Epilepsy Research (2015) 111, 10—17

journal homepage: www.elsevier.com/locate/epilepsyres

Consanguinity and epilepsy in Oran, Algeria: A case—control study

Amina Chentouf[a,*], Randa Talhi[b], Aicha Dahdouh[c], Latifa Benbihi[a], Soumia Benilha[b], Mohand Laid Oubaiche[a], Malika Chaouch[d]

[a] Department of Neurology, Oran University Hospital, 31000, Algeria
[b] Department of Biostatistics, Faculty of Medicine, Oran 31000, Algeria
[c] Department of Psychiatry, Oran University Hospital, 31000, Algeria
[d] Department of Neurologie, Benaknoun University Hospital, Algiers 16000, Algeria

Received 15 September 2014; received in revised form 27 December 2014; accepted 30 December 2014
Available online 8 January 2015

KEYWORDS
Epilepsy;
Consanguinity;
Risk factors;
Oran;
Algeria

Summary
Purpose: The goal of this case—control study was to identify the significance of consanguinity and other risk factors for epilepsy in Oran, Algeria.
Methods: Unrelated epileptic patients upwards of 16 years, who attended the Neurology Department between October 2013 and March 2014 were included in the study. Controls, matched for age and sex, were selected among non-epileptic patients attending the same department during the same period. The risk factors evaluated were: consanguinity, family history of epilepsy, perinatal complications, infection of the central nervous system, mental retardation, neurological impairment, history of febrile seizures, severe head trauma, cerebrovascular diseases, and addiction.
Results: 101 cases and 202 controls participated in the study. Multivariate logistic regression identified five factors significantly associated with epilepsy: first-degree of consanguinity (odds ratio (OR) = 2.15), history of epilepsy in first-degree relatives (OR = 4.03), antecedent of febrile seizures (OR = 5.38), severe head injury (OR = 2.94) and mental retardation (OR = 9.32).
Conclusion: Consanguinity, family history of epilepsy, history of febrile seizures, severe head trauma and mental retardation are risk factors for epilepsy. The implementation of a strategy for prevention and awareness of the impact of consanguineous marriages as well as genetic counseling for couples with a family history of epilepsy are needed.

* Corresponding author at: Department of Neurology, University Hospital, Oran 31000, Algeria. Tel.: +213 41465869; fax: +213 41465869.
E-mail address: amina.chentouf@yahoo.com (A. Chentouf).

http://dx.doi.org/10.1016/j.eplepsyres.2014.12.014
0920-1211/

Introduction

Consanguinity is a reproductive relationship between two individuals who share a common ancestor. In other words, consanguineous marriages refer to marriages contracted between individuals biologically related. These unions are still widespread especially in the Middle East and North Africa where they are favored by traditions and cultural practices (Dahdouh-Guermouche et al., 2013). Such inbreeding is associated with an increased rate of birth defects and perinatal mortality. In addition, the offspring of consanguineous marriages are at increased risk of recessive diseases due to the expression of autosomal recessive genetic mutations inherited from a common ancestor. The closer the biological relationship between the parents, the greater the likelihood that their offspring will inherit one or more of the same harmful recessive genes copies (Hamamy et al., 2011).

Epilepsy is a brain disease defined by any of the following conditions: (1) at least two unprovoked (or reflex) seizures occurring >24 h apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; (3) diagnosis of an epilepsy syndrome (Fisher et al., 2014). According to data from WHO, there are 50 million people with epilepsy worldwide, 80% in developing countries (World Health Organization, 2005). Despite new exploration techniques, the etiology remains unknown in almost two thirds of cases (Sander, 2003). Over the past three decades, several case—control studies on epilepsy have been conducted (Rocca et al., 1987; Casetta et al., 2002; Ogunniyi et al., 1987; Edwards et al., 2008). Although these studies have identified numerous risk factors associated with epilepsy, the results were highly variable. While stroke and head injury have been implicated as factors for adults from high-income countries (Guekht et al., 2010; Pi et al., 2014), epilepsy was associated with parasitic diseases, perinatal insults and central nervous system (CNS) infections in developing countries (Ogunrin et al., 2013; Asadi-Pooya and Hojabri, 2005; Osakwe et al., 2014).

The association of epilepsy with inbreeding has been poorly studied in developed countries probably because of the scarcity of family inbreeding in these populations (0.2% in the U.S., 0.8% in France, 1.1% in Italy and 0.2% in Australia) (Romeo et al., 1981; Port and Bittles, 2001). In the Arab world where first-degree consanguineous marriages represent more than 60% of all unions (Etude, 2007), the association to epilepsy has been suggested by some studies (Asadi-Pooya, 2005; Choueiri et al., 2001; Khedr et al., 2013; Benamer and Grosset, 2009; Bourrous et al., 2010) and refuted by others (Daoud et al., 2003; Cansu et al., 2007; Huseyinoglu et al., 2012; Yemadje et al., 2012).

In Algeria, where the prevalence of epilepsy is estimated at 8.32/1000 (Moualek et al., 2012) and the rate of inbreeding at 38% (18% in Oran) (Fondation, 2007), very few epidemiological studies on epilepsy have been published and none has evaluated the association with risk factors.

Given the important role attributed to inbreeding in the development of birth defects and genetically determined diseases such as hemoglobinopathies, hereditary hearing loss, G6PD deficiency, encephalopathies and schizophrenia (Dahdouh-Guermouche et al., 2013); and given also the heterogeneity of existing data, it seemed necessary to conduct an epidemiological survey based on two aims — assessing the relationship between epilepsy and inbreeding in those patients 16 years and older treated at the Neurology Department of Oran University Hospital; and identifying other risk factors associated with epilepsy in the same population.

Materials and methods

We conducted an analytical retrospective matched case—control study over six months — from October 1st, 2013 to March 31st, 2014.

Study population

We included 101 unrelated epileptic patients aged 16 years and over, presenting to the Neurology Department of Oran University Hospital (the main general Neurology clinic in this city) between October 1st, 2013 and March 31st, 2014. Patients having a history of febrile convulsions without epilepsy were not included in the study.

202 controls having no personal history of epilepsy, matched for age and sex, were selected among patients attending the same clinic during the same period but for another neurological disorder.

The number of subjects needed (2 controls per case) was calculated by the software BiostaTGV using a first order risk of 5%, a power of 80%, and taking as reference the lowest OR (2.11 found in an Indian study, Nair and Thomas, 2004) and the frequency of inbreeding in Oran (18% according to data from the National Foundation for the Promotion of Health and Development Research in 2007).

Data of cases and controls were obtained using a prepared and structured questionnaire conducted through personal interviews after an informed consent was signed.

Definitions

Epilepsy definition and seizure type description followed the criteria of the International League Against Epilepsy (Berg et al., 2005). Inbreeding was defined as a reproductive relationship between two individuals who share the same ancestor. The degree of consanguinity was determined by the total number of generations separating two individuals from their common ancestor (Dahdouh-Guermouche et al., 2013). A family history of epilepsy was considered positive if at least one family member (among first-, second- or third-degree relatives) was affected by epilepsy in addition to the proband. First-degree relatives comprise parents, siblings, and children; second-degree relatives comprise grandparents, grandchildren, aunts, uncles, nieces and nephews; and third-degree relatives comprise cousins. Febrile seizures were defined as seizures accompanied by fever (temperature $\geq$ 100.4 °F or 38 °C by any method) without CNS infection, that occurs in infants and children from 6 to 60 months of age (Subcommittee on Febrile Seizures and American Academy of Pediatrics, 2011). Head injury was considered severe if accompanied by loss of consciousness for more than 24 h, subdural hematoma or brain contusion

(Lowenstein, 2009). History of CNS infection was considered significant if meningitis or encephalitis was confirmed by lumbar puncture showing an inflammatory cellular response. The presence of perinatal insults was based on history of admission to a neonatal intensive care facility or respiratory distress at birth. Mental retardation (MR) was defined according to the classification system of the DSM IV TR by an intelligence quotient (IQ) less than 70, onset before age 18, and the existence of deficits or alterations in the functioning adaptive (Juhel, 1997).

Statistical analysis

The collected data were coded and entered into the SPSS 21.0 for Mac OS X. First, we conducted a descriptive analysis of cases involving the calculation of averages and standard deviations for quantitative variables and percentages for categorical variables. Univariate analysis (chi-square) was carried out to determine factors influencing the patient and control groups. The relative risk factors included in the univariate analysis were estimated by odds ratio (OR) and the 95% confidence interval (CI) calculated. Variables significant at the 5% nominal level were considered for multivariate analysis by logistic regression backward: conditional.

Results

A total of 303 individuals including 101 cases and 202 controls participated in the study. The M/F ratio in both case and control patients was 1.29. The mean age was 37 years and six months ± 14 years, ranging from 16 to 67 years. Thirty-eight subjects (9.2%) were under 20 years and twenty-three (7.6%) were older than 60 years. The rate of parental consanguinity was 36.6% in cases and 17.3% in controls.

The mean duration of follow-up in cases was 7 years and 4 months ± 4 years, with a minimum of two years and a maximum of 25 years. The medium age at seizure onset was 17 ± 9 years. Table 1 shows clinical characteristics of cases.

Table 1 Characteristics of 101 cases.

Characteristics of cases	*N* (%)
Type of seizures	
Generalized	52 (51.5)
Focal	45 (44.5)
Unclassified	3 (4.0)
Status epilepticus	8(7.9)
Syndromic classification	
Genetic	21 (20.9)
Familial temporal lobe epilepsy	10(9.9)
Progressive myoclonic epilepsy	3(3)
Juvenile myoclonic epilepsy	4(4)
Genetic epilepsy with febrile seizures plus	3(3)
Juvenile absence epilepsy	1(1)
Structural/metabolic	32(31.6)
Unknown	48 (47.5)
Seizure control	83(82.2)
Antiepileptic drug	
Valproic acid	32 (31.7)
Carbamazepin	24(23.7)
Levetiracetam	19(18.8)
Lamotrigin	9(8.9)
Polytherapy	17(16.8)

Univariate analysis

In univariate analysis, consanguinity, family history of epilepsy in first- and second-degree relatives, history of febrile seizures, antecedent of CNS infection, severe head trauma and mental retardation were found to be significantly associated with epilepsy (Table 2). Those factors were entered into multiple logistic regression models, with probability for entry of the variables fixed at 0.05 and that for removal at 0.10.

Multiple regression analysis

In the final multivariate model, first-degree consanguinity (2.15, 1.08—4.30, $P = 0.029$), history of epilepsy in first-degree relatives (4.03, 1.88—8.66, $P = 0.000$), antecedent of febrile seizures (5.38, 1.65—17.56, $P = 0.005$), mental retardation (9.32, 1.91—45.5, $P = 0.006$) and severe head trauma (2.94, 1.18—7.27, $P = 0.020$) emerged as strong independent risk factors of epilepsy (Table 3).

Discussion

The determination by a country of its own risk factors for epilepsy will make an important contribution to the fight against epilepsy. In this study, we caution that controls were not healthy individuals but patients with other neurological disorders such as Parkinson's disease, migraine, neuropathy and myasthenia.

The male-to-female ratio was 1.29. This male predominance is inline with previous reports (Attia-Romdhane et al., 1993; Al Rajeh et al., 2001).

Idiopathic epilepsies represent up to 47% of all epilepsies and they are assumed to have a strong genetic component, being monogenic or oligo/polygenic with different recurrence risks in the same family (Helbig et al., 2008). However, even in monogenic epilepsy, additional genes and non-genetic factors may modulate its expression, thus resulting in incomplete penetrance and variable phenotype. Previous twin studies have shown higher concordance in monozygotic than dizygotic pairs; and estimates of heritability vary between studies, with some estimates reaching 70% (Berkovic et al., 1998; Kjeldsen et al., 2003; Miller et al., 1998).

These data are consistent with the strong association we found with family history of epilepsy and further supported by previous research conducted in Iran (Asadi-Pooya and Hojabri, 2005), Jordan (Daoud et al., 2003), Tanzania (Matuja et al., 2001), Kenya (Mung'ala-Odera et al., 2008) and India (Nair and Thomas, 2004; Kannoth et al., 2009) which also highlighted this association. However, it is well known that epilepsy is a multifactorial disease, and we recognize that members of the same family may also share other non-genetic factors such as socio-economic status,

Table 2 Univariate analysis of the distribution of risk factors between controls and cases.

Variables with $P < 20\%$	OR	CI 95%	P
Gender			
Female	1		
Male	1.20		NS
Consanguinity			
No	1	–	
First-degree	2.71	[1.48–4.94]	0.001
Second-degree	2.93	[1.08–7.94]	0.034
Family history of epilepsy			
No	1	–	
First-degree relatives	5.37	[2.64–10.91]	0.000
Second-degree relatives	3.87	[1.27–7.39]	0.017
Third-degree relatives	1.77	[0.68–4.74]	NS
Perinatal insults			
No	1	–	
Yes	1.60	[0.58–4.42]	NS
Cerebrovascular diseases			
No	1	–	
Yes	1.18	[0.45–3.10]	NS
History of febrile seizures			
No	1	–	
Yes	4.81	[1.62–14.27]	0.005
CNS infection			
No	1	–	
Yes	5.21	[1.21–27.33]	0.051
Severe head trauma			
No	1	–	
Yes	2.56	[1.10–5.95]	0.028
Mental retardation			
No	1	–	
Yes	14.62	[3.23–66.20]	0.000
Neurological impairment			
No	1	–	
Yes	1.10	[0.53–2.25]	NS
Chronic alcoholism			
No	1	–	
Yes	0.28	[0.03–1.81]	NS
Illicit drug use			
No	1	–	
Yes	6.15	[0.63–59.91]	0.19

infectious diseases, malnutrition and consumption of alcohol or drugs (Birbeck et al., 2007; Noronha et al., 2007).

Earlier studies of the link between consanguinity and epilepsy have produced conflicting results. Asadi-Pooya (2005) reported that the risk of epilepsy was 2.2 times higher if parents were first cousins and 3.8 times higher if they were second cousins. Choueiri et al. (2001) compared the rate of inbreeding among patients with incidental seizures, patients with febrile seizures and patients with epilepsy. Inbreeding rates were respectively 0%, 4% and 19.5%. Another study by Ramasundrum and Tan, also found an increased risk of idiopathic and cryptogenic epilepsy in children born to consanguineous marriages (Ramasundrum and Tan, 2004). These results are in contrast with those of Daoud et al. (2003) who did not find a significant association. Differences in sampling methods, inclusion criteria and statistical analysis strategies might explain the different results found in those studies.

In our study, the higher rate of consanguineous marriages among cases (36.6%) vs controls (17.3%) may reflect the social stigma toward individuals with epilepsy in Algeria, making it more convenient to enter into intra-familial relationships.

Table 3 Results of multiple logistic regression analysis.

Variables with $P < 5\%$	Adjusted OR	CI 95%	P
Consanguinity			
No	1	–	
1st degree	2.15	[1.08–4.30]	0.029
2nd degree	2.31	[0.77–6.91]	NS
Family history of epilepsy			
No	1	–	
1st degree relatives	4.03	[1.88–8.66]	0.000
2nd degree relatives	2.90	[0.91–9.25]	NS
3rd degree relatives	1.20	[0.40–3.61]	NS
History of febrile seizures			
No	1	–	
Yes	5.38	[1.65–17.56]	0.005
Severe head trauma			
No	1	–	
Yes	2.94	[1.18–7.27]	0.020
Mental retardation			
No	1	–	
Yes	9.32	[1.91–45.5]	0.006

First-degree parental consanguinity seems to increase the risk of developing both monogenic and polygenic epilepsies by a factor of 2.15. There are several reasons why this variable should be expected to have a significant effect:

- First, some epileptic syndromes in our sample are probably monogenic and inherited as an autosomal recessive trait. Indeed, it is admitted that consanguineous unions increase the rate of homozygosity according to the principle of identical by descent (Woods et al., 2006).
- On the other hand, recent progress in genetic analysis revealed that only about 1–2% of genetic epilepsies seem to be monogenic, whereas most of them are believed to be polygenic, such as childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME), and epilepsy with generalized tonic–clonic seizures on awakening (Weber and Lerche, 2008; Steinlein, 2008; Lowenstein and Messing, 2007). Even in this forms of epilepsy, consanguinity has an important role. Indeed, during the last decade several studies have demonstrated the significant effect of inbreeding not only on single gene disorders but also on numerous polygenic and multifactorial traits (Rudan et al., 2006). Moreover, according to Bittles' explanations, consanguinity would be expected to exert a great influence on the etiology of complex diseases if rare autosomal recessive alleles are causally implicated (Bittles and Black, 2010).

History of febrile seizures increased five-fold the risk of developing epilepsy, which is consistent with results of previous studies (Daoud et al., 2003; Cansu et al., 2007). The strong association with febrile seizures does not reflect a causal relationship, but may mean that febrile seizures represent an early expression of a low seizure threshold in patients genetically predisposed to epilepsy. Indeed, febrile seizures can be the gateway to a numerous genetic epileptic syndromes such as Genetic Epilepsy with Febrile Seizures Plus (GEFS+) (Goldberg-Stern et al., 2014), epileptic syndrome by febrile infection (FIRES) (Moreno de Flagge, 2013), severe myoclonic epilepsy in infancy (Dravet syndrome) (Brunklaus and Zuberi, 2014) and temporal lobe epilepsy (McClelland et al., 2011; Abou-Khalil et al., 2007).

In this study, the strong positive association found between mental retardation and epilepsy ($P = 0.006$) confirms literature data. Several studies have reported an increased prevalence of epilepsy among subjects with MR compared to the general population with rates ranging from 14% to 44% (Bowley and Kerr, 2000). Other studies have shown an increased rate of MR in epileptic children compared to healthy children (Wakamoto et al., 2000; Camfield and Camfield, 2007). This may be explained by the existence of genetic factors contributing to vulnerability to both conditions simultaneously. Indeed, syndromic entities with monogenic forms of epilepsy and mental retardation are typical situations of this comorbidity (Carrascosa-Romero et al., 2012). Additionally, the cognitive decline observed in some epileptic patients could be a secondary consequence of anti-epileptic drugs, repeated injuries or anoxic episodes during status epilepticus (Abou-Khalil and Schmidt, 2012; Krsek et al., 2004).

The incidence of epilepsy after traumatic brain injury has been studied in both adults and children (Cansu et al., 2007). Generally these studies show an increased risk of epilepsy after severe head injury. Inline with these results, our study showed that subjects with a history of severe head trauma had a three times higher risk of developing epilepsy compared to their controls. Yemadje et al. (2012) found no significant association between head trauma and epilepsy. However, they defined head trauma as head injury after road accident or war, with or without coma and this broad definition may explain their results.

In contrast with results reported by previous studies (Daoud et al., 2003; Kannoth et al., 2009), we did not find significant association between epilepsy and perinatal complications. In our study 66.3% of cases and 68.3% of controls were born in a suitable private or public facility which could justify our results.

The concept of vascular epilepsy is not new. It was conceptualized by John Hughlings Jackson in 1864 and William Gowers in 1885, the latter having reported on 66 cases of what he called ''post-hemiplegic epilepsy''. Since the work of these pioneers, several epidemiological studies have shown that stroke was the leading cause of epilepsy beginning after the age of 60 years (Chen et al., 2012; Menon and Shorvon, 2009). Inline with the study of Ogunniyi et al. (1987) we have not found significant differences between the two groups with regard to cerebrovascular disease. We acknowledge though that the 60—67 years age group represented only 7.4% of our study population.

Yemadje and colleagues found a strong association between epilepsy and CNS infection but as pointed out by the author, Benin is an endemic area and the population is exposed to inappropriate self-medication (Yemadje et al., 2012). In our study, although the CNS infection was five times more frequent in cases than in controls, the association was not statistically significant. This is probably due to the fact that our study included all types of CNS infections whereas other studies supporting statistical significance excluded aseptic meningitis (Cansu et al., 2007).

We did not find an association between chronic alcoholism, illicit drug intake and epilepsy. We believe that the percentage of alcoholics and drug addicts among cases and controls is underestimated — the majority of patients will not admit consummation of these products since it remains a taboo subject within our society.

Contrary to previous reports (Cansu et al., 2007), we did not find any association between neurological deficit and epilepsy, probably because control patients were recruited at the Neurology Department where they were already being treated for a chronic disease.

The limitations of our study should be highlighted. This was a hospital-based study so the study population was not representative of general population. Nevertheless we believe the findings of this study will draw attention to the possible risk factors of epilepsy within our everyday clinical environment. The study was retrospective and was thus exposed to bias in data collection. Although we made several efforts to obtain complete patient details and verify the accuracy of this information against official records, such efforts were not entirely successful. For example, it was difficult to obtain birth history, particularly for elderly patients, more than a third of whom were born at home and had no document to confirm their statements. This exposed the study to recall bias. The study also lacks genetic analysis because of financial and technical impediments.

Conclusion

While this retrospective study has some limitations, it is the first report from Algeria studying the relationship between consanguinity and epilepsy. First-degree parental consanguinity, family history of epilepsy, history of febrile convulsions, severe head trauma and mental retardation were shown to have a statistically significant association with epilepsy in patients attending Oran University Hospital. Our results provide support for the interplay between genetic predisposition and acquired environmental factors in the pathogenesis of epilepsy. These findings deserve special attention and require the implementation of a strategy for prevention and awareness of the adverse consequences of inter family marriages. Increasing public literacy about consanguinity could be achieved by providing proper education and training to primary health care workers on all health and social issues related to inbreeding. Genetic counseling for couples with a family history of epilepsy is also necessary. We believe that further prospective investigations into the above clinical and genetic factors are bound to improve our understanding of the biological and clinical phenomenology associated with epilepsy. Based on these findings, we plan to establish a research program in order to identify susceptibility genes to epilepsy in consanguineous families where several individuals are affected. The identification of these genes could lead to a better understanding of epilepsy mechanisms.

Acknowledgments

We thank all the patients for their voluntary participation in the present study. We are grateful to Michael Sexton, Amel Chentouf, Farouk Mesli, Mohamed Bouziani and Adnane Abdelouahab for carefully reviewing the manuscript.

References

Abou-Khalil, B., Schmidt, D., 2012. Antiepileptic drugs: advantages and disadvantages. 1. Handb. Clin. Neurol. 108, 723—739.

Abou-Khalil, B., Krei, L., Lazenby, B., Harris, P.A., Haines, J.L., Hedera, P., 2007. Familial genetic predisposition, epilepsy localization and antecedent febrile seizures. Epilepsy Res. 73, 104—110.

Al Rajeh, S., Awada, A., Bademosi, O., Ogunniyi, A., 2001. The prevalence of epilepsy and other seizure disorders in an Arab population: a community-based study. Seizure 10, 410—414.

Asadi-Pooya, A.A., 2005. Epilepsy and consanguinity in Shiraz, Iran. Eur. J. Pediatr. Neurol. 9, 383—386.

Asadi-Pooya, A.A., Hojabri, K., 2005. Risk factors for childhood epilepsy: a case—control study. Epilepsy Behav. 6, 203—206.

Attia-Romdhane, N., Mrabet, A., Ben, H.M., 1993. Prevalence of epilepsy in Kelibia, Tunisia. Epilepsia 34, 1028—1032.

Benamer, H.T., Grosset, D.G., 2009. A systematic review of the epidemiology of epilepsy in Arab countries. Epilepsia 50 (10), 2301—2304.

Berg, A.T., Berkovic, S.F., Brodie, M.J., Buchhalter, J., Cross, H., van Emde Boas, W., et al., 2005—2009. Révision Terminologique et Conceptuelle de l'organisation des crises épileptiques et des épilepsies: Rapport de la Commission de ILAE sur la Classification et la Terminologie.

Berkovic, S.F., Howell, R.A., Hay, D.A., Hopper, J.L., 1998. Epilepsies in twins: genetics of the major epilepsy syndromes. Ann. Neurol. 43 (4), 435—445.

Birbeck, G., Chomba, E., Atadzhanov, M., Mbewe, E., Haworth, A., 2007. The social and economic impact of epilepsy in Zambia: a cross-sectional study. Lancet Neurol. 6 (1), 39—44.

Bittles, A.H., Black, M.L., 2010. Evolution in health and medicine Sackler colloquium: consanguinity, human evolution and

complex diseases. Proc. Natl. Acad. Sci. U. S. A. 107, 1779—1786.
Bourrous, M., Elibrahimi, I., Draiss, G., Safini, F., Amine, M., Bouskraoui, M., 2010. Caractéristiques des enfants ayant une épilepsie suivis au CHU de Marrakech. Rev. Neurol. 166, 921—926.
Bowley, C., Kerr, M., 2000. Epilepsy and intellectual disability — a review. J. Intell. Disabil. Res. 44, 1—15.
Brunklaus, A., Zuberi, S.M., 2014. Dravet syndrome — from epileptic encephalopathy to channelopathy. Epilepsie 55 (7), 979—984.
Camfield, C.S., Camfield, P.R., 2007. Preventable and unpreventable causes of childhood-onset epilepsy plus mental retardation. Pediatrics 120, 52—55.
Cansu, A., Serdaroğlu, A., Yüksel, D., Doğan, V., il Özkan, S., Hırfanoğlu, T., et al., 2007. Prevalence of some risk factors in children with epilepsy compared to their controls. Seizure 16, 338—344.
Carrascosa-Romero, M.C., Suela, J., Alfaro-Ponce, B., Cepillo-Boluda, A.J., 2012. X-chromosome-linked ichthyosis associated to epilepsy, hyperactivity, autism and mental retardation, due to the Xp22.31 microdeletion. Rev. Neurol. 54 (February (4)), 241—248.
Casetta, I., Monetti, V.C., Malagù, S., 2002. Risk factors for cryptogenic and idiopathic partial epilepsy: a community-based case—control study in Copparo, Italy. Neuroepidemiology 21, 251—254.
Chen, T.-C., Chen, Y.-Y., Cheng, P.-Y., Lai, C.-H., 2012. The incidence rate of post-stroke epilepsy: a 5-year follow-up study in Taiwan. Epilepsy Res. 102 (3), 188—194.
Choueiri, R.N., Fayad, M.N., Farah, A., Mikati, M.A., 2001. Classification of epilepsy syndromes and role of genetic factors. Pediatr. Neurol. 24 (1), 37—43.
Dahdouh-Guermouche, A., Taleb, M., Courtet, P., Semaoune, B., Malafosse, A., 2013. Consanguinité, schizophrénie et trouble bipolaire. Ann. médico-psychol. 171, 246—250.
Daoud, A.S., Batieha, A., Bashtawi, M., El-Shanti, H., 2003. Risk factors for childhood epilepsy: a case—control study from Irbid, Jordan. Seizure 12 (April (3)), 171—174.
Edwards, T., Scoot, A.G., Munyoki, G., 2008. Active convulsive epilepsy in a rural district of Kenya: a study of prevalence and possible risk factors. Lancet Neurol. 7, 50—56.
Etude de la consanguinité dans la population marocaine. Impact sur le profil de la santé., 2007. Antropo.
Fisher, R.S., Acevedo, C., Arzimanoglou, A., Bogacz, A., Cross, J.H., Elger, C.E., Engel Jr., J., Forsgren, L., French, J.A., Glynn, M., Hesdorffer, D.C., Lee, B.I., Mathern, G.W., Moshé, S.L., Perucca, E., Scheffer, I.E., Tomson, T., Watanabe, M., Wiebe, S., 2014. ILAE official report: a practical clinical definition of epilepsy. Epilepsia 55 (April (4)), 475—482.
Fondation Nationale pour la Promotion de la Santé et le Développement de la Recherche, 2007.
Goldberg-Stern, H., Aharoni, S., Afawi, Z., Bennett, O., Appenzeller, S., Pendziwiat, M., et al., 2014. Broad phenotypic heterogeneity due to a novel SCN1A mutation in a family with genetic epilepsy with febrile seizures plus. J. Child Neurol. 29 (February (2)), 221—226.
Guekht, A., Allen Hauser, W., Milchakova, L., Churillin, Y., Shpak, A., Gusev, E., 2010. The epidemiology of epilepsy in the Russian Federation. Epilepsy Res. 92, 209—218.
Hamamy, H., Antonarakis, S.E., Cavalli-Sforza, L.L., Temtamy, S., Romeo, G., Ten Kate, L.P., et al., 2011. Consanguineous marriages, pearls and perils: Geneva International Consanguinity Workshop Report. Genet. Med. 13 (September (9)), 841—847.
Helbig, I., Scheffer, I.E., Mulley, J.C., Berkovic, S.F., 2008. Navigating the channels and beyond: unravelling the genetics of the epilepsies. Lancet Neurol. 7 (March (3)), 231—245.
Huseyinoglu, N., Ozben, S., Arhan, E., Palanci, Y., Gunes, N., 2012. Prevalence and risk factors of epilepsy among school children in eastern Turkey. Pediatr. Neurol. 47, 13—18.
Juhel, J.-C., 1997. la déficience intellectuelle: connaître, comprendre, intervenir. Les Presses de l'Université Laval, pp. 395.
Kannoth, S., Unnikrishnan, J.P., Santhosh Kumar, T., Sarma, P.S., Radhakrishnan, K., 2009. Risk factors for epilepsy: a population-based case—control study in Kerala southern India. Epilepsy Behav. 16, 58—63.
Khedr, E.M., Shawky, O.A., Ahmed, M.A., Abo Elfetoh, N., Al Attar, G., Ali, A.M., et al., 2013. A community based epidemiological study of epilepsy in Assiut Governorate/Egypt. Epilepsy Res. 103, 294—302.
Kjeldsen, M.J., Corey, L.A., Christensen, K., Friis, M.L., 2003. Epileptic seizures and syndromes in twins: the importance of genetic factors. Epilepsy Res. 55 (June—July (1—2)), 137—146.
Krsek, P., Mikulecka, A., Druga, R., Kubova, H., Hlinak, S., Suchomelova, L., Mares, P., 2004. Long-term behavioural and morphological consequences of non-convulsive status epilepticus in rats. Epilepsy Behav. 5, 180—191.
Lowenstein, D.H., 2009. Epilepsy after head injury: an overview. Epilepsia 50, 4—9.
Lowenstein, D., Messing, R., 2007. Epilepsy genetics: yet more exciting news. Ann. Neurol. 62, 549—550.
Matuja, W.B., Kilonzo, G., Mbena, P., Mwango'mbola, R.L., Wong, P., Goodfellow, P., et al., 2001. Risk factors for epilepsy in a rural area in Tanzania. A community-based case—contrôl study. Neuroepidemiology 20 (4), 242—247.
McClelland, S., Dubé, C.M., Yang, J., Baram, T.Z., 2011. Epileptogenesis after prolonged febrile seizures: mechanisms, biomarkers and therapeutic opportunities. Neurosci. Lett. 497 (3), 155—162.
Menon, B., Shorvon, S.D., 2009. Ischaemic stroke in adults and epilepsy. Epilepsy Res. 87 (1), 1—11.
Miller, L.L., Pellock, J.M., De Lorenzo, R.J., Meyer, J.M., Corey, L.A., 1998. Univariate genetic analyses of epilepsy and seizures in a population-based twin study: the Virginia Twin Registry. Genet. Epidemiol. 15, 33—49.
Moreno de Flagge, N., 2013. Simple febrile seizure, complex seizure, generalized epilepsy with febrile seizure plus, FIRES and new syndromes. Medicina (B Aires) 73 (1), 63—70.
Moualek, D., Ali Pacha, L., Abrouk, S., Kediha, M.I., Nouioua, S., Ait Aissa, L., et al., 2012. Multicenter transversal two-phase study to determine a national prevalence of epilepsy in Algeria. Neuroepidemiology 39, 131—134.
Mung'ala-Odera, V., White, S., Meehan, R., et al., 2008. Prevalence, incidence and risk factors of epilepsy in older children in rural Kenya. Seizure 17, 396—404.
Nair, R.R., Thomas, S.V., 2004. Genetic liability to epilepsy in Kerala state, India. Epilepsy Res. 62, 157—164.
Noronha, A.L.A., Borges, M.A., Marques, L.H.N., Zanetta, D.M.T., Fernandes, P.T., de Boer, H., et al., 2007. Prevalence and pattern of epilepsy treatment in different socioeconomic classes in Brazil. Epilepsia 48 (5), 880—885.
Ogunniyi, A., Osuntokun, B.O., Bademosi, O., Adeuja, A.O.G., Schoenberg, B.S., 1987. Risk factors for epilepsy: case—control study in Nigerians. Epilepsia 28, 280—285.
Ogunrin, O.A., Ademola, A., Philomena, A., 2013. Etiologies of epilepsy and health-seeking itinerary of patients with epilepsy in a resource poor setting: analysis of 342 Nigerian Africans. Seizure 22, 572—576.
Osakwe, C., Otte, W.M., Chimhurumnanya, A., 2014. Epilepsy prevalence, potential causes and social beliefs in Ebonyi State and Benue State, Nigeria. Epilepsy Res. 108 (February (2)), 316—326.
Pi, X., Zhou, L., Cui, L., Liu, A., Zhang, J., Ma, Y., et al., 2014. Prevalence and clinical characteristics of active epilepsy in southern Han Chinese. Seizure 23 (September (8)), 636—640.

Port, K.E., Bittles, A.H., 2001. A population-based estimate of the prevalence of consanguineous marriage in Western Australia. Community Genet. 4, 97—101.

Ramasundrum, V., Tan, C.T., 2004. Consanguinity and risk of epilepsy. Neurol. Asia 9 (1), 10.

Rocca, W.A., Sharbrough, F.W., Hauser, W.A., Annegers, J.F., Schoenberg, B.S., 1987. Risk factors for absence seizures: a population-based case—control study in Rochester, Minnesota. Neurology 37, 1309—1314.

Romeo, G., Menozzi, P., Mastella, G., Giunta, A., Lodi, G., Constantini, D., et al., 1981. Studio genetico ed epidemiologico della fibrosi cistica in Italia. Riv. Ital. Pediatr. 7, 201—209.

Rudan, I., Campbell, H., Carothers, A.D., Hastie, N.D., Wright, A.F., 2006. Contribution of consanguinuity to polygenic and multifactorial diseases. Nat. Genet. 38, 1224—1225.

Sander, J.W., 2003. The epidemiology of epilepsy revisited. Curr. Opin. Neurol. 16, 165—170.

Steinlein, O.K., 2008. Genetics and epilepsy. Dialogues Clin. Neurosci. 10, 29—38.

Subcommittee on Febrile Seizures, American Academy of Pediatrics, 2011. Neurodiagnostic evaluation of the child with a simple febrile seizure. Pediatrics 127 (February (2)), 389—394.

Wakamoto, H., Nagao, H., Hayashi, M., Morimoto, T., 2000. Long-term medical, educational, and social prognoses of childhood-onset epilepsy: a population-based study in a rural district of Japan. Brain Dev. 22, 246—255.

Weber, Y.G., Lerche, H., 2008. Genetic mechanisms in idiopathic epilepsies. Dev. Med. Child Neurol. 50 (September (9)), 648—654.

Woods, C.G., Cox, J., Springell, K., Hampshire, D.J., Mohamed, M.D., McKibbin, M., 2006. Quantification of homozygosity in consanguineous individuals with autosomal recessive disease. Am. J. Hum. Genet. 78 (May (5)), 889—896.

World Health Organization, 2005. Atlas: Epilepsy Care in the World 2005. WHO Press, Geneva, pp. 11—13.

Yemadje, L.P., Houinato, D., Boumédiène, F., Ngoungou, E.B., Preux, P.M., Druet-Cabanac, M., 2012. Prevalence of epilepsy in the 15 years and older in Benin: a door-to-door nationwide survey. Epilepsy Res. 99, 318—326.