



Familial epilepsy in Algeria: Clinical features and inheritance profiles



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ABSTRACT

Purpose: To document the clinical characteristics and inheritance pattern of epilepsy in multigeneration Algerian families.

Methods: Affected members from extended families with familial epilepsy were assessed at the University Hospital of Oran in Algeria. Available medical records, neurological examination, electroencephalography and imaging data were reviewed. The epilepsy type was classified according to the criteria of the International League Against Epilepsy and modes of inheritance were deduced from pedigree analysis.

Results: The study population included 40 probands; 23 male (57.5%) and 17 female subjects (42.5%). The mean age of seizure onset was 9.5 ± 6.1 years. According to seizure onset, 16 patients (40%) had focal seizures and 20 (50%) had generalized seizures. Seizure control was achieved for two patients (5%) for 10 years, while 28 (70%) were seizure-free for 3 months. Eleven patients (27.5%) had prior febrile seizures, 12 were diagnosed with psychiatric disorders and four families had syndromic epilepsy. The consanguinity rate among parents of affected was 50% with phenotypic concordance observed in 25 families (62.5%). Pedigree analysis suggested autosomal dominant (AD) inheritance with or without reduced penetrance in 18 families (45%), probable autosomal recessive (AR) inheritance in 14 families (35%), and an X-linked recessive inheritance in one family.

Conclusion: This study reveals large Algerian families with multigenerational inheritance of epilepsy. Molecular testing such as exome sequencing would clarify the genetic basis of epilepsy in some of our families.

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1. Introduction:

Epilepsy is the most common neurological condition, affecting more than 50 million people in the world, with a 3% risk of developing epilepsy across all ages [1,2]. A genetic contribution to epilepsy has been recognized since Antiquity and is well established through twin studies [3–5]. Family studies have also suggested the involvement of genetic factors in different forms of generalized and partial epilepsies, showing a higher risk of epilepsy in proband's first-degree relatives (children, siblings and parents) as compared to the general population [6,7].

During the past three years, novel technologies and an unprecedented level of international collaboration has resulted in the discovery of novel genes for monogenic epilepsies. Indeed, the use of massive parallel sequencing technologies has allowed for the identification of *PRRT2* as the long-sought gene for Benign Familial Infantile Seizures (BFIS) [8,9], and the *KCNT1* mutations in Malignant Migrating Partial Seizures of Infancy (MMPSI) and severe Autosomal Dominant Nocturnal Frontal Lobe Epilepsy (ADNFLE) [10,11]. In addition, we have recently identified a novel gene in one family with monozygotic twins affected by temporal lobe epilepsy. Exome sequencing revealed a novel de novo mutation (p.A39E) in the galanin gene, which acts as a potent anticonvulsant and regulate epileptic seizures in animal models. Functional analysis of the mutant galanin peptide showed antagonist effects on galanin receptor 1 (GalR1) and reduced agonist effects on GalR2. These

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findings could potentially have direct implications for the development of anti-epileptic treatment [12].

During our fieldwork, we have identified many additional families with several members affected with epilepsy. While consanguineous marriages comprise 22–39% [13–15] of all marriages in Algeria, which may predispose offspring to rare autosomal recessive conditions, to our knowledge, there have been no reports describing the inheritance patterns of familial epilepsy in Algeria.

In this paper, we present genealogical analysis, clinical characteristics and the probable patterns of inheritance in 40 Algerian families with epilepsy in order to perform further genetic analysis for the detection of the pathogenic variation that may help in carrier detection and family planning.

2. Materials and methods

2.1. Family recruitment, inclusion criteria and clinical evaluation

This is a prospective study done at the Neurology Department at Oran University Hospital, which is the main regional hospital in Oran, from June 2011 to June 2014. Families were included when their past history showed that there are other affected members in the extended family.

All possibly affected individuals available underwent clinical evaluation; and whenever possible, EEG and MRI were performed. A bilingual trained psychiatrist (French-Arabic) assessed individuals with psychiatric disorders using the Mini International Neuropsychiatric Interview (MINI).

Forty families agreed to participate in the study. A three-generation pedigree with details regarding seizures, congenital malformations, comorbidities and consanguinity in parents was drawn for each family using “Genial Pedigree” software (<http://www.pedigreedraw.com/>), through a structured interview that took 50–60 min. Interviews were done either on the telephone or in person and responses were crosschecked with family members who were invited to participate in the study.

We excluded from the study five 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.

Pedigree analysis concluded that the inheritance pattern in a family was classified as autosomal dominant if there were multiple generations affected in a vertical pattern, and if both males and females were affected. It was classified as autosomal recessive if the affected individuals were seen in only one generation in a horizontal pattern, if males and females were affected and if parents were related. It was classified as X-linked recessive if only males were affected, if the affected males were related through putative carrier females, and if there was no male-to-male transmission. Considering the possibility of endogamous marriages, we proposed AR as the probable mode of inheritance when there were multiple affected in a sibship with non-affected parents who both originate from the same small village.

2.2. Seizure type and epileptic syndrome identification

We obtained information regarding seizure manifestations from patients as well as observers. We reviewed all available medical records, neurological examination, electroencephalography and imaging data. Based on the combined results, each patient’s epilepsy was characterized, and whenever possible, classified.

2.3. Definitions

Seizures and epilepsy syndromes were classified according to the International League against epilepsy recommendations

[16,17]. Families were classified according to the proband’s epilepsy syndrome. To ensure comparability with previous studies on the same field, we did not use the recommendations of the ILAE/2010 classification for seizures and epilepsies.

The proband was defined as the first affected family member who sought medical attention at hospital and met the inclusion and exclusion criteria.

We considered as “familial epilepsy” the occurrence of epilepsy in at least two members of the same family including the proband. First-degree relatives comprised parents, siblings, and children; second-degree relatives comprised grandparents, aunts, and uncles; and third-degree relatives comprised first cousins.

In clinical genetics, consanguinity is defined as a marital relationship between two individuals who share the same ancestor and the degree of consanguinity is not beyond second cousins. In this study, however, further genetic relations were also considered when assessing the mode of inheritance in order to include any possible founder mutations in this highly consanguineous population. Families are defined as phenotypically concordant if all affected relatives have the same clinical feature (epileptic syndrome or seizure type, age at onset, response to treatment and EEG findings).

Age of onset was defined as the age when the patient, his/her family members or friends first noticed the disease. We defined controlled epilepsy as the absence of seizures for at least six months.

The likely modes of inheritance were based on the family pedigree that was documented in the file.

The purpose of the study was explained to the patient/family and informed consent was obtained from patients, parents or legal guardians.

2.4. Statistical analysis

The collected data were coded and entered into the SPSS 21.0 for Mac OS X. We conducted a descriptive analysis of cases involving the calculation of averages and standard deviations for quantitative variables and percentages for categorical variables.

3. Results

3.1. Family features

Forty families with two or more members affected by idiopathic epilepsy participated in the study. We collected data from 907 subjects, of whom 156 (17.2%) showed epilepsy. The mean number of individuals (both with and without epilepsy) was 22.7 per family with a mean of 4-affected individuals per family.

In addition to the 40 probands, 61 first-, 17 second- and 19 third-degree relatives had epilepsy. In the collected sample, only two sets of monozygotic twins were present. Consanguinity was reported among parents in 20 out of 40 families with 16 (40%) first cousins and 4 (10%) second cousins. In 25 families (62.5%) affected members shared the same phenotype for epilepsy, while the others appeared to have a range of different phenotypes.

With regard to epileptic features in general, pedigrees were compatible with autosomal dominant (AD) inheritance with or without reduced penetrance in 18 families (45%). In 14 families (35%), an autosomal recessive (AR) transmission could also be hypothesized, and an X-linked recessive inheritance (XR) was assigned in only one family. In the remaining families, the pedigree analysis was inconclusive or suggested more than one possible mode of inheritance (Fig. 1a and b).

3.2. Probands clinical data

There were 23 male (57.5%) and 17 female subjects (42.5%) in the study group, with ages ranging from 4 to 59 years (mean

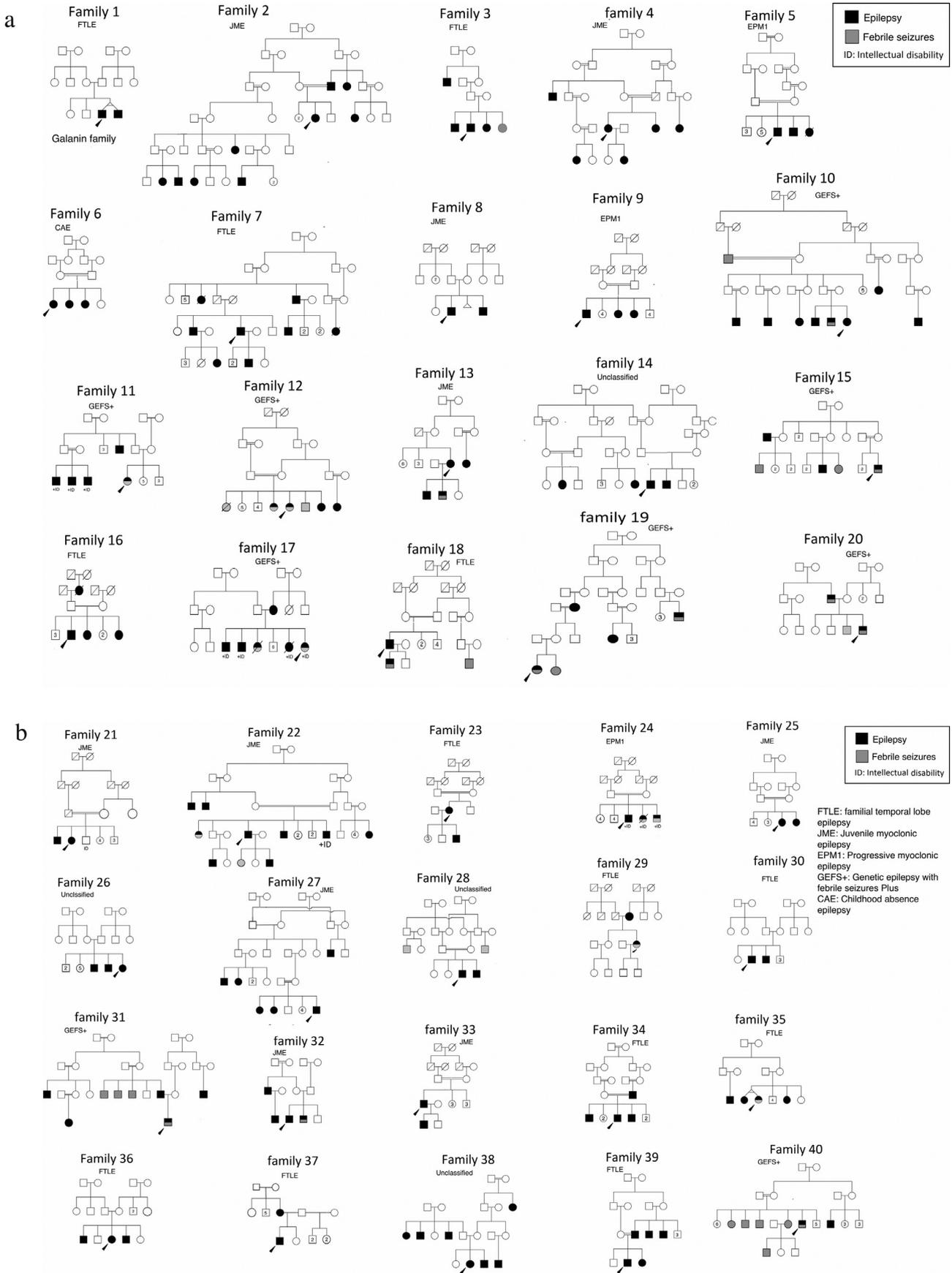


Fig. 1. Pedigrees of the 40 families.

27.7 ± 13.2 years). This was a predominantly adult population (72.5% were over 18 years). The age of seizure onset ranged from three months to 22 years (mean: 9.5 ± 6.1 years). According to seizure onset, 16 patients (40%) had focal seizures and 20 (50%) had generalized seizures. The remaining four patients (10%) could not be classified as having either focal or generalized seizures because both partial and generalized onset seizures were noted.

Among all probands, 11 (27.5%) had prior febrile seizures (FS) and 8 of them (72.7%) had family history of FS.

The distribution of probands with respect to ILAE epilepsy syndrome diagnosis is summarized in Table 1.

Twenty-four patients (60%) were on monotherapy, twelve (30%) were on two antiepileptic medications, and two (5%) were on

three antiepileptic drugs. The most common antiepileptic medications used were valproic acid (22/40, 55%), carbamazepin (11/40, 27.5%) and levetiracetam (8/40, 20%).

At the time of analysis, seizure control was achieved in 21 patients (52.5%) using mono or polytherapy. 28 (70%) were seizure-free for 3 months and two (5%) have been weaned for 10 years. The other twelve patients (30%) continued to experience seizures despite trials of several antiepileptic medications.

Two probands were diagnosed with intellectual disability and 12 with a psychiatric comorbidity: 4 with depression, 6 with anxiety, one with attention deficit hyperactivity disorder (ADHD) and one with schizophrenia; all were under psychiatrist follow up (AD).

Table 1

Clinical features, EEG findings and the probable modes of inheritance in the 40 families.

Proband according to family number	Age at onset (years)	Seizure type	Epilepsy syndrome	EEG findings	Neurological examination	Probable mode of inheritance
1 (Galanin family)	13	Complex partial	FTLE	Focal temporal spikes	Normal	De novo [15]
2	15	Myoclonic	JME	Generalized polyspikes	Normal	AD reduced penetrance
3	18	Simple partial	FTLE	Focal slow waves	Normal	AD reduced penetrance
4	18	Myoclonic	JME	Generalized polyspikes	Normal	AD reduced penetrance? AR?
5	10	Myoclonic	EPM1	Generalized Polyspikes and waves photosensitivity	Dysarthria, ataxia	AR
6	5	Absence	CAE	Generalized 3 Hz spike waves	Normal	AR
7	15	Complex partial	FTLE	Central and temporo-parietal spikes	Normal	AD
8	11	Myoclonic	JME	Generalized polyspikes waves	Normal	XR? AD with reduced penetrance?
9	11	Myoclonic	EPM1	Diffuse spikes and polyspikes	Cerebellar ataxia, ID	AR
10	2	Myoclonic	GEFS+	Photosensitivity	Normal	AD reduced penetrance? AR?
11	3	Generalized tonic-clonic	GEFS+	Generalized spike waves	Normal	AD
12	4	Unknown	GEFS+	Focal temporo-parietal epileptic activity	Normal	AR
13	5	Myoclonic	JME	Generalized polyspikes	Normal	AR
14	11	Generalised tonic clonic	Unclassified	Normal	Blindness, deafness, ID	AR
15	5	Complex partial	GEFS+	Focal parieto-occipital epileptic activity	Normal	AD reduced penetrance
16	16	Complex partial	FTLE	Focal spikes in temporo-parietal region	Normal	AD reduced penetrance
17	4	Generalised tonic clonic	GEFS+	Diffuse slowing	Spastic paraplegia	IDAD
18	1	Simple partial	FTLE	Frontal and temporal spikes	Normal	AD
19	1	Generalised tonic clonic	GEFS+	Focal temporo-parietal spikes	Normal	AD? AR?
20	12	Complex partial	GEFS+	Temporal spike-waves	Normal	AD
21	17	Myoclonic	JME	Generalized polyspikes	Normal	AR
22	17	Myoclonic	JME	Generalized polyspikes	Normal	AR
23	16	Complex partial	FTLE	Temporo-occipital spikes	Blindness	AD
24	6	Myoclonic	EPM1	Generalized polyspikes	Dysarthria, ataxia	ID AR
25	9	Myoclonic	JME	Generalized polyspikes	Normal	AR
26	22	Unknown	Unclassified	Normal	Normal	AD
27	9	Myoclonic	JME	Generalized polyspikes	Normal	AD reduced penetrance? AR?
28	15	Complex partial	Unclassified	Slow waves in occipital regions	Normal	AD reduced penetrance? AR?
29	3	Complex partial	FTLE	Temporal epileptic activity	Normal	AD?
30	10	Complex partial	FTLE	Fronto-temporal spikes	Normal	XR
31	1	Simple partial	GEFS+	Generalized epileptic activity	Normal	AR
32	8	Myoclonic	JME	Spike waves in frontal region	Normal	AD variable penetrance
33	1	Myoclonic	JME	Generalized polyspikes	Normal	AD
34	12	Complex partial	FTLE	Focal spikes in temporal region	Normal	AD? AR?
35	4	Unknown	FTLE	Normal	Normal	AD variable penetrance
36	15	Generalised tonic clonic	FTLE	Normal	Normal	AD
37	19	Simple partial	FTLE	Temporal spikes	Normal	AD
38	1	Unknown	Unclassified	Multifocal spikes	Microcephaly	ID AD variable penetrance
39	4	Complex partial	FTLE	Temporal and occipital spikes	Normal	AD
40	14	Complex partial	GEFS+	Frontal epileptic activity	Normal	AD

AD: Autosomal dominant, AR: autosomal recessive, XR: X-linked recessive, CAE: childhood absence epilepsy, JME: juvenile myoclonic epilepsy, EPM1: progressive myoclonic epilepsy type 1, GEFS+: genetic epilepsy with febrile seizure plus, FTLE: familial temporal lobe epilepsy, ID: intellectual disability, ADHD: attention deficit hyperactivity disorder.

Clinical features, neurological examination, EEG findings and the probable modes of inheritance are summarized in Table 1. Brain imaging (CT scan or MRI) was normal in all cases.

In families 5,9,14 and 24, epilepsy was associated with other manifestations such as intellectual disability, ataxia and blindness, probably due to undiagnosed autosomal recessive syndromes (Table 1).

4. Discussion

Familial epilepsy encompasses several different syndromes, which are generally diagnosed by clinical features. The key element in making the correct diagnosis is obtaining a comprehensive clinical history and establishing a detailed pedigree.

The availability of extensive genealogical data can provide large pedigrees, potentially very informative for genetic analysis.

We present here the clinical profile and inheritance pattern of familial idiopathic epilepsies in Algerian families. In this study, the population sample was taken from Oran, the major city on the northwestern Mediterranean coast of Algeria with a population of approximately 1,500,000. Many of our patients originate from Sidi Ali, a small village about 80 km away from Oran. Previous reports have ascertained a high rate of consanguineous unions of up to 34% in Tlemcen, a region about 150 km away from Oran [13]. Given the existence of numerous large and multigenerational pedigrees with several affected members, the Oran are thus emerging as an interesting population for genetic research on the epilepsies.

In this study, 40% of parents of affected individuals were first cousins. This is in line with the results of a recent study conducted in Oran and which recognized parental consanguinity as significant risk factor for both monogenic and polygenic epilepsies ($p = 0.029$) [18].

Similar results have been reported in other inbreeding populations. For instance, Masri et al. reported a high rate of parental consanguinity (61.3%) among 31 Jordanian families with familial childhood epilepsy [19]. Premarital counselling for couples who have a family history of epilepsy is recommended.

Epilepsy was more frequent in first- than in second-degree relatives. We have already shown in a previous study involving subjects belonging to the same region that family history of epilepsy in first-degree relatives increased significantly the risk of developing epilepsy ($p < 10^{-4}$) [18]. Similarly, in a large Turkish cohort of 3098 epileptic patients, 19.9% had at least one epileptic family member with first-degree relatives being twice more affected than second-degree relatives (202/94) [20].

Most families (62.5%) shared the same phenotype while the remaining appeared to have a range of different epilepsy phenotypes. This finding could have two possible interpretations: It could be that certain variants may predispose to a relatively narrow clinical phenotype while others result in a much more varied phenotype or that this clinical heterogeneity could reflect the possibility that individuals within some families may possess additional genetic variants or share non-genetic factors that influence phenotypic expression.

In our study population, there was a slight male predominance of 23M/17F. Most studies of epilepsy indicate that males are more frequently affected than females, although the difference is seldom statistically significant [21].

The mean age at seizure onset was around 10 years, probably because of the predominance in our sample of epilepsy syndromes starting in adolescence or later, such as juvenile myoclonic epilepsy [22], progressive myoclonic epilepsy [23,24], and familial temporal lobe epilepsy [25].

Among probands, 40% had partial seizures and 50% had generalized seizures. This is in agreement with studies from the Arab countries, which had found partial seizures less common than

generalized seizures [26] matching Asian and sub-Saharan African studies [27,28]. In USA, Abou Khalil reported that patients with generalized epilepsy were more likely to have first and second degree relatives with than those with partial epilepsy (40.2% versus 31.2%, $p = 0.001$) [29].

Prior febrile seizures (FS) were reported among 11 probands (27.5%), and three quarters of them had a family history of FS. These results are consistent with those of Abou Khalil et al., who reported that epileptic patients with prior FS were more likely to have a family history of FS than those without prior FS ($p < 0.000001$). In a multivariate analysis, Hwang identified family history of epilepsy as a significant predictor of unprovoked seizures after FS ($p = 0.019$) [30]. This finding suggests that FS represent an early expression of a low seizure threshold in patients genetically predisposed to epilepsy. Indeed, FS can be the gateway to numerous genetic epileptic syndromes such as Genetic Epilepsy with Febrile Seizures Plus (GEFS+) [31], epileptic syndrome by febrile infection (FIRES) [32], severe myoclonic epilepsy in infancy (SMEI) [33] and temporal lobe epilepsy (TLE) [29,34].

Only 60% were seizure-free for three months, while 40% continued experiencing seizures. This could be explained by the fact that many patients had myoclonic epilepsy (juvenile or progressive) known to be drug-resistant or drug dependant. It should also be noted that some patients did not observe correctly the prescribed treatment.

Psychiatric comorbidities were reported among 12 probands (30%). In recent years, several studies have shown clear links between epilepsy and various neuropsychiatric disorders including psychosis and depression. Rates of mood disorders ranged from 25% to 48% and anxiety disorders from 14% to 31% [35,36]. Rates of major depressive episodes are increased in patients with epilepsy and range from 11% to 62%, compared with 3.7% to 6.7% for the general population [37]. Furthermore, the percentage of deaths by suicide in patients with epilepsy ranges from 11% to 33%, with an overall average of 11.5% [38]. The association of epilepsy with psychosis is also striking, where the prevalence of the interictal psychosis of epilepsy ranges in different studies between 4.3% and 44%. In a recent review, rates of 19.4% and 15.2% in generalized epilepsies (GE) and TLE groups, respectively, were reported [39].

Very recently, it has become clear that neuropsychiatric disorders may share common genetic variation with epilepsy. Indeed, genetic studies of copy number variants (CNVs) have shown that in some cases, the same CNV occurs in neuropsychiatric illness and epilepsy. Several studies have demonstrated an association between large rare recurrent CNVs and epilepsy, autism, schizophrenia, mental retardation, and attention deficit hyperactivity disorder [40,41]. Of particular relevance is the observation that an individual CNV can contribute risk to more than one type of neuropsychiatric disorder. This has led to the suggestion that schizophrenia, autism, and intellectual disability may be rather overlapping phenotypes from shared disturbed neural development [42].

There were 13 families with TLE: 7 families had features consistent with mesial TLE (simple partial seizures with intense feelings of *deja vu* at times associated with dizziness or nausea, complex partial seizures with altered awareness and staring) and 6 families had autosomal dominant epilepsy with auditory features (ADEAF) previously denoted as autosomal dominant lateral temporal lobe epilepsy. An AD trait was deduced in 76.9% of these families (Table 1). It is well known that ADEAF follows AD inheritance with decreased penetrance. Thus, by analysing data from 24 previously published families with ADEAF and mutations in the leucin-rich glioma inactivated gene (*LGI*), Rosanoff and Ottman found that the overall penetrance of the disorder was 67% and did not vary according to mutation type or location in the gene [43]. Hedera et al. reported a 4-generation Caucasian family in

which 11 living individuals had features consistent with mesial TLE. Three unaffected family members had affected offspring, suggesting AD inheritance with incomplete penetrance [44].

Juvenile myoclonic epilepsy (JME) was reported in 9 families. Pedigrees were compatible with a probable AD inheritance in 3 families and AR in 4 families. In the remaining two families, pedigree analysis suggested more than one possible mode of inheritance. The exact type of inheritance in JME is currently not known; the rare family and genetic studies indicate rather contradictory modes: AD, AR, maternal or complex [45].

Three families had Progressive Myoclonic Epilepsy type 1 (EPM1) with AR pattern of inheritance. EPM1 or Unverricht–Lundborg disease (ULD) is an AR neurodegenerative disorder characterized by action- and stimulus-sensitive myoclonus, tonic-clonic seizures, progressive cerebellar ataxia, preserved cognition, and poor outcome. Mutations in the gene encoding cystatin B (*CSTB*), a cysteine protease inhibitor, are responsible for the primary defect underlying EPM1 [46].

In our study population, there were 9 families with GEFS+ phenotype. Five families showed an AD probable mode of inheritance and two others an AR pattern. To our knowledge, all GEFS+ families, described in OMIM (Online Mendelian Inheritance in Man—<http://www.ncbi.nlm.nih.gov/omim>) database, exclusively show an AD mode of inheritance. Recently, Belhedi et al. described the first consanguineous GEFS+ Tunisian family with a putative AR mode of inheritance, a transmission previously described in a Moroccan consanguineous family, showing FS and temporal lobe epilepsy phenotypes [47].

Only one family showed CAE with AR trait. Familial form of typical childhood absence epilepsy with an AR mode of inheritance was also reported in five Tunisian consanguineous families [48]. Four of our families (10%) had syndromic epilepsy with suggested autosomal recessive inheritance pointing to the significant role of consanguinity in the expression of rare recessive variants.

5. Limitations of the study

Our study has several limitations including the relatively small sample size. It was a clinic-based study and may not represent the full spectrum of familial epilepsies. Furthermore, patient and family recall of epilepsy carried an inherent risk of incompleteness or inaccuracy.

Due to the unavailability of ictal EEG recording, we were unable to classify seizure type in four patients with some atypical features.

6. Conclusion

This study confirms that there are large families in the Algerian population with multigenerational inheritance of familial epilepsy and phenotypic heterogeneity.

Seizures are well controlled in most cases except in myoclonic syndromes, which are more difficult to deal with despite trials of several antiepileptic drugs. Psychiatric disorders are often associated with epilepsy suggesting possible common genetic underpinnings.

Autosomal recessive mode of inheritance was proposed in 35% of our cases of familial epilepsy. The higher rate of consanguineous unions reported in our population probably contributes to the genetic epilepsy types encountered.

Our cohort of families with epilepsy represents a valuable resource for the identification of novel epilepsy genes. Further, molecular testing such as deep sequencing for rare variants could be used to clarify the genetic basis of epilepsy in some of our families.

Conflict of interest statement

The author has not received any financial support to produce this work, and has no relationship to people or organization that would influence this work. The author otherwise has nothing to disclose.

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