium, urea, electrolytes, liver enzymes and blood gases; full blood count; cerebrospinal fluid (CSF) analysis (glucose, lactate, protein and cell counts) and cultures of blood, CSF and urine. Other investigations performed when serum ammonia, lactate, uric acid, amino acids, biotinidase, urinary organic acids and toxoplasma rubella, cytomegalovirus and herpes simplex screening are indicated. Genetic test including chromosome and mutation study were requested as indicated. Immune workup including serum immunoglobulin was done when indicated. Radiological tests were done for some patients. This includes cranial ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI) of the brain. Electroencephalography (EEG) was performed for all patients. Awake and sleep EEG by sleep deprivation was performed. Hyperventilation, photic stimulation and other maneuvers were performed using the epilepsy protocol. The EEG and the brain image were reported by the paediatric neurologist.

The EEG abnormalities reported included the presence of an abnormal slowing in background activities and epileptiform activity, either focal or generalised. These EEG abnormalities in addition to the clinical characteristics of the patients and the result of their investigations were used to define the aetiology and classify the type of seizures according to the ILAE guidelines in 2010

[6]. Based on this classification, subjects were divided into three groups: structural/metabolic, genetic and unknown.

STATISTICAL ANALYSIS

The data were analysed using SPSS version 17 (SPSS Inc., Chicago, IL). Statistical tests used were chi-square and Yates' chi-square test. Mean, median and standard deviations were used in the descriptive data. Differences between groups were considered significant if $P < 0.05$.

This study was approved by the Intuitional Research Board at SSH, Alkhobar, Saudi Arabia.

RESULTS

Medical records of all children diagnosed with epilepsy and presented in the first 2 years of life were studied. Out of 221 patients identified, 31 with conditions mimic epilepsy were excluded. Based on clinical characteristics, laboratory and EEG findings, these patients were classified into Group A, structural/metabolic, 82 (43%) patients; Group B, genetic, 24 (13%) and Group C, unknown, 84 (44%) (Tables 1 and 2). The majority of patients with epilepsy (62%) presented with their first seizure after the neonatal period. Perinatal insults (mostly hypoxic ischemic encephalopathy) were the most common cause of

Table 1 - Characteristics and clinical features of 190 patients with structural/metabolic, genetic and unknown causes of epilepsy.

Variables	Group (A) structural/ metabolic	Group (B) genetic	Group (C) unknown	*P*-value
Total number	82 (43%)	24 (13%)	84 (44%)	
Sex distribution				
Male	52 (63.4%)	10 (41.7%)	40 (47.6%)	0.056
Female	30 (36.6%)	14 (58.3%)	44 (52.4%)	
Age at presentation				
0–7 days	14 (17.1%)	1 (4.2%)	12 (14.3%)	
8–30 days	18 (22.0%)	3 (12.5%)	25 (29.8%)	0.133
1–24 month	50 (61.0%)	20 (83.3%)	47 (56.0%)	
Seizures type				
Focal seizures	6 (7.3%)	2 (8.3%)	7 (8.3%)	0.967
Generalised seizures				
Tonic	2 (2.4%)	0 (0%)	0 (0%)	0.264
Tonic-clonic	47 (57.3%)	18 (75.0%)	41 (48.8%)	0.070
Myoclonic	9 (11.0%)	2 (8.3%)	11 (13.1%)	0.793
Atonic	7 (9%)	0 (0%)	9 (10.7%)	0.249
Clonic	11 (13.4%)	2 (8.3%)	16 (19.0%)	0.361
Pyramidal signs	15 (18.3%)	1 (4.2%)	0 (0%)	<0.0001
Hypotonia	11 (13.4%)	0 (0%)	0 (0%)	<0.0001
Global developmental delay	21 (25.6%)	5 (20.8%)	0 (0%)	<0.0001
Dysmorphic features	3 (3.7%)	2 (8.3%)	0 (0%)	0.059
Micro/macrocephaly	11 (13.4%)	0 (0%)	0 (0%)	<0.0001
Abnormal CT and/or MRI brain finding	35 (42.7%)	1 (4.2%)	0 (0%)	<0.0001
Abnormal EEG finding	66 (80.5%)	12 (50.0%)	58 (69.0%)	0.011

structural/metabolic epilepsy in this cohort, which was reported in 41 (50%) children, followed by metabolic causes in 24 (29.3%) children (Table 2). Genetic causes included disorders of amino acids, organic academia, urea cycle defects, fatty acid oxidation defects, neuronal ceroid lipofuscinosis, peroxisomal disorders and lysosomal storage diseases. Details of genetic causes of epilepsy of this cohort were published elsewhere [10].

Tonic–clonic seizures were observed in 106 (56%) patients, followed by clonic 29 (15.3%) and myoclonic seizures 22 (11.6%). Clinical examination of the study group revealed the statistically significant presence of pyramidal signs, global developmental delay, hypotonia and micro/macrocephaly in the structural/metabolic group ($p < 0.05$). There were abnormal brain radiological findings (CT and/or MRI brain) in 36 patients; mostly in the structural/metabolic group, $p < 0.0001$. In comparison, 136 (72%) patients showed abnormal EEG findings; mainly in the structural/metabolic group (80%), followed by the unknown group (69%), $p = 0.011$. Epilepsy syndrome was documented in four patients with the West syndrome who had hypsarrhythmia on EEG. The majority of patients with conditions mimic epilepsy were found to have gastroesophageal reflux, 12 (39%) and breath-holding attacks, 10 (32%) (Table 3).

DISCUSSION

Epilepsy is one of the leading neurological problems in children faced by paediatricians. Data on the exact incidence of childhood epilepsy, especially in infancy, are limited in Saudi Arabia. In our study, we included all children with epilepsy who had their first seizure in the first 2 years of life. Nevertheless, the majority of our patients presented after the neonatal period.

Table 2 - Aetiology of structural/metabolic seizures in 82 children.

Cause	Number (%)
Perinatal insult	41 (50%)
Metabolic	24 (29.3%)
Infectious	6 (7.3%)
Traumatic	6 (7.3%)
Others	5 (6.1%)

This agrees with reports from Jordan and Poland where a peak age of presentation of seizure was identified late in the first year, extending to the second year of life [8,11].

In the current study, 43% of patients had structural/metabolic epilepsy, and 44% had unknown epilepsy. Similar results were reported by Kroczka et al. [8] who showed that structural/metabolic epilepsy (previously known as symptomatic epilepsy) is common in infants admitted with seizures. This type of epilepsy usually results from organic brain lesions that present with developmental delay, neurological abnormalities and abnormal EEG [8,10]. In our study, perinatal insults (mainly hypoxic ischemic encephalopathy) were the most common cause of structural/metabolic epilepsy, followed by metabolic disorders, infections, and trauma. Similarly, previous studies that were investigated [10] reported different causes with variable frequencies, including intracranial infection cerebral malformation, degenerative brain disease and perinatal brain damage [8]. The type of seizures in the structural/metabolic group varied widely among different studies. In our cohort, we found that generalised seizures, especially tonic–clonic seizures, were more common compared to focal seizures. Similar results were reported by

Table 3 - Clinical features of 31 patients with conditions mimicking epilepsy.

Variables	Number
Total number	31
Sex distribution	
Male	17 (55%)
Female	14 (45%)
Age at presentation	
0–7 days	6 (19%)
8–30 days	25 (81%)
1–24 month	0 (0%)
Type of condition	
Breath holding spells	10 (32%)
Gastroesophageal reflux	12 (39%)
Extrapyramidal movements	5 (16%)
Jitteriness	3 (9.6%)
Torticollis	1 (3.2%)

Khreisat et al. [11] who showed that generalised tonic–clonic seizures were the most common type of seizure in structural/metabolic epilepsy. This prevalent generalised epilepsy can be explained by the fact that caregivers, as well as physicians, may sometimes miss the onset of seizures, which may have started as focal and became generalised. In contrast to our findings, a study from Argentina with 471 patients reported symptomatic partial epilepsy in 28% of cases and structural/metabolic generalised epilepsy in 33%.

We observed unknown epilepsy in 44% of our patients with the majority presenting as generalised tonic–clonic seizures. In contrast, Khreisat et al. reported that only 20% of their cohort had cryptogenic epilepsy (currently known as unknown epilepsy). Unlike the group with an unknown cause, genetic epilepsy is a direct result of a known or presumed genetic defect(s), in which seizures are the core symptom of the disorder [6]. According to these criteria, 13% of our patients were diagnosed with genetic epilepsy. This percentage of patients may be less representative of the contribution of the genetic factors to the development of epilepsy. This could be explained by the limited genetic tests available in our institute. With the recent advances in the genetic and molecular diagnostic methods, more genetic contributions to epilepsy are recognised. However, it may often be difficult to characterise genetic causes of epilepsy. For example, ARX, a homeobox gene, is associated with West syndrome as well as lissencephaly [6].

Abnormal brain imaging (CT and/or MRI brain) findings were reported in 36 patient in our cohort, mainly in the structural/metabolic group (p = 0.000). This reflects the extent of brain insult associated with the structural/metabolic group compared to the other groups. It is a common practice to perform neuroimaging in children with suspected epilepsy. This modality examines the relationship between abnormalities of brain function and anatomical distribution of brain pathology [13]. Also, it helps to identify the aetiology of symptomatic epilepsy and the extent of the associated pathology. Non-urgent neuroimaging such as CT and MRI should be considered following afebrile seizures in children aged <1 year, especially in those with focal seizures or an abnormal neurological examination [13]. However, some of the abnormalities could not be detected early by neuroimaging and became obvious with age, especially focal cortical dysplasia. Similarly, a recent study from Saudi Arabia demonstrated a high prevalence of abnormalities (42.7%) identified on brain CT in children who presented with their first apparent seizure [14]. This suggests that emergency CT should be considered in children presenting with their first seizure. This high positive predictive value of brain CT could be explained by the fact that patients were studied after their first seizure, and some of them may not necessarily have had epilepsy. Also, patients presenting with their first seizures in an emergency department are likely to have an acute brain insult, such as infection or trauma. Compared to neuroimaging, EEG is more useful and cost-effective investigative technique that is usually performed in the majority of patients with epilepsy [6,7]. EEG can be helpful in the classification of seizure type, identification of a specific syndrome and consequently, prediction of long-term outcome [7,13]. The present study showed abnormal EEG findings in the majority of patients in the structural/metabolic group compared to the other groups (p = 0.011). This result can be explained by the fact that the aetiology of brain insult in the structural/metabolic group tends to be more pertinent and, therefore, likely to show abnormal EEG findings. Similar results were reported in previous studies [10].

The limitations of this study include that not all patients had detailed neuroimaging, genetic and metabolic investigations. As a retrospective study, some information in the history and clinical examination was missing. This study was based on the 2010 ILAE classification that was in use at the time of the study in 2010–2011. Therefore, we were unable to use the recently released 2017 ILAE classification in our study [15]. The 2017 ILAE report classifies epilepsy into five categories: structural, infectious, immune, genetic and unknown causes. This classification fills the gap in pinpointing the aetiology of epilepsy. The current advances in genetic studies including the emerging whole exome and whole genome sequencing will facilitate pinpointing the aetiology of epilepsy.

In the conclusion, this sudy suggests that the aetiology of epilepsy in the majority of patients in

this cohort aged <2 years was mainly unknown or secondary to structural/metabolic causes.

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