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Landscape of childhood epilepsies – A multi-ethnic population-based study

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ABSTRACT

Objective: To describe the clinical features of childhood epilepsy in Qatar.
Methods: A retrospective cross-sectional chart review analysis was conducted at the only tertiary pediatric hospital in Qatar in 1422 patients with epilepsy followed between November 2016 and October 2019.
Results: 55% (781) were males and 70% were non-Qatari. Age of epilepsy onset was in the neonatal period in 9% (114/1207 patients). In the non-neonatal cohort, mean age of onset was 4 yrs 9mos (± 1.4mos). Focal epilepsy was the predominant epilepsy type in 45% (594/1314 patients) versus generalized epilepsy in 37% and combined focal/generalized epilepsy in 12%. Etiology was unknown in most children (782/1363, 57%) whereas structural and genetic causes represented 23% and 11% of cases respectively. No differences in epilepsy type and etiology were found between different ethnic groups. Children with genetic or structural epilepsies had an earlier epilepsy onset compared to those with unknown etiologies. At the last follow up, only 36% of patients were seizure-free and 12% (170/1422) had a history of status epilepticus. Medically refractory epilepsy was found in 37% (527/1407) of patients, with the most common etiologies being unknown (36%) and structural (37%). Neurodevelopmental co-morbidities were present in most patients (62%), with global developmental delay (47%) and learning/school difficulties (22%) being the most prevalent. 94% of patients with somatic co-morbidities had concomitant neurodevelopmental co-morbidities. Risk factors associated with an increased risk of co-morbidities and intractable epilepsy included early age of epilepsy onset (< 2 years of age); etiology; antenatal risk factors; history of previous central nervous system infection; history of status epilepticus and a family history of consanguinity and epilepsy.
Significance: This large multi-ethnic population-based study confirms that the prevalence, incidence and clinical features of epilepsy in Qatar is in accordance with other epidemiologic studies and highlights risk factors for the development of co-morbidities and medically-intractable epilepsy.

1. Introduction

Epilepsy is a common pediatric neurologic condition, defined as "a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiologic, cognitive, psychological, and social consequences of this condition" (Fisher et al., 2005). Most patients with epilepsy begin to manifest with seizures in childhood, with the worldwide incidence estimated at 41–187/100,000 (Camfield and Camfield, 2015; Shinnar and Pellock, 2002). Causes of epilepsy in children are diverse and vary from acquired brain injury (perinatal asphyxia, trauma, infections, stroke, brain tumors) to inherited etiologies (brain malformations, neurogenetic syndromes, channelopathies). In a considerable proportion of patients however, the cause of the epilepsy remains unknown (Camfield and Camfield, 2015; Wirrell et al., 2011).

Various epidemiologic studies have demonstrated that in many cases, the prognosis in childhood epilepsies is good, with up to 70–80% of children having their seizures well controlled with antiseizure medications (ASMs) and eventually attaining remission (Berg and Shinnar, 1994; Geerts et al., 2010). Despite this, up to 30% of children with childhood epilepsies have a more severe course characterized by medically intractable seizures and significant medical and psychosocial co-morbidities leading to a diminished quality of life (Ferro, 2014).

Behavioral and neurocognitive deficits are among the most important co-morbidities and are seen in up to 35–50% of children with epilepsy, with rates higher than 50% in children with intractable epilepsy

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(Sillanpaa et al., 2016). Deficits range from learning disabilities, academic difficulties, attentional deficits, language and memory impairments to frank severe intellectual impairment (Wei and Lee, 2012) and are often the second most important concern raised by patients and their care givers (Arunkumar et al., 2000). Among five common chronic conditions seen in children, epilepsy has been demonstrated to be the second most common disease after asthma to result in significant adverse effects on academic performance and health related outcomes (Miller et al., 2016). Cognitive deficits appear to be present early, are seen even in children with well controlled epilepsy and are related to various factors including medication side effects, structural brain abnormalities, etiology as well as to the severity and duration of the epilepsy (Fastenau et al., 2008; Bailet and Turk, 2000; Aldenkamp et al., 2005).

Situated in the Arabian Peninsula, the state of Qatar constitutes a population of approximately 2.8 million, of whom only 10–15% are Qatari nationals whilst the remaining represent an expatriate population comprising of about 100 different nationalities. Despite the significant health and psychosocial burdens inherent of this chronic neurological disorder, few epidemiological studies in epilepsy have been carried out in Qatar. Adetailed cross-sectional study involving 468 patients published in 2016 demonstrated an annual incidence of epilepsy of 174 per 100,000 (Haddad et al., 2016). In this study, which comprised predominantly of adults, the most common causes of epilepsy were stroke in the Qatari native population and neurocystircercosis in patients of South Asian descent. In 57% of patients, no identifiable cause was found. The pediatric literature is even scantier with only one small retrospective study reviewing the clinical features of 25 patients presenting with convulsive status epilepticus and reporting an estimated incidence of 12 per 100,000 (Alshami et al., 2008).

To address this huge gap in knowledge, a detailed cross-sectional study was carried out in the only tertiary pediatric hospital in the country which, until 2020, was the sole care provider for all children with epilepsy. The objective of this study is to describe the landscape of childhood epilepsies in Qatar by providing insight into demographics, etiologies, epilepsy types and severity, risk factors, co-morbidities and outcomes.

2. Methodology

2.1. Study design and patient population

This study was done at a single tertiary pediatric center, Sidra Medicine, which cares for all pediatric patients with epilepsy in the country. A retrospective chart review analysis was carried out for epilepsy patients followed in the Neurology outpatient clinics between November 2016 and October 2019 inclusive (3-year period).

Inclusion Criteria:

1. Age: Birth to 18 years (inclusive);
2. Diagnosis of epilepsy as per the International League Against Epilepsy (ILAE) criteria; (Fisher et al., 2017)
3. At least two neurology clinic visits documented with sufficient clinical data available

Exclusion Criteria:

1. Children presenting with one unprovoked seizure not meeting the ILAE criteria (Fisher et al., 2017);
2. Children with provoked seizures including but not limited to febrile convulsions, post-traumatic seizures, neonatal seizures due to perinatal asphyxia;
3. Children with paroxysmal non-epileptic events and/or an unclear diagnosis for epilepsy;

2.2. Data collection

The initial step in patient identification involved the extraction of electronic medical records (EMRs) of all patients seen in the Neurology outpatient clinics between November 1st 2016 and October 31st 2019, which yielded a total of 5988 patients. Out of this list, EMRs with a diagnosis of epilepsy using the International Classification of Diseases (ICD) for epilepsy 345 * and all terms under this hierarchy (ICD-9-CM Diagnosis Codes: Epilepsy and recurrent seizures, 2013) were selected. This initial step in cohort identification yielded a total of 1671 patient records with a presumptive diagnosis of epilepsy that were then selected for a subsequent complete chart review.

During the chart review phase, only patients meeting the inclusion criteria and not the exclusion criteria were selected for further data analysis. Various clinical variables were collected including demographic data (age, sex, country of origin); epilepsy details (age of onset, seizure types, epilepsy type, epilepsy severity, etiology); treatment details (number and type of antiseizure medications), associated neurodevelopmental co-morbidities (developmental delay, intellectual impairment, autism spectrum disorder, learning/school difficulties, behavioral difficulties, swallowing difficulties, visual and hearing impairment); somatic co-morbidities (cardiac, respiratory, genito-urinary, gastro-intestinal, orthopedic, etc); risk factors, family history, and investigations. Investigations included results from video electroencephalograms (EEGs), which had been carried out as per institution protocol and were of a minimum duration of 40 min, including wake and sleep tracings. Neuroimaging studies involved results from Magnetic resonance imaging (MRI), done either on a 1.5Tesla or 3Tesla magnet, with or without dedicated epilepsy protocol. Genetic testing included molecular karyotype (comparative genomic hybridization, CGH), gene panels and/or whole exome sequencing. All clinical variables were collected for each patient and entered into an electronic database for analysis.

2.3. Statistical analysis

The data was coded and entered into SPSS 22.0 software (SPSS Inc., Chicago, IL, USA). Demographic and clinical characteristics available for each variable are reported as descriptive statistics using counts (percentage). Due to the inherent limitations of chart review analysis, data was not available for each variable for all patients. As such, the descriptive statistics are described as a percentage of the counts available for each variable. Evaluation of the risk factors contributing to the presence of co-morbidities and intractability of the epilepsy was estimated by odds ratio (OR) and the 95% confidence interval (CI) was calculated. Multivariate analysis was carried out using logistic regression for binary data and p-value of ≤ 0.05 was considered significant. Incidence was calculated based on the number of new patients diagnosed with epilepsy in the last year of the study (300 patients) divided by the total number of children in the country (~400,000 as per the Planning and Statistics Authority, Qatar in Figures, 2020, 35th Issue). The 3-year prevalence was calculated based on the total number of children with epilepsy during the study period (1422) divided by 400,000.

3. Results

249 out of the 1671 patients included for the initial chart review were excluded from further analysis for the following reasons: established diagnosis of epilepsy but insufficient documentation to enable adequate epilepsy characterization (39 patients, 16%); isolated unprovoked seizure not meeting the diagnosis for epilepsy (42 patients, 17%); recurrent provoked seizures (67 patients, 27%); non-epileptic events such as tics, syncope, breath holding spells, migraine equivalents, pseudoseizures or other abnormal non-epileptic movements (101 patients, 41%).

Data collected from a total of 1422 patients meeting the ILAE criteria for the diagnosis of epilepsy were included in the subsequent detailed data analysis. Of these, 641 (45%) were females and 781 (55%) were males. 70% of patients were non-Qatari whereas the remaining 30% were of Qatari nationality (Table 1). The mean age at the last clinic visit was 9.5 yrs ± 4.3 yrs (range 2 months to 18 years) (Table 1). The age of onset of the epilepsy was found to be in the neonatal period in 9% of patients (114/1207 patients) whereas in the remaining patients (1093/1207 patients), the mean age of onset of the epilepsy was 4 yrs 9mos (± 1.4mos). Further breakdown in the distribution of the onset of the epilepsy revealed that in most cases (53%, 642/1207 patients), the onset of the first unprovoked seizure was in the childhood period (2 yrs to 10 yrs) whereas the neonatal and adolescent onset groups represented the minority of cases (Fig. 1). The onset of the epilepsy was more commonly seen in pre-school aged (≤ 5 yrs) children (69%, 838/1207 patients) as opposed to school aged (> 5 yrs) children (30%, 369/1207 patients).

Data regarding the seizure semiology, epilepsy type and etiology are summarized in Table 1. Focal epilepsy was the predominant epilepsy type seen in 45% of patients (594/1314 patients) as opposed to generalized epilepsy in 37% (484/1314 patients) and combined focal/generalized epilepsy in 12% (157/1314 patients). Etiology was unknown in most children (782/1363, 57%) whereas structural and genetics causes represented 23% (310/1363) and 11% (152/1363) respectively (Table 1). Fig. 2A illustrates the distribution of the epilepsies based on etiology (structural, metabolic, genetic, immune, infectious, unknown or multiple). In 6% of children (87/1363), multiple etiologies were identified, the majority (60/87 patients) of which were combined structural/genetic such as in patients with Tuberous sclerosis complex (TSC) and other neurogenetic disorders with associated structural brain anomalies. Genetic and structural epilepsies were more often seen with onset in infancy (< 2 yrs of age) as opposed to unknown etiologies that were more likely to start in childhood (≥ 2 yrs of age). In the 4 patients with immune-mediated epilepsy, onset was in the childhood period (Fig. 2B). Epilepsy type and etiology were compared across different ethnic groups including those from the Middle East North African Region (MENA), Asian, African and Caucasian. No differences were noted between the different ethnic cohorts with respect to epilepsy type or epilepsy etiology (Supplementary Table 1).

Table 1
Summary of patient demographics and epilepsy characteristics.

Gender	Male	781 (55%)
	Female	641 (45%)
Nationality	Non-Qatari	997 (70%)
	Qatari	425 (30%)
Mean age at the last clinic visit (yrs ± STD)		9.5 yrs ± 4.3 yrs
Epilepsy Characteristics		
Mean age of onset of epilepsy (yrs ± STD)	Neonatal Onset (9%, 114/1207)	-
	Non-Neonatal Onset (91%, 1093/1207)	4.75 yrs ± 1.4mos
Seizure Types (%, 1422)	Focal	621 (44%)
	Generalized	546 (38%)
	Focal + Generalized	115 (8%)
	Undetermined	140 (10%)
Epilepsy Type (%, 1314)	Focal	594 (45%)
	Generalized	484 (37%)
	Combined Focal/Generalized	157 (12%)
	Unknown	79 (6%)
Epilepsy Etiology (%, 1363)	Structural	310 (23%)
	Genetic	152 (11%)
	Infectious	29 (2%)
	Metabolic	6 (0.4%)
	Immune	4 (0.3%)
	Unknown	782 (57%)
	Multiple	87 (6%)

± STD (± standard deviation)

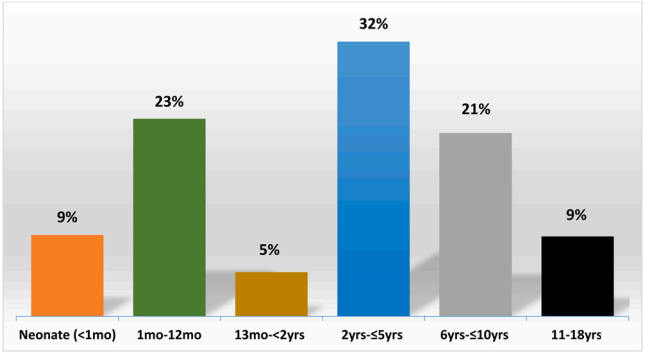


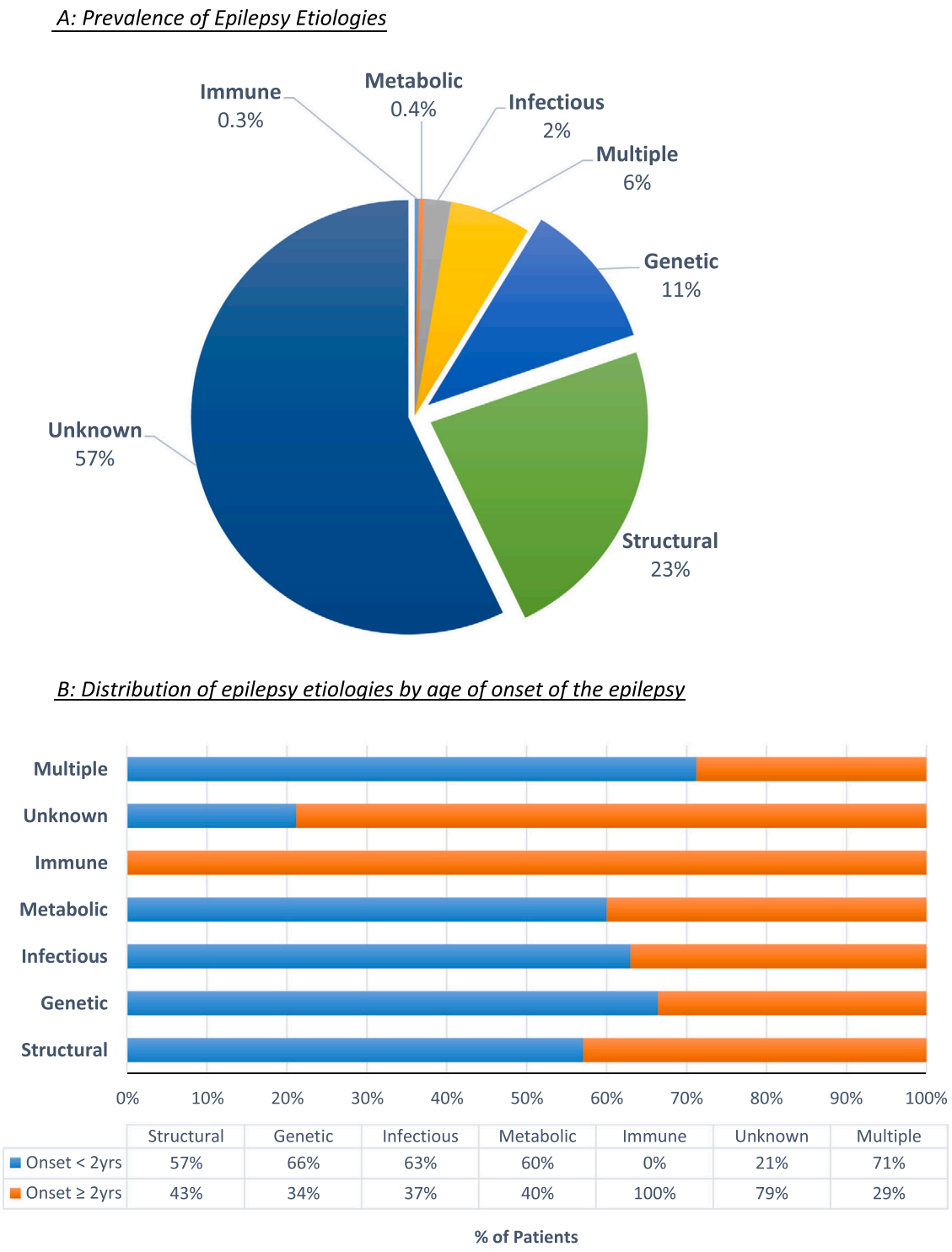
Fig. 1. Distribution by age of epilepsy onset.

Childhood epilepsy syndromes were identified in 20% of patients (292/1422 patients). Rolandic epilepsy (self-limited epilepsy with centro-temporal spikes) was the most common epilepsy syndrome and occurred in 82 patients. Supplementary Table 2 summarizes the breakdown of the epilepsy syndromes identified in this cohort.

Evaluation of seizure burden included review of seizure frequency, number of antiseizure medications (ASMs), history of status epilepticus and presence of medically refractory epilepsy as defined by the ILAE [18] (Table 2). At the last clinic visit, only 36% of patients had reported seizure-freedom over the past 2 years whereas most patients (64%) reported seizures of variable frequencies (Table 2). A review of seizure burden revealed that ~ 9% of patients in this epilepsy cohort reported daily or multiple seizures per day and at least 12% (170/1422 patients) had a history of hospital admissions for status epilepticus. At the last clinic visit, 737 patients (53%) were on at least one ASM whereas 31% (429/1385 patients) were on 2 or more ASMs (Table 2). 69% (349/5050) of patients who had been seizure free over the past 2 years were still on ASMs. The criteria for medically refractory epilepsy was met in 37% (527/1407) of patients. In this subgroup, structural and unknown were the most common etiologies seen in 37% (195/527) and 36% (191/527) of patients respectively. Furthermore, approximately a quarter of the medically refractory group had a genetic epilepsy.

Many patients underwent investigations at some point during their care. Abnormalities on neuroimaging were found in 51% (548/1075) of patients and included congenital and acquired structural changes. Malformations of brain development were the most common neuroimaging abnormalities, seen in 18% (98/548 patients), followed by sequelae of remote hypoxic-ischemic brain injury in 14% of patients. Supplementary Table 3 summarizes the different neuroimaging abnormalities identified in this cohort. EEG abnormalities were more common, noted in 79% (973/1226 patients). 783 patients had undergone some form of genetic testing (molecular karyotype, gene panels, whole exome sequencing). In 35% (271/783) of patients, positive results included pathogenic changes explaining the epilepsy as well as variants of unclear significance (VUS) that were yet to be resolved. Examples of identified pathogenic changes included de novo copy number variants (CNVs) resulting in deletion and duplications; syndromes (Angelman, Fragile X, Trisomy 21, Wolf-Hirschorn, Turner); de novo and inherited pathogenic mutations in known epilepsy genes (examples: SCN1A, SCN3A, PNPO, MECP2, CDKL5, PRRT2, TSC1, TSC2) including mitochondrial genes (examples: DARS2, MICU, NDUFV2, ST3GAL5) as well as pathogenic mutations in genes with multisystem involvement and epilepsy (example: EIF2AK3 mutations in Wolcott Rallison syndrome).

Data regarding the prevalence of co-morbidities was available in 1350 patients and is summarized in Table 3. Neurodevelopmental co-morbidities (ND) were present in 62% of patients. Global developmental delay was the most common ND co-morbidity reported in up to 47% of children followed by learning/school difficulties (22%) and intellectual impairment (17%) (Table 3, Fig. 3). 8% of patients in this



	Structural	Genetic	Infectious	Metabolic	Immune	Unknown	Multiple
Onset < 2yrs	57%	66%	63%	60%	0%	21%	71%
Onset ≥ 2yrs	43%	34%	37%	40%	100%	79%	29%

Fig. 2. Etiology of Epilepsy Fig. 2A: Prevalence of Epilepsy Etiologies Fig. 2B: Distribution of epilepsy etiologies by age of onset of the epilepsy.

epilepsy cohort had a concomitant diagnosis of autism spectrum disorder. Patients with either one or a combination of two or ≥ 3 ND co-morbidities were equally distributed and were found to be ~ 20% (Table 3). Somatic co-morbidities were present in 341 patients, with the most common being endocrinologic (18%), orthopedic (18%), gastro-intestinal (11%), genito-urinary (9%) and cardiac (8%) (Table 3). The majority of patients with somatic co-morbidities (322/341, 94%) had concomitant ND co-morbidities.

Multivariate analysis was carried out to identify risk factors associated with an increased risk of co-morbidities and medical intractability. As illustrated in Table 4, an early age of epilepsy onset (<2 years), structural and genetic etiologies, presence of medically intractable epilepsy and a history of status epilepticus were associated with a statistically increased odds ratio for the presence of co-morbidities. Other risk factors contributing to an increased risk for co-morbidities included a history of antenatal risk factors, history of previous CNS infection, the presence of consanguinity and a family history of febrile convulsions and epilepsy (Table 4). Similar risk factors for medically intractable epilepsy were identified, with an unknown etiology and the presence of ND co-morbidities associated with an increased odds ratio for intractable

Table 2
Seizure Burden and Epilepsy Treatments.

Seizure Frequency (n = 1393)	Daily	61 (4.4%)
	Multiple per day	59 (4.2%)
	At least once a week	67 (4.8%)
	At least once a month	99 (7.1%)
	At least once per year	215 (15.4%)
	At least one over the past 2 yrs	259 (18.6%)
	Seizures present but frequency not well defined	128 (9.2%)
	Seizure-free ≥ 2 yrs	505 (36.2%)
Patients with history of status epilepticus (SE)		172 (12%)
Number of ASMs* at the last clinic visit (n = 1385)	0	219 (16%)
	1	737 (53%)
	2	272 (20%)
	3 or more	157 (11%)
Total number of ASMs* tried (n = 1407)	0	46 (3%)
	1	645 (46%)
	2	329 (23%)
	3 or more	387 (28%)
Patients meeting criteria for medically refractory epilepsy (n = 1407)		527 (37%)
Epilepsy patients receiving other treatment modalities	Dietary (ketogenic diet/ modified Atkins diet)	46 (16%)
	Respective/Disconnective surgery	20 (7%)
	Neuromodulation (Vagal Nerve Stimulation)	13 (4%)

*Antiseizure Medications (ASMs)

Table 3
Prevalence of Risk Factors and Co-morbidities in Children with Epilepsy.

Prenatal Risk Factors (n = 640)		132 (21%)
Perinatal Risk Factors (n = 769)		172 (12%)
Postnatal Risk Factors (n = 760)		302 (40%)
Family History (n = 1110)	Positive*	480 (43%)
	Consanguinity	202 (18%)
	Febrile convulsions	45 (4%)
	Epilepsy	233 (21%)
	GDD/ID* *	39 (3%)
	Recurrent Miscarriages	7 (1%)
Epilepsy Risk Factors (n = 1422)	Head trauma	51 (4%)
	CNS infection	37 (3%)
	Febrile Seizures	97 (7%)
ND^{+} Co-morbidities (n = 1350)	GDD	628 (47%)
	Intellectual Disability	226 (17%)
	Autism Spectrum Disorder	109 (8%)
	Learning/school difficulties[¶]	302 (22%)
	Behavioral disabilities[¶¶]	217 (16%)
	Swallowing Difficulties	177 (13%)
	Visual impairment	148 (11%)
	Hearing impairment	26 (2%)
ND Co-morbidities per patient (n = 1350)	No co-morbidities	512 (38%)
	1 co-morbidity	276 (20%)
	2 co-morbidities	255 (19%)
	≥ 3 co-morbidities	307 (23%)
Somatic Co-morbidities (n = 341)	Endocrinologic	63 (18%)
	Orthopedic	62 (18%)
	Gastro-intestinal	36 (11%)
	Genito-urinary	30 (9%)
	Cardiac	29 (8%)
	Respiratory	24 (7%)
	Ophthalmologic	15 (4%)
	Sleep disturbances	15 (4%)
	Immune related	13 (4%)
	Headache syndromes	9 (3%)
	Psychiatric	7 (2%)
	Other	38 (11%)

*presence of a family history of any neurological disorder; * *GDD: global developmental delay (significant delays in ≥ 2 developmental spheres); ID: Intellectual impairment (GDD persisting beyond 5 yrs or formal diagnosis of ID on neuropsychological evaluation); $^{+}$ND: Neurodevelopmental; [¶] Reported by caregiver or formally diagnosed on neuropsychological evaluation; [¶¶] Includes hyperactivity, aggressive behavior and other behavioral complaints raised by the care giver or diagnosed formally by psychiatry

epilepsy (Table 5).

4. Discussion

This is the first study to identify the clinical features of epilepsy in the pediatric population of Qatar and to our knowledge, the first in the region to include a large pediatric cohort. Despite the fact that this is a population-based study conducted in one country, it is important to highlight the heterogeneity of this patient cohort which included a variety of ethnic backgrounds from 55 different countries of origin. Although the majority (64%) of children in this cohort originated from the Middle East North African (MENA) region and from Asian countries (24%), a small proportion (4%) also represented children from Caucasian (European, North American, and Australian) and African descent (7%). The uniqueness of this multiethnic cohort offers a generalizable value to the findings of this study as they are drawn from an "international" population.

In this cohort, the incidence epilepsy calculated in the last year of the study was ~ 75 per 100,000 person-years. Our findings are comparable to the pooled incidence rate from a meta-analysis of 13 studies in the literature (61 per 100,000 person-years). Fiest et al. (2017) Likewise, our 3-year prevalence (3.5 per 1000 persons) was within the range of the previously reported figures from other countries, although previous studies reported a wide variation in the prevalence rates from one population to the other (2.26–6.8 per 1000). Mani et al. (1998); Morgan et al. (2000); Onal et al. (2002); Stranjalis et al. (2009); Wallace et al. (1998); Parko and Thurman, (2009).

Most children in this study presented with onset of epilepsy in childhood as opposed to the neonatal or adolescent period. Congruent with previous studies (Durá-Travé et al., 2008; Freitag et al., 2001), we found the prevalence of epilepsy was generally higher in the youngest age groups, with the majority (60% of cases) being in pre-school aged children. Structural, genetic and metabolic etiologies were more prevalent in infants (< 2years of age), suggesting that symptomatic causes of epilepsies are more likely to present at an earlier age of onset and highlighting the importance of early diagnostic investigations in attaining a diagnosis in younger patients. In addition, an earlier age of onset for epilepsy was associated with a higher risk of co-morbidities and intractable epilepsy, with an odds ratio of 5.2 (CI 3.9–6.9) and 3.2 (2.5–4.1) respectively. These findings concur with the extensive literature highlighting the negative long-term impact of seizures on the developing brain (Berg et al., 2012; Holmes, 2016) and underline the importance of early diagnosis and efficient treatment of seizures in infancy and early childhood.

Similar to reports from previous epidemiologic studies (Sillanpää, 2000; Berg et al., 1999; Oka et al., 1989), focal seizures and focal

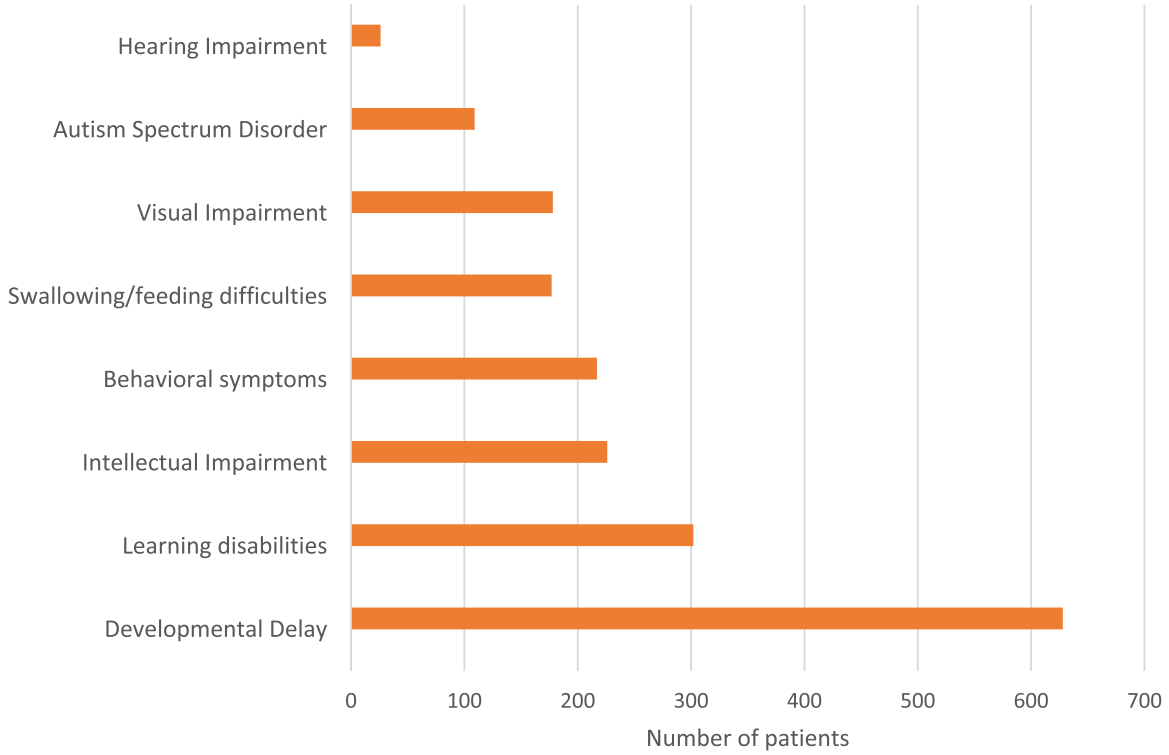


Fig. 3. Distribution of Co-Morbidities.

epilepsy were the most common seizure and epilepsy types identified, with no differences between the different ethnic groups (Supplementary Table 1). Also consistent with other studies (Sillanpää, 2000; Berg et al., 1999; Oka et al., 1989; Thomas and Berkovic, 2014), the etiology of epilepsy was unknown in the majority (57%) of children in this cohort. Despite advances in neuroimaging which have enhanced the identification of subtle structural anomalies (Coryell et al., 2018), and the increased recognition of autoimmune epilepsies (Dubey et al., 2017), the cause of epilepsy remains unknown in over 50% of cases in most studies. There is increasing recognition that a myriad of predisposing factors is likely at play in these epilepsies, including complex genetic, epigenetic and environmental factors (Thomas and Berkovic, 2014). Interestingly, an unknown epilepsy etiology was associated with an increased risk for medically refractory epilepsy in our cohort, highlighting the need for further research efforts aimed at elucidating the pathophysiology underlying this chronic disorder and subsequently promoting optimization of personalized therapeutics for patients with epilepsy.

55% of the patients in this cohort were investigated for a genetic etiology, which was confirmed in 11% of the entire cohort and was the third most common etiology after unknown and structural etiologies. A little over one third of the tested patients had an abnormal result or a variant of uncertain significance, whereas a confirmed genetic etiology was established in only 19.4% of tested patients. Establishing a genetic diagnosis of childhood epilepsy is crucial to provide disease-specific treatments. In a recent study [36], the diagnostic yields of WES and next-generation sequencing epilepsy panels in epilepsy patients was demonstrated at 37% and 19% respectively. This had a direct treatment implication in 6% of patients with treatable metabolic disorders, and in another 30% of patients with channelopathies who would benefit from applying effective antiseizure medications or the ketogenic diet therapy. The above highlights the great potential for identifying the genetic etiology in a larger proportion of patients if genetic testing was expanded to include more individuals. This is particularly important in our cohort which has a remarkably elevated consanguinity rate (18%).

Neurodevelopmental (ND) co-morbidities in children with epilepsy often result in poor academic achievements and a negative impact on quality of life (Ferro, 2014; Sillanpaa et al., 2016; Wei and Lee, 2012; Arunkumar et al., 2000; Miller et al., 2016; Fastenau et al., 2008; Bailet and Turk, 2000; Aldenkamp et al., 2005). In this study, ND co-morbidities were common, noted in 62% of patients, with global developmental delay being the most prevalent, followed by learning/-school difficulties and intellectual impairment. Interestingly, the majority of children with somatic co-morbidities (94%) had concomitant ND co-morbidities. These findings confirm the pervasiveness of epilepsy as a disorder that extends beyond seizures and emphasize the importance of screening for and addressing concomitant neurodevelopmental disorders in epilepsy patients. Similar to other studies, children in this cohort identified to be at risk for developing co-morbidities included those with early onset epilepsy; structural and genetic etiologies; medically intractable epilepsy and a history of status epilepticus (Fastenau et al., 2008; Bailet and Turk, 2000; Aldenkamp et al., 2005). Interestingly, in our cohort, the presence of consanguinity and a family history of febrile convulsions and epilepsy were also associated with an increased odds ratio for developing co-morbidities, suggesting that genetic factors underlying the neurobiological mechanisms leading to epilepsy also contribute to the aberrancies in other neurodevelopmental spheres seen in children with epilepsy.

In this study, although 527 patients (37%) met the criteria of medically refractory epilepsy, only 15% of patients received non-pharmacologic treatments including epilepsy surgery, dietary therapy or neurostimulation therapy. This could be due to a number of reasons including lack of awareness among pediatric neurologists of the efficacy and low morbidity of non-pharmacologic treatments of epilepsy, especially epilepsy surgery (Cossu et al., 2008; Teutonico et al., 2013; Kloss et al., 2002). Furthermore, there might be some ambiguity about the definition of intractability and how many antiseizure medications (ASMs) should be tried before declaring a patient medically intractable. For this reason, the ILAE published a revised definition of intractable epilepsy as the failure of adequate trials of two tolerated, appropriately chosen and used ASMs (Kwan et al., 2010). Another potential reason to explain the low rate of non-pharmacologic treatments in our cohort includes the fact that the first specialized Pediatric Epilepsy Center in

Table 4
Risk Factors for Co-morbidities in Children with Epilepsy.

Risk Factor	Odds Ratio	95% Confidence Interval	p value
Gender (Female)	0.956	0.767 – 1.193	0.691
Nationality (Qatari)	1.191	0.934 – 1.519	0.158
Epilepsy Onset < *2 yrs*	5.178	3.886 – 6.900	< 0.001 *
Epilepsy Type			
Focal	0.859	0.405–1.825	0.693
Generalized	1.443	0.674 – 3.091	0.345
Combined	2.065	0.930 – 4.582	0.075
Unknown	3.790	1.464–9.807	0.006 *
Epilepsy Etiology			
Structural	3.712	1.158 – 11.900	0.027 *
Genetic	6.998	2.294 – 21.342	< 0.001 *
Infectious	3.166	0.814 – 12.313	0.096
Metabolic	2.219	0.386 – 12.763	0.372
Immune	1.100	0.164 – 7.399	0.922
Unknown	0.514	0.158 – 1.673	0.269
Total Number of ASMs tried [a]			
1	1.677	0.866 – 3.248	0.125
2 or more	7.378	3.788 – 14.373	< 0.001 *
History of Status Epilepticus	3.578	2.767 – 4.627	< 0.001 *
Medically Intractable Epilepsy	2.047	1.365 – 3.069	< 0.001 *
Prenatal Risk Factors	2.362	1.483 – 3.764	< 0.001 *
Perinatal Risk Factors	4.270	2.635 – 6.917	< 0.001 *
Postnatal Risk Factors	3.940	2.700 – 5.750	< 0.001 *
Previous personal history of:			
Head Trauma	1.571	0.835 – 2.954	0.161
CNS Infection [b]	3.283	1.359 – 7.930	0.008 *
Febrile Convulsions	1.518	0.962 – 2.397	0.073
Family History			
Consanguinity	2.466	1.525 – 3.986	< 0.001 *
Febrile Convulsions	0.286	0.134 – 0.608	0.001 *
Epilepsy	0.202	0.125 – 0.327	< 0.001 *
GDD/ID [c]	1.948	0.781 – 4.861	0.153
Abnormalities on investigations			
Abnormal MRI [d]	5.893	4.443 – 7.818	< 0.001 *
Abnormal EEG [e]	2.006	1.500 – 2.682	< 0.001 *
Abnormal Genetic results	8.784	5.271 – 14.638	< 0.001 *

*Denotes statistical significance; [a]Antiseizure medications (ASMs); [b]central nervous system; [c]global developmental delay/intellectual impairment; [d]Magnetic resonance imaging; [e]electroencephalogram

Table 5
Risk Factors for Medical Intractability in Children with Epilepsy.

Risk Factor	Odds Ratio	95% Confidence Interval	p value
Gender (Female)	1.392	1.121 – 1.728	0.003 *
Nationality (Qatari)	1.170	0.926 – 1.479	0.189
Epilepsy Onset < 2 yrs	3.197	2.503 – 4.082	< 0.001 *
Epilepsy Type			
Focal	0.492	0.240 – 1.008	0.053
Generalized	0.825	0.401 – 1.694	0.600
Combined	1.407	0.669 – 2.956	0.368
Unknown	0.432	0.183 – 1.020	0.055
Epilepsy Etiology			
Structural	0.978	0.567–1.686	0.937
Genetic	1.405	0.850 – 2.324	0.185
Infectious	1.634	0.715 – 3.734	0.245
Metabolic	1.230	0.443 – 3.413	0.691
Immune	1.53e+ 9	0.000 -.	0.999
Unknown	0.332	0.183 – 0.604	< 0.001 *
History of Status Epilepticus	2.760	1.990 – 3.828	< 0.001 *
Presence of Co-morbidities			
1 CM	3.010	2.182 – 4.152	< 0.001 *
2 or more CM	4.234	3.225 – 5.558	< 0.001 *
Prenatal Risk Factors	1.105	0.751 – 1.627	0.612
Perinatal Risk Factors	1.246	0.897 – 1.732	0.190
Postnatal Risk Factors	1.277	0.957 – 1.704	0.097
Previous personal history of:			
Head Trauma	1.204	0.681 – 2.128	0.523
CNS Infection	2.556	1.314 – 4.973	0.006 *
Febrile Convulsions	0.873	0.564 – 1.349	0.540
Family History			
Consanguinity	1.883	1.261 – 2.813	0.002 *
Febrile Convulsions	0.611	0.3030 – 1.234	0.170
Epilepsy	0.632	0.417 – 0.960	0.031 *
GDD/ID	1.027	0.516 – 2.044	0.940
Abnormalities on investigations			
Abnormal MRI	2.319	1.896 – 2.836	< 0.001 *
Abnormal EEG	3.361	2.383 – 4.740	< 0.001 *
Abnormal Genetic results	2.111	1.565 – 2.847	< 0.001 *

Qatar was only established in 2019. Prior to that date, patients' access to advanced treatments of epilepsy was rather limited. Currently, after the initiation of programs for epilepsy surgery, ketogenic diet therapy and neuro stimulation therapy for children in Qatar, the number of patients receiving care through these programs is expected to rise.

One of the limitations of this study is its retrospective design and the dependency on the availability and completeness of data in the patients' files. As a result, due to incomplete records, some data was not available for some of the variables studied for some patients. Nevertheless, this limitation did not hinder the data analysis and percentage counts were represented as a proportion of the data available for each variable studied. Another limitation was the inability to assess seizure burden through frequency of Emergency Department (ED) visits. Although our tertiary care center caters to all patients with epilepsy, these patients can present to any pediatric emergency center in the country for breakthrough seizures. Unfortunately, the electronic medical records from these centers were not accessible for this research study and as such, ED visits could not be evaluated as an indicator of seizure burden. To obviate this limitation, other variables (seizure frequency, history of status epilepticus, number of ASMs were used as indicators for seizure burden.

5. Conclusions

In conclusion, this large multi-ethnic population-based study confirms that the prevalence, incidence and clinical features of epilepsy in Qatar is in accordance with many epidemiologic studies done elsewhere. The results of this study highlights the prevalence and risk factors for the development of co-morbidities and medically-intractable epilepsy, and lays the groundwork for identifying and prioritizing public health interventions and further research in this field.

Disclosure of conflict of interest

None of the authors have any conflict of interest. This study was approved by Sidra Medicine's Institutional Review Board (IRB) (IRB # 1804023255).

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.eplepsyres.2022.106936.

References

Aldenkamp, A.P., Weber, B., Overweg-Plandsoen, W.C.G., Reijs, R., van Mil, S., 2005. Educational underachievement in children with epilepsy: a model to predict the effects of epilepsy on educational achievement. J. Child Neurol. 20, 175–180.

Alshami, R., Bessisso, M., El Said, M.F., Al, Ansari, K., 2008. Epidemiology of Status epilepticus among children in Qatar in 2008. Qatar Med. J. 21 (1), 9–11.

Arunkumar, G., Wyllie, E., Kotagal, P., Ong, H.T., Gilliam, F., 2000. Parent- and patient-validated content for pediatric epilepsy quality-of-life assessment. Epilepsia 41 (11), 1474–1484.

Bailet, L.L., Turk, W.R., 2000. The impact of childhood epilepsy on neurocognitive and behavioral performance: a prospective longitudinal study. Epilepsia 41, 426–431.

Berg, A.T., Shinnar, S., 1994. The contributions of epidemiology to the understanding of childhood seizures and epilepsy. J. Child Neurol. 9 (Suppl 2), 19–26.

Berg, A.T., Shinnar, S., Levy, S.R., Testa, F.M., 1999. Newly diagnosed epilepsy in children: presentation at diagnosis. Epilepsia 40 (4), 445-52.

Berg, A.T., Zelko, F.A., Levy, S.R., 2012. Age at onset of epilepsy, pharmacoresistance, and cognitive outcomes: a prospective cohort study. Neurology 79, 1384–1391.

Camfield, P., Camfield, C., 2015. Incidence, prevalence and aetiology of seizures and epilepsy in children. Epileptic Disord. 17 (2), 117-23.

Coryell, J., Gaillard, W.D., Shellhaas, R.A., Grinspan, Z.M., Wirrell, E.C., Knupp, K.G., Wusthoff, C.J., Keator, C., Sullivan, J.E., Loddenkemper, T., Patel, A., Chu, C.J., Massey, S., Novotny Jr., E.J., Saneto, R.P., Berg, A.T., 2018. Neuroimaging of early life epilepsy. Pediatrics 142, 3 (Sep).

Cossu, M., Lo Russo, G., Francione, S., Mai, R., Nobili, L., Sartori, I., Tassi, L., Citterio, A., Colombo, N., Bramerio, M., Galli, C., Castana, L., Cardinale, F., 2008. Epilepsy surgery in children: results and predictors of outcome on seizures. Epilepsia 49 (1), 65–72 (Jan).

Dubey, D., Alqallaf, A., Hays, R., Freeman, M., Chen, K., Ding, K., Agostini, M., Vernino, S., 2017. Neurological autoantibody prevalence in epilepsy of unknown etiology. JAMA Neurol. 74 (4), 397–402.

Durá-Travé T., Yoldi-Petri ME, Gallinas-Victoriano F. Incidence of epilepsies and epileptic syndromes among children in Navarre, Spain: 2002 through 2005. J Child Neurol. 2008 Aug;23(8):878–82.

Fastenau, P., Shen, J., Dunn, D.W., Austin, J.K., 2008. Academic underachievement among children with epilepsy: proportion exceeding psychometric criteria for learning disability and associated risk factors. J. Learn Disabil. 41, 195–197.

Ferro, M.A., 2014. Risk factors for health-related quality of life in children with epilepsy: a meta-analysis. Epilepsia 55 (11), 1722-31.

Fiest, K.M., Sauro, K.M., Wiebe, S., Patten, S.B., Kwon, C.S., Dykeman, J., Pringsheim, T., Lorenzetti, D.L., Jetté, N., 2017. Prevalence and incidence of epilepsy: a systematic review and meta-analysis of international studies. Neurology 88 (3), 296–303. Jan 17.

Fisher, R.S., van Emde Boas, W., Blume, W., Elger, C., Genton, P., Lee, P., Engel Jr., J., 2005. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia 46 (4), 470–472.

Fisher, R.S., Cross, J.H., French, J.A., et al., 2017. Operational classification of seizure types by the International League against epilepsy: position paper of the ILAE Commission for Classification and Terminology. Epilepsia 58 (4), 522–530.

Freitag, C.M., May, T.W., Pfäfflin, M., König, S., Rating, D., 2001. Incidence of epilepsies and epileptic syndromes in children and adolescents: a population-based prospective study in Germany. Epilepsia 42 (8), 979-85.

Geerts, A., Arts, W.F., Stroink, H., Peeters, E., Brouwer, O., Peters, B., Laan, L., van Donselaar, C., 2010. Course and outcome of childhood epilepsy: a 15-year follow-up of the dutch study of epilepsy in childhood. Epilepsia 51 (7), 1189–1197.

Haddad, N., Melikyan, G., Al Hail, H., Al, Jurdi, A., et al., 2016. Epilepsy in Qatar: causes, treatment, and outcome. Epilepsy Behav. 63, 98–102.

Holmes, G.L., 2016. Effect of seizures on the developing brain and cognition. Semin. Pedia Neurol. 23 (2), 120–126.

Kloss, S., Pieper, T., Pannek, H., Holthausen, H., Tuxhorn, I., 2002. Epilepsy surgery in children with focal cortical dysplasia (FCD): results of long-term seizure outcome. Neuropediatrics 33 (1), 21–26 (Feb).

Kwan, P., Arzimanoglou, A., Berg, A.T., Brodie, M.J., Allen Hauser, W., Mathern, G., Moshé, S.L., Perucca, E., Wiebe, S., French, J., 2010. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on therapeutic strategies. Epilepsia 51 (6), 1069-77.

Mani, K.S., Rangan, G., Srinivas, H.V., et al., 1998. The Yelandur study: a community-based approach to epilepsy in rural South India–epidemiological aspects. Seizure 7, 281–288.

Miller, G.F., Coffield, E., Leroy, Z., Wallin, R., 2016. Prevalence and costs of five chronic conditions in children. J. Sch. Nurs. 32 (5), 357–364.

Morgan, C.L., Ahmed, Z., Kerr, M.P., 2000. Social deprivation and prevalence of epilepsy and associated health usage. J. Neurol. Neurosurg. Psychiatry 69, 13–17.

Oka, E., Yamatogi, Y., Ohtsuka, Y., Ohtahara, S., 1989. Clinical course and prognosis of childhood epilepsy. Pediatr. Int. 31 (3).

Onal, A.E., Tumerdem, Y., Ozturk, M.K., et al., 2002. Epilepsy prevalence in a rural area in Istanbul. Seizure 11, 397–401.

Parko, K., Thurman, D.J., 2009. Prevalence of epilepsy and seizures in the Navajo Nation 1998-2002. Epilepsia 50, 2180–2185.

Shinnar, S., Pellock, J.M., 2002. Update on the epidemiology and prognosis of pediatric epilepsy. J. Child Neurol. 17 (Suppl 1). S4-17.

Sillanpaa, M., Besag, F., Aldenkamp, A., 2016. Psychiatric and behavioral disorders in children with epilepsy (ILAE Task Force Report): epidemiology of psychiatric/behavioral disorder in children with epilepsy. Epileptic Disord. 18 (Suppl.1), S2–S7.

Sillanpää, M., 2000. Long-term outcome of epilepsy. Epileptic Disord. 2 (2), 79–88. Aug 28.

Stranjalis, G., Tsamandouraki, K., Gazonis, S., et al., 2009. Low occurrence of epileptic seizures and epilepsy in a defined area of Northwest Greece. Seizure 18, 206–210.

Teutonico, F., Mai, R., Veggiotti, P., Francione, S., Tassi, L., Borrelli, P., Balottin, U., LoRusso, G., 2013. Epilepsy surgery in children: evaluation of seizure outcome and predictive elements. Epilepsia 54 (Suppl 7), 70–76 (Oct).

Thomas, R.H., Berkovic, S.F., 2014. The hidden genetics of epilepsy-a clinically important new paradigm. Nat. Rev. Neurol. 10 (5) (May).

Wallace, H., Shorvon, S., Tallis, R., 1998. Age-specific incidence and prevalence rates of treated epilepsy in an unselected population of 2052922 and age-specific fertility rates of women with epilepsy. Lancet 352, 1970–1973.

Wei, S.H., Lee, W.T., 2012. Comorbidity of childhood epilepsy. J. Formos. Med. Assoc. 114 (11), 1031–1038.

Wirrell, E.C., Grossardt, B.R., Wong-Kisiel, L.C., Nickels, K.C., 2011. Incidence and classification of new-onset epilepsy and epilepsy syndromes in children in Olmsted County, Minnesota from 1980 to 2004: a population-based study. Epilepsy Res. 95 (1–2), 110–118.