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Clinical and inheritance profile of familial childhood epilepsy in Jordan

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ABSTRACT

Purpose: To present the clinical profiles and inheritance patterns of familial childhood epilepsy in the highly consanguineous population of Jordan.
Methods: This retrospective study examined children diagnosed with epilepsy and having at least one epileptic parent or sibling. The epilepsy type was classified according to the criteria of the International League Against Epilepsy. Patients were monitored for a period of 6 months to 5 years.
Results: The study population included 39 children belonging to 31 families; 21 boys (53.8%) and 18 girls (46.2%). The age at onset ranged from one month to 16 years. Generalized seizures were observed in 23 patients (58.9%), partial seizures in 14 patients (35.8%); and generalized and partial seizures in two patients (5.1%). Seizure control was achieved in 33 patients (84.6%), and 13 patients (33.3%) were seizure-free for at least two years. Withdrawal of antiepileptic medication was successful in five of these 13 patients (38.5%), while seizures recurred in the other eight (61.5%) on withdrawal. The consanguinity rate among parents of affected children was 61.3%. Pedigree analysis suggested probable autosomal dominant (AD) inheritance with or without reduced penetrance in 13 families (41.9%), probable autosomal recessive (AR) inheritance in 6 families (19.4%), and an X-linked recessive inheritance (XR) in one family.
Conclusions: This is the first report on familial epilepsy involving first degree relatives in Jordan. Genetic testing including exome sequencing could help in reaching the accurate diagnosis and may also reveal novel autosomal recessive genes associated with pediatric idiopathic epilepsy.
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1. Introduction

Consanguineous marriages comprise 20–40% of all marriages in Jordan[1–4] which may predispose offspring to rare autosomal recessive conditions.[5–7] Previous studies have indicated that consanguineous marriage is a major risk factor contributing to epilepsy in the neonatal and infancy periods.[8,9]

Genes implicated in idiopathic epilepsies include the *SCN1A* gene, encoding the voltage-gated Na channel α1 subunit ($Na_v1.1$), in some autosomal dominant epilepsies (prolonged, myoclonic, and absence seizures)[10] and the *TBC1D24* gene, encoding an AFR6-interacting protein, in autosomal recessive idiopathic epilepsy.[11] While the Jordanian population has a high rate of consanguineous marriages, to our knowledge there have been no reports describing the inheritance patterns of familial epilepsy.

This study aims to describe the inheritance patterns, clinical profiles, treatment responses, and prognoses of epileptic children with a positive history of epilepsy in their first degree relatives.

2. Patients and methods

This retrospective study was conducted at a child neurology clinic at Jordan University Hospital, a tertiary care referral hospital located in Amman, over a 10 years period from January 2001 to August 2010.

All children aged one month to 18 years presenting with epilepsy during the study period and with a positive family history of epilepsy in at least one first degree relative were included in this study. Identification of these patients was possible through a personal data base of the first author that includes all patients presenting to the child neurology clinic since January 2001. Files for all patients that were identified as epileptic and having a positive family history of epilepsy were revised. To fulfill the inclusion criteria, the pedigrees documented in the files were revised. In the child neurology clinic, family history is usually obtained by the child neurologist from the parent accompanying the child (father, mother or both) with pedigree constructed and stored in the file. Because of the high stigma of epilepsy in Jordan, it is common practice to rely on the parents' reports, without going further and interviewing other family members such as grandmothers or grandfathers who

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probably know more details about the family history. Patients for whom a parent was not available due to death, divorce or other reasons leading to inability to take full family history and difficulty in constructing a pedigree were excluded from the study. Postulation of mode of inheritance of epilepsy was based on the family pedigree that was documented in the file since genetic studies were not done for the families. Due to the retrospective nature of the study, it was not possible to recontact seven families who show pedigrees with data for only two generations (Fig. 1). Children with a family history of febrile convulsions only, a family history of epilepsy but not in first degree relatives, or a family history of epilepsy due to neurodegenerative or neurometabolic disorders or due to symptomatic epilepsy were excluded.

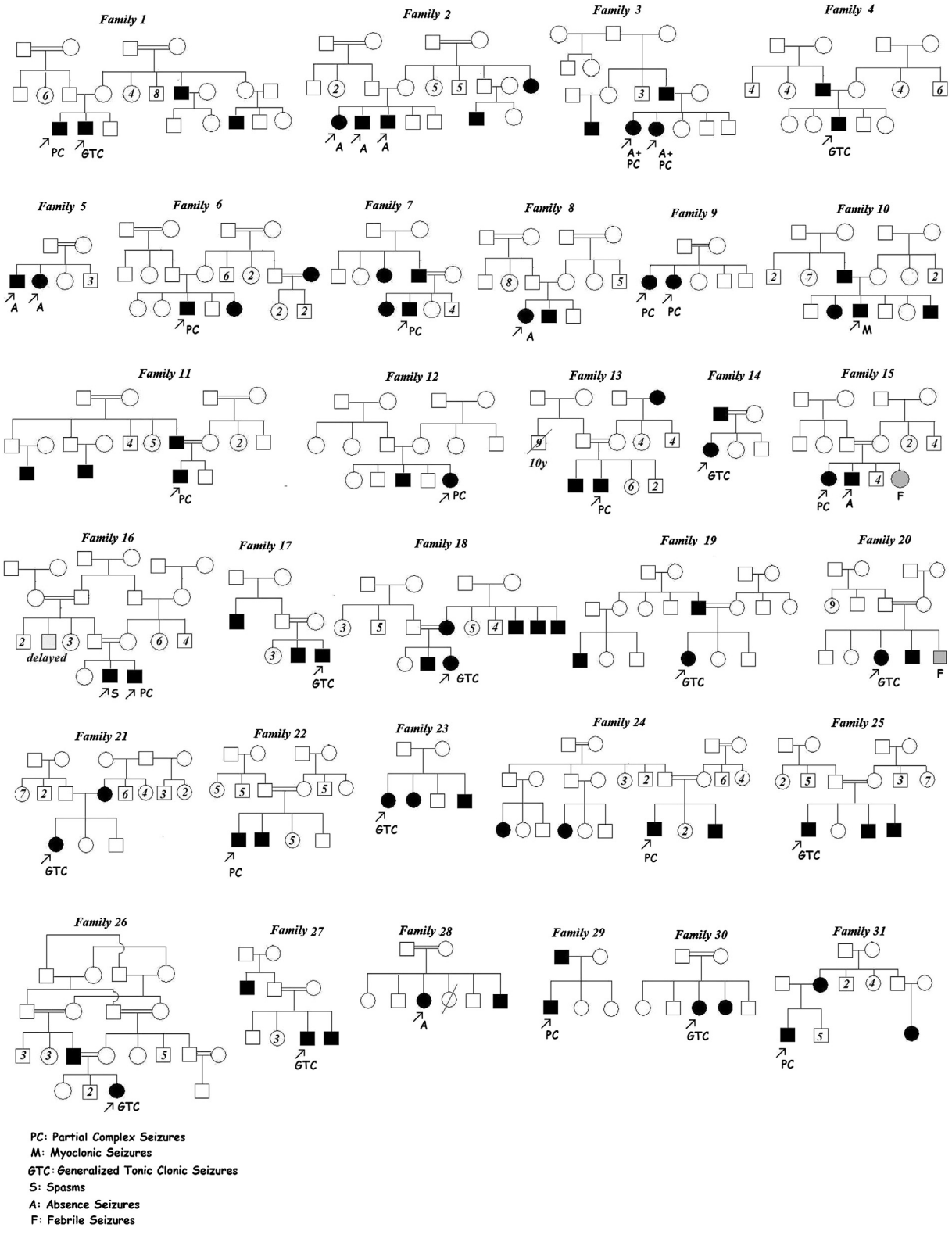

Fig. 1. Pedigrees of the 31 families.

In addition to the family pedigree, files were also reviewed to collect data on the age of onset of seizure, type of seizures, type of treatment, control of epilepsy, follow up period, neurological examination findings, developmental history and or school performance before and after the seizures, results of neuroimaging and EEG findings. Files lacked information on details of the epilepsy in the affected family members and their data were not included in this study.

3. Definitions

The definition and classification of seizures and epilepsies were based on criteria set by the International League Against Epilepsy.[12] For the purposes of this study, we defined controlled epilepsy as no seizures for at least four months. Although this is not a widely accepted criterion, it is a good indicator of seizure control and allowed the inclusion of more patients in the study who satisfied the inclusion criteria. Global developmental delay was defined as a significant delay in two or more developmental domains (gross/fine motor, cognition, speech/language, personal/social, or activities of daily living).[13] In clinical genetics, a consanguineous marriage usually describes a union between second cousins or closer relatives. This definition was applied in the present study and is equivalent to a coefficient of inbreeding in the progeny of $F \geq 0.0156$. This would include the categories of first cousins (including double first cousins), first cousins once removed, and second cousins.[14]

The ethical committee at Jordan University Hospital approved this study.

4. Results

The study population included 39 children with pediatric epilepsy belonging to 31 families and satisfying the inclusion criteria of the study. All 39 patients attended the pediatric neurology clinic over the study period and were examined, managed and followed up by a child neurologist. There were 21 boys (53.8%) and 18 girls (46.2%) in the study group. The age of seizure onset ranged from one month to 16 years, with the first seizure occurring at or before age ten in 31 patients (79%), and before age six in 19 patients (49%). Twenty-three patients (59%) were treated at our clinic within one year of disease onset.

Twenty three patients (58.9%) had generalized epilepsy, 14 patients (35.8%) had partial epilepsy and two patients (5.1%) had both generalized and partial epilepsy. The most common type of generalized epilepsy was generalized tonic–clonic seizures, observed in 13 patients (33.3%). The most common partial epilepsy was partial complex seizures, observed in 13 patients (33.3%) (Table 1). Only two patients (5.1%) had experienced status epilepticus.

Table 1
Types of seizures in 39 patients.

Type of seizure	Number of patients (%)
Generalized seizures	**23(58.9%)**
Generalized tonic–clonic seizures	13 (33.3%)
Absence seizures	8 (20.5%)
Myoclonic seizures	1 (2.6%)
Spasms	1 (2.6%)
Partial seizures	**14 (35.8%)**
Simple partial seizures	1 (2.5%)
Partial complex seizures	13(33.3%)
Generalized and partial	**2 (5.1%)**
Absence + partial complex epilepsy	2 (5.1%)

Syndromic classification was possible in only 9 patients (23%); 8 patients presented with absence epilepsy and one patient presented with West syndrome; the rest of patients remained unclassified.

Twenty nine patients (74.4%) were on monotherapy, five (12.8%) were on two antiepileptic medications, and five (12.8%) were on three antiepileptic medications. Seizure control was achieved in 33 patients (84.6%) using mono- or polytherapy. The other six patients (15.4%) continued to have seizures despite trials of several antiepileptic medications, although four of these drug-refractory patients achieved a 25–50% reduction in seizure frequency. None of the six patients with refractory epilepsy received any other modality of treatment including ketogenic diet, vagal nerve stimulation or epilepsy surgery.

The follow-up period at our clinic ranged from 6 months to 5 years. Thirteen patients (33.3%) were seizure-free for at least two years. Withdrawal of antiepileptic treatment was successful in five of these patients (5/13, 38.5%), while seizures recurred during dose tapering in the other eight (61.5%) (Table 2).

The most common antiepileptic medications used as monotherapy were carbamazepine (10/39, 25.6%) and valproic acid (18/39, 46.1%).

Results of neurological examinations were normal in 37 patients (95%). The two patients exhibiting neurological deficits were brothers (family 16 in Fig. 1). One of them was born prematurely with diplegic cerebral palsy and had partial complex epilepsy. The other brother had West syndrome, microcephaly, and spasticity. The parents are paternal parallel first cousins, and they have a paternal uncle with consanguineous parents who is also reported to have developmental delay. The condition in this family may represent an X-linked or autosomal recessive syndrome.

Brain MRI showed no abnormalities in all probands except in the male patient with diplegic cerebral palsy in family 16, who showed periventricular white matter changes.

Before the onset of epilepsy, development/school performance was reported to be normal in 33 patients (84.6%) and abnormal in 6 patients (15.4%). After the onset of epilepsy, global developmental delay or poor school performance was seen in an additional five patients (12.8%).

4.1. Family history of epilepsy in the 31 families (Fig. 1)

Consanguinity was reported among parents in 19 of the 31 families (61.3%). Among the 31 nuclear families included in this study, 22 had two or three affected children. In nine families (29%) the father of the proband had epilepsy, while in three families (9.7%) the mother had epilepsy. The rate of epilepsy was similar in children of mothers with epilepsy (33.3%) and children of fathers with epilepsy (34.2%) (Fig. 1). In addition to a positive history of epilepsy in siblings or parents, some families had a positive family history of epilepsy in other relatives, including aunts in two families (6.5%), uncles in four families (13%), and cousins in seven families (22.6%). In families where one of the parents had epilepsy, the total number of children ranged from 2 to 7 (average of 4) compared to 2–11 (average of 5) among the 22 families in which neither parent was epileptic. In the 9 families with one epileptic parent, 17/50 offspring (34%) were also diagnosed with epilepsy. In the 22 families with no epileptic parent, 41/99 offspring (42.4%) were epileptic (Fig. 1).

Genetic studies were not performed at the time of study due to technical and financial constraints. The application of exome sequencing in clinical practice is recent, but could be envisaged for some families in this study, possibly on research basis, specifically those with possible autosomal recessive inheritance. Ascertainment of the modes of inheritance were deduced from pedigree analysis (Fig. 1) and pointed to a probable autosomal dominant

Table 2
Description of seizures, responses to treatment (antiepileptic drug), EEG findings, and the probable modes of inheritance in 31 families with familial epilepsy.

Family number as in Fig. 1	*Age of onset*, clinical description, response to treatment (antiepileptic drug), and follow-up period	Type of seizures/epilepsy syndrome	EEG characteristics	Development before/ after epilepsy onset	Probable mode of inheritance
Family 1	*Onset at 5 years*	Partial complex/unclassified	Focal spikes	Normal/poor school performance	XR
1-boy	Staring, eye deviation, then secondary GTC				
2-boy	Last visit: two years with no seizures (1), plans to taper treatment				
	Onset at 9 years	GTC/unclassified	Normal	Normal/poor school performance	
	GTC				
	Last visit: three years with no seizures (1), plans to taper treatment				
Family 2					AD with reduced penetrance
1-boy	*Onset at 10.5 years*	Absence/absence epilepsy	Generalized	Normal/normal	
	Staring		3 Hz spikes	Normal/normal	
2-boy	Last visit: 17 months with no seizures (2)		Generalized		
3-girl	*Onset at 12 years*		3 Hz spikes		
	Last visit: two years with no seizures (2), plans to taper treatment	Absence/absence epilepsy	Generalized		
	Onset at 15 years		3 Hz spikes		
	Staring				
	Last visit: 10 months with no seizures (2)	Absence/absence epilepsy		Normal/normal	
Family 3					AD with reduced penetrance
1-girl	*Onset at 11 years*	Absence and partial complex	Generalized	Normal/normal	
	Staring for a few seconds and attacks of prolonged staring lasting a few minutes		3 Hz spikes and focal temporal		
2-girl	Last visit: 6 months with no seizures (2)	Absence and partial complex	Generalized 3 Hz spikes and focal temporal	Normal/normal	
	Onset at 10 years				
	Staring for few seconds and attacks of prolonged stare lasting a few minutes				
	Last visit:7 months with no seizures (2)				
Family 4					AD
1-boy	*Onset at 12 years*	GTC/unclassified	Normal	Normal/normal	
	Up rolling of eyes + GTC				
	Last visit: 7 months with no seizures(2)				
Family 5					AR
1-girl	*Onset at 14 years*	Absence/absence epilepsy	Generalized	Normal/normal	
2-boy	Staring with GTC		3 Hz spikes		
	Last visit: 3.5 years with no seizures (2 + 3), plans to taper treatment				
	Onset at 4 years		Generalized		
	Staring		3 Hz spikes	Normal/normal	
	Received treatment for 2 years then recurrence during tapering. Treatment restarted	Absence/absence epilepsy			
	Last visit: 1.5 years with no seizures (2)				
Family 6					?
1-boy	*Onset at 11 years*	Partial complex/unclassified	Normal	Normal/normal	
	Awakens from sleep dizzy and afraid, mouth deviation to one side				
	Clonic movement of upper and lower limbs, then vomiting				
	Received treatment for 2 years then recurrence during tapering. Treatment restarted				
	Last visit: 2 years with no seizures (1), plans to taper treatment again				
Family 7					AD
1-boy	*Onset at 2.5 years*	Partial complex /unclassified	Temporal epileptic activity	Normal/normal	
	Staring, pallor, then GTC				

	Received treatment for 2 years with recurrence. Treatment restarted for another 2 years. Second recurrence during tapering. Treatment restarted Last visit: 4 months with no seizures (1)				
Family 8					?
1-girl	*Onset at 7 years* Staring Last visit: 2 years with no seizures (2), plans to taper treatment	Absence/absence epilepsy	Generalized 3 Hz spikes	Normal/normal	
Family 9					AR
1-girl	*Onset at 6 years* Staring, left clonic movement of upper limb Received treatment (1) for 2 years then tapering Last visit: no seizures at last follow-up	Partial complex /unclassified	Normal	Normal/normal	
2-girl	*Onset at 5.5 years* Staring Received treatment for 2 years with recurrence during tapering. Treatment restarted for another 2 years with another recurrence during tapering. Treatment restarted again (1) Last visit: no seizures for the last one year	Partial complex /unclassified	Normal	Normal/normal	
Family 10					AD
1-boy	*Onset at 2.5 years* Myoclonic jerk with drop attacks Uncontrolled seizures in the first 3 years of life Last visit: controlled for the last 4 years (2)	Myoclonic/unclassified	Generalized polyspikes	Delayed/delayed	
Family 11					AD with reduced penetrance
1-boy	*Onset at 7 months* Deviation of eyes to one side, clonic movements of upper and lower limbs, frequent falls Last visit: 10 months on polytherapy (1 + 2 + 4), still uncontrolled seizures	Partial complex/unclassified	Normal	Normal/delayed	
Family 12					?
1-girl	*Onset at 10 years* Staring Received treatment for 2 years then treatment tapered (1), lost during follow-up	Partial complex /unclassified	Focal temporoparietal epileptic activity	Normal/normal	
Family 13					?
1-boy	*Onset at 6 years* Uprolling of eyes, stares, drop attacks more than 10 times/day Received treatment for 2 years then recurrence during tapering. Treatment restarted (1 + 5) Last visit: 20 months with no seizures	Partial complex /unclassified	Focal spikes in temporoparietal regions	Normal/normal	
Family 14					?
1-girl	*Onset at 10 years* Decrease tone, cyanosis, tonic contraction of upper and lower limbs Last visit: 12 months with no seizures (1 + 2), lost during follow-up	GTC/unclassified	Normal	Normal/delayed	
Family 15					AR
1-boy	*Onset at 16 years* Awakens from sleep, eye and mouth deviation, then GTC Received treatment for 2 years then tapered (2) Last visit: off treatment with no seizures for the past year	Simple focal with secondary generalization /unclassified	Normal Generalized	Normal/normal	
2-girl	*Onset at 9.5 years* Awakens from sleep, up rolling of eyes, then GTC. Patient later developed absence seizures Received treatment for 2 years then recurrence during tapering. Treatment restarted (3)	Absence/absence epilepsy	3 Hz spikes	Normal/normal	

Table 2 (*Continued*)

Family number as in Fig. 1	*Age of onset*, clinical description, response to treatment (antiepileptic drug), and follow-up period	Type of seizures/epilepsy syndrome	EEG characteristics	Development before/ after epilepsy onset	Probable mode of inheritance
	Last visit: 21 months with no seizures				
Family 16					?
1-boy 2-boy	*Onset at 6.5 months* Spasms in series Last visit: still on treatment (2 + 5 + 6), uncontrolled for the last 3.5 years	Spasms/West syndrome	Hypsarrhythmia	Delayed/delayed	
	Onset at 7 months Staring, eye myoclonous, focal right side seizures Uncontrolled seizures in the first three years of life (2 + 3 + 4), then seizures stopped. At 5 years, the treatment was tapered Last visit: off treatment with no seizures for the past year	Partial complex/unclassified	Focal spikes	Delayed/delayed	
Family 17					AD with reduced penetrance
1-boy	*Onset at one month* GTC Last visit: controlled for the past 6 months (1) then lost during follow-up	GTC/unclassified	normal	Normal/normal	
Family 18					AD
1-girl	*Onset at 5.5 years* GTC followed by vomiting in a series over 15 min Last visit: uncontrolled seizures for the past 1.5 years (1 + 2)	Generalized/unclassified	Generalized spikes	Normal/school difficulties	
Family 19	*Onset at 9 years*	Generalized/unclassified	Generalized spikes	Normal/normal	AD with reduced penetrance
1-girl	Up rolling of eyes with loss of consciousness, followed by vomiting Last visit: only two seizures over past two years, parents withdrew patient from treatment (2), lost during follow-up				
Family 20					AR
1-girl	*Onset at 9 years* GTC Received treatment for 2 years, recurrence during tapering. Treatment restarted Last visit: on treatment (2) with no seizures for the past 15 months	GTC/unclassified	Generalized spikes	Normal/normal	
Family 21					AD
1-girl	*Onset at 2 years* Pallor, sweating, and loss of consciousness Last visit: 1.5 years with no seizures (2)	Generalized/unclassified	Generalized spikes	Normal/normal	
Family 22					?
1-boy	*Onset at 12 years* Dizzy and change in level of consciousness Last visit: 4 months with no seizures (2)	Partial complex/unclassified	Focal spikes in temporoparietal regions	Normal/normal	
Family 23					?
1-girl	*Onset at 6 months* GTC followed by vomiting Last visit: still having seizures every month at the age of 8 years (2)	GTC/unclassified	Generalized spikes	Normal/school difficulty	
Family 24					AD with reduced penetrance
1-boy	*Onset at 5.5 years* Awakens from sleep, afraid, abnormal behavior for 2 min Last visit: 2 years with no seizures, plans to taper treatment (2)	Partial complex/unclassified	Generalized spikes	Normal/normal	
Family 25					?
1-boy	*Onset at 4 months* GTC upon awakening Last visit: still having uncontrolled seizures at the age of 15 years on polytherapy (1 + 7)	GTC/unclassified	Generalized spikes	Delayed/delayed	

Family 26					?
1-girl	*Onset at 4 months* GTC (only during sleep) Last visit: 7 months on polytherapy(2 + 4 + 7), uncontrolled	GTC/unclassified	normal	Normal/normal	
Family 27					AD with reduced penetrance
1-boy	*Onset at 10 years* GTC only during sleep Last visit: 7 months on treatment (1)with no seizures	GTC/unclassified	Generalized spikes	Normal/poor school performance	
Family 28					AR
1-girl	*Onset at 8.5 years* Absence Last visit: 20 months with no seizures(2)	Absence/absence epilepsy	Generalized spikes 3 cycles/s	Poor school performance/ poor school performance	
Family 29					AD
1-boy	*Onset at one month* Seizures only at the beginning of sleep. Tonic contraction of right upper limb, chewing movements in the mouth, and change in the level of consciousness Presented at 6 years of age with seizures every 6 months Last visit: 2 years with no seizures(2), plans to taper treatment	Partial complex/unclassified	Focal slow waves	Normal/normal	
Family 30					AR
1-girl	*Onset at one month* GTC Presented at the age of 5 years with daily seizures Last visit: 4 months with no seizures(1 + 3 + 6)	GTC/unclassified	Normal	Delayed/delayed	
Family 31					AD with reduced penetrance
1-boy	*Onset at 10 years* Feels dizzy, falls, GTC Received treatment for 2 years then recurrence during tapering. Restarted treatment for another 2 years, then another recurrence upon tapering. Treatment restarted again (1) Last visit: controlled on treatment for the last one year	Partial complex/unclassified	Focal temporal spikes	Normal/poor school performance	

AD, autosomal dominant; AR, autosomal recessive; XR, X-linked recessive; GTC, generalized tonic–clonic seizures. Antiepiletic drugs: (1) carbamazepine, (2) valproic acid, (3) lamotragine, (4) levetaricitam, (5) topiramate, (6) clonazepam, (7) phenobarbital.

(AD) inheritance with or without reduced penetrance in 13 families (41.9%), a probable autosomal recessive (AR) inheritance in 6 families (19.4%), and an X-linked recessive inheritance (XR) in one family. In the remaining 11 families, pedigree analysis was inconclusive or suggested more than one possible mode of inheritance. For example it was difficult to decide on whether the mode of inheritance is XR or AR where only male offspring are affected and parents are consanguineous. For some families, such as for example in family 6 where there are more than one affected offspring and the parents are not affected and not consanguineous, compound heterozygosity cannot be excluded.

5. Discussion

This study presents the clinical and inheritance profiles of 39 Jordanian children belonging to 31 families with familial epilepsy having at least one first degree relative affected by epilepsy. Among the 31 sibships, the majority of parents (61.3%) were consanguineous. Previous studies from Jordan proved consanguinity to be a major risk factor for neonatal and infantile epilepsy.[8,9] Generalized epilepsies were more common than partial epilepsies. Ascertainment of the modes of inheritance deduced from pedigree analysis pointed to a probable autosomal dominant (AD) inheritance with or without reduced penetrance in 13 families, a probable autosomal recessive (AR) inheritance in 6 families, an X-linked recessive inheritance (XR) in one family and could not be determined in 11 families.

The age of seizure onset in our patients ranged from one month to 16 years. Early onset may increase the risk of these patients also producing epileptic children. Children of epileptic parents with seizure onset before age 20 years carry a 2.3–6% risk of epilepsy, while onset after age 20 years confers only a 1–3.6% risk of epilepsy in the offspring.[15] In contrast, there is no increased risk of epilepsy in the offspring of parents with epilepsy onset after age 35 years.[16] It would be interesting to follow the patients in this study after their marriage and study the risk of epilepsy in their offspring.

Generalized epilepsies were more common than partial epilepsies. The variety of different clinical forms of seizures described in these patients and our inability to definitively classify many patients suggests that there may be more distinct idiopathic epilepsies in our population than reported here or described in the literature (Table 2 presents descriptions of seizures in each patient).

Most of the patients (74.4%) required only monotherapy, and seizure control was acceptable in most cases (84.6%). Furthermore, most patients exhibited no signs of developmental delay or neurological deficits (aside from seizures), indicating that the familial epilepsies described in this study population were relatively benign. Six patients (15.4%) were drug refractory, and the majority of these patients had onset in the first year of life. All six exhibited developmental delay or poor school performance. Thus, early onset and developmental delay may predict poor outcome in response to anticonvulsant treatment for control of seizures.

Although most cases were well controlled, the recurrence rate after treatment withdrawal was relatively high (61.5%), indicating that many of these epilepsy cases will persist into adolescence and adulthood.

The rate of consanguinity among parents of affected in the nuclear families was 61.3%. The rate of consanguinity in Jordan, including marriages between second cousins and closer relatives, was reported to be around 38%.[2] The findings of a more recent study in Amman revealed a drop in the rate of first-cousin marriages from 28.5% during the period 1950–1979 to 19.5% for marriages after 1980.[1] The higher consanguinity rate among parents of probands than among the general population (61.3% vs. around 20–30% at present) suggests that some cases of epilepsy in this study may follow an autosomal recessive mode of inheritance (Fig. 1). However, it is also possible that the higher rate of consanguineous marriage may reflect negative attitudes toward epileptic patients in Jordan,[17] making it more convenient for members of families with chronic or stigmatizing diseases such as epilepsy to contract intrafamilial unions.

Few studies from highly consanguineous populations discussed familial epilepsy and the role of consanguinity[18–20]; their results were dependent on the methods used and the inclusion criteria. In Turkey, 9.5% of 3098 epileptic patients had first or second degree relatives affected with epilepsy, and a positive family history of consanguinity was reported in around 19% of the familial cases.[18] Saadeldin et al. studied Saudi patients with benign familial and non familial infantile seizures and reported the existence of this epileptic syndrome for the first time in the Arab population.[19] Similarly, Abouda et al. reported a familial form of typical childhood absence epilepsy in five Tunisian consanguineous families and suggested an autosmal recessive mode of inheritance in these families.[20] Unlike the latter 2 studies which focused on specific epileptic syndromes with variable age groups, our study included all types of seizures and focused on children below 18 years of age.

In these 31 families, 38.5% of all offspring were epileptic. This percentage is higher than expected for autosomal recessive inheritance (25%) and lower than expected for autosomal dominant inheritance (50%). This suggests that autosomal recessive inheritance is more probable in some families, while autosomal dominant inheritance with or without reduced penetrance is more probable in others. An interesting finding is that among the 9 families in which one parent was epileptic, 34% of the offspring were also affected, while among the 22 families with no affected parent, 41% of offspring were epileptic. This finding suggests that these 22 families may harbor an autosomal dominant candidate gene that has reduced penetrance. Application of high-throughput sequencing and exome sequencing in these families could reveal causative dominant or recessive genes associated with epilepsy.[21]

The inclusion criteria selected for a high rate of affected relatives. The overall risk to family members of individuals with epilepsy is low, though higher than in the general population. More than 90% of individuals with epilepsy have no affected relatives, and most parents with epilepsy have no children with epilepsy.[15] Results from previous studies reported risks ranging from 2.4% to 4.6% for offspring of parents with any kind of epilepsy.[12] A maternal effect has been described, although the mechanism is still not fully understood.[22] Mothers with epilepsy have higher rates of affected offspring (2.8–8.7%) compared to fathers with epilepsy (1.0–3.6%).[22] In our case series, however, the rate of epilepsy was similar in children of mothers with epilepsy (33.3%) and children of fathers with epilepsy (34.2%) (Fig. 1). Around 29% of the families had a father with epilepsy, while only around 10% had a mother with epilepsy. The presence of a higher percentage of affected fathers in our series might be related to cultural issues; females with chronic diseases such as epilepsy may be less likely to marry and have children due to the stigma of the disease.

Married couples with one epileptic partner had about the same number of children on average (four) as couples in which neither was epileptic (five). This finding is in contrast to previous studies reporting that parents with epilepsy have fewer children than parents without epilepsy.[23] The benign nature of the epilepsy syndromes in these families may account for this result. Alternatively, any effect may be overshadowed by the general trend for large families in Jordan.

5.1. Limitations of the study

This retrospective study has several limitations including the relatively small sample size and the referral and tertiary care bias. Due to the difficulty in contacting the affected in the family who were not seen in the clinic resulted in the lack of details of the types, and management protocols of epilepsy in these affected family members. The study also lacks formal neuropsychological assessment and genetic analysis because of financial and technical impediments.

6. Conclusions

While this retrospective study has several limitations, it is the first report on familial epilepsy involving first degree relatives from a country with a high rate of consanguineous marriage. Several important conclusions can be drawn from this study. First, Seizures in children who had parents with epilepsy were generally well controlled, but tapering antiepileptic treatment may be difficult. Second, the mode of inheritance could be autosomal dominant with reduced penetrance or autosomal recessive. While genetic testing including exome sequencing has not been done yet, it will be helpful to clarify the pathogenic mechanisms of epilepsy in these families and aid in genetic counseling. Moreover, such genetic analyses may also reveal novel autosomal recessive genes associated with epilepsy.

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