Consanguinity in patients with mesial temporal lobe epilepsy due to hippocampal sclerosis in a Saudi population

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ABSTRACT

Objectives: To investigate if there is an association between consanguinity and hippocampal sclerosis (HS) in the Saudi population.

Methods: A retrospective case-control study was conducted by assessing the prevalence of consanguinity in patients with pathologically proven HS, who underwent epilepsy surgery at King Faisal Specialist Hospital and Research Center, Jeddah, Saudi Arabia, between January 2004 and December 2015. We reviewed the medical records to extract data, which included: age, gender, duration of epilepsy, history of febrile seizure, family history of epilepsy in a first or second-degree relative, and pathology reports.

Results: A total of 120 patients, out of which 40 patients (65% male) having mesial temporal lobe epilepsy due to HS, and 80 controls (56% male) with cryptogenic epilepsy, were identified. Twenty-two patients (53.5%) in the HS group had a history of consanguinity. In the control group, 30 patients (37.5%) had a history of consanguinity. The odds ratio was 2.04 (95% confidence interval = 0.94 - 4.4, p=0.052). A family history of epilepsy was found in 28% of the patients with HS and 32.5% cryptogenic epilepsy. Only 8 patients (19.5%) with HS reported a history of febrile seizure.

Conclusions: Our retrospective case-control study suggests that consanguinity might increase the likelihood of developing HS.

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Consanguineous marriage, in clinical genetics, is defined as a union between couples related as second cousins or closer.1 Saudi Arabian culture has a higher consanguinity rate than other Arab, Asian, and Western communities. Consanguinity is not known to increase the risk of idiopathic or cryptogenic epilepsy, based on recent studies from Saudi Arabia and UAE.2,3

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However, there is a strong evidence that the marriage of first cousins is one of the main reasons for the increased prevalence of autosomal recessive diseases. The association between consanguinity and epilepsy due to hippocampal sclerosis (HS), the most common pathology found in patients with intractable focal epilepsy, has not been adequately studied. A familial type of mesial temporal lobe epilepsy (FMTLE) has been described with homogeneous and heterogeneous clinical manifestations. Moreover, magnetic resonance imaging (MRI) of the brain of asymptomatic first-degree relatives of patients with confirmed FMTLE showed evidence of HS, which supports the genetic predisposition to FMTLE. Although, FMTLE is widely recognized as an autosomal dominant disease with incomplete penetrance, autosomal recessive or X-linked forms have also been reported. Still, they have not been confirmed by extensive studies.

In this study, we aimed to investigate the association between consanguinity and HS in a Saudi population. This study may help expand our knowledge of the underlying mechanisms of HS and may shed some light on a possible genetic substrate that contributes to the development of HS in this population.

Methods. This retrospective case-control study aimed to explore the prevalence of consanguinity in patients with pathologically proven HS, who underwent temporal lobectomy between January 2004 and December 2015, at King Faisal Specialist Hospital and Research Center, Jeddah, Saudi Arabia.

Patients with cryptogenic epilepsy were used as a control group. The case ratio between the control group and the study group was 1:2. The institutional review board approved the study (IRB # 2015-60). Patients’ consent was waived due to the retrospective nature of the study.

Medical records of the patients were reviewed to extract data, and patients with incomplete data were contacted, and verbal consent was obtained for the missing data. Data collected included their age, gender, the onset of epilepsy and the duration, history of febrile seizure (FS), family history of epilepsy in a first or second-degree relative, neuroimaging findings, and pathology reports. We included all operated patients with messiah temporal lobe epilepsy (MTLE) due to pathologically-confirmed HS. Patients with symptomatic MTLE were excluded due to pathologies other than HS.

In the control group, we included patients who have had focal and generalized cryptogenic epilepsy consecutively, while patients with symptomatic or idiopathic epilepsy were excluded.

Patients with cryptogenic epilepsy were chosen as the control group because we aimed to investigate the potential genetic background of HS, we wanted to compare patients with HS to a control group with epilepsy that is not known to be of genetic or structural etiology. This requirement does not apply to symptomatic epilepsy because of the structural etiology nor does it apply to idiopathic epilepsy due to its probable genetic cause.

On the other hand, cryptogenic epilepsy was chosen as a control group because it possesses the characteristics of epilepsy of unknown etiology.

Statistical analysis was performed using SPSS version 16.0 for Windows (SPSS Inc., Chicago, IL, USA). The ratio of the case-control was 1:2. The odds ratio (OR) with a confidence interval (CI) was used for risk estimation of consanguinity in the 2 groups, using the chi-squared test. Fisher’s exact test was used to calculate the P-value (Table 1).

Table 1 - Chi-square and risk estimate.

| Patients with HS | Odds ratio- 95% CI | P-value |
|------------------|--------------------|---------|
| Consanguinity 1st and 2nd cousins | 2.037 (0.943 - 4.40) | 0.052 |
| First cousin | 1.400 (0.630 - 3.11) | 0.417 |
| Second cousin | 2.698 (0.840 - 8.66) | 0.117 |

HS: hippocampal sclerosis

Results. A total of 40 patients with MTLE due to HS (65% males) and 80 controls (56% males) with cryptogenic epilepsy were identified (Table 2). Twenty-two patients (55%) in the HS group had a history of consanguinity, with majority of the cases involving first cousins (68%). In the control group, 30 patients (37.5%) had a history of consanguinity, with 80% of the cases involving first cousins. The estimated chance of consanguinity occurrence in the HS group, in comparison with the control group, was statistically significant (OR, 2.04 [95% CI = 0.94-4.4], p=0.052).

A family history of epilepsy (first and second degree) was found in 11 (28%) patients with HS and 26 (32%)
patients with cryptogenic epilepsy. Eight (19.5%) patients in the HS group, and 9 (11%) patients in the control group had a history of FS.

Successful surgical outcome was seen in 65% of the patients with HS.

### Discussion.

This retrospective case-control study was conducted at one of the epilepsy centers in Saudi Arabia, to determine if consanguinity is associated with HS in patients with TLE. The ratio of the number of individuals in the HS group to those in the control group in this study was 1:2. This study suggests that parental consanguinity might have a positive association with HS. A review on focal drug-resistant epilepsy by a Moroccan group found that mesial temporal lobe syndrome is associated with a high frequency of febrile convulsions and parental consanguinity. However, their cohort included only 6 patients with parental consanguinity. The association between consanguinity and epilepsy was also investigated by Babtain et al., who observed a lack of association between first-degree consanguinity and the risk of developing epilepsy, in the southern region of Saudi Arabia. However, in this study, second-degree consanguinity increased the risk of developing epilepsy. The social stigma of epilepsy possibly contributes to the observed lack of association between epilepsy and first-degree consanguinity. It seems that due to unfortunate social stigma experienced by patients with epilepsy, people with epilepsy avoid getting married to first-degree relatives, and they also think of avoiding the “transmit” of the disease to their children should they indulge.

Thus, a second-degree marriage is quite common, as an alternative to first-degree in Saudi Arabia and considered “ideal way” by many families to avoid having children with genetically inherited disease. It is well known that a family history of epilepsy is strongly associated with epilepsy, which was also noted in this study. Khan et al. examined the association between parental consanguinity and family history with the risk of developing idiopathic epilepsy; 17% of the observed epilepsy cases were associated with a history of parental consanguinity, but consanguinity was also observed in 31% of the control group, which consists of non-epileptic cohort extracted randomly from the same hospital record. On the other hand, a family history of epilepsy was observed in 81% of the epilepsy cases, while it was found in only 17% of the controls. It is worthy of note that this study considered only 76 patients. It is also important to note that a family history of epilepsy seems to have a strong association with the risk of developing epilepsy in the 2 studies mentioned above. This observation was validated in this current study. In the same Saudi population, a relationship between parental consanguinity and presumed familial type of multiple sclerosis was reported by Jumah et al. Such findings and the ones from this study may contribute to the field by enhancing existing knowledge regarding the risk of developing such neurological disorders without known inheritance patterns or described association with parental consanguinity.

Our results suggested that consanguineous marriage could be a direct or indirect contributing factor in focal epilepsy due to HS.

Gambardella et al. reported 8 patients from Italy with autosomal dominant FMTLE, but with incomplete penetrance, all patients had controlled seizures on antiepileptic drugs. In another study on FMTLE, a benign pattern was also observed in patients with and without HS; the prevalence of refractory epilepsy in FMTLE is less than that in typical surgical MTLE. Moreover, varying degrees of HS was observed in asymptomatic family members of patients with FMTLE, suggesting that the hippocampal abnormalities could be inherited. The degree of HS severity on MRI alone was not directly related to seizure severity and the development of refractory epilepsy, which is rather due to the complexity of MTLE pathogenesis and its underlying multifactorial etiologies. These findings are replicated in other studies where detecting HS in MRI.

### Table 2 - Characteristics of 120 patients.

| Variables                      | HS group (n=40) | Control group (n=80) |
|--------------------------------|----------------|----------------------|
| **Gender**                     |                |                      |
| Male                           | 26             | 45                   |
| Female                         | 14             | 35                   |
| **Mean age at onset (range)**  | 11.5 years (1-36) | 13 years (1-50)      |
| **Mean age at diagnosis (range)** | 30 years (15-54) | 31 years (9-68)      |
| **Parental consanguinity**     |                |                      |
| First cousin                   | 22 (55.0)      | 30 (37.5)            |
| Second cousin                  | 15 (68.0)      | 24 (80.0)            |
| **History of febrile seizure** | 7 (32.0)       | 6 (20.0)             |
| **The family history of epilepsy** | 8 (19.5)     | 9 (11.0)             |
| **Seizure freedom**            | 11 (28.0)      | 26 (32.0)            |
| **Seizure freedom after epilepsy surgery in HS group and seizure control in patients with cryptogenic epilepsy at the time of conducting the study** | 26 (65.0) | 34 (42.5) |

HS: hippocampal sclerosis. Seizure freedom after epilepsy surgery in HS group and seizure control in patients with cryptogenic epilepsy at the time of conducting the study.
was found in many patients with benign MTLE.\textsuperscript{14,15} However, a recent prospective study on patients with mild MTLE associated with the presence of HS leads to the progression of benign to refractory MTLE that requires surgical intervention.\textsuperscript{16} Genetic etiology has been demonstrated by several types of focal epilepsy in adult patients. The genetic basis of autosomal dominant partial epilepsy with auditory features was described by Winawer et al.\textsuperscript{17} The predisposing gene is localized in the 10 cM regions on chromosome 10q24. Angelicheva et al\textsuperscript{18} examined the genetic basis of early-onset TLE syndrome in the Gypsy population. They identified an association between the syndrome and the loci 5q31.3-q32 and 10p12. These findings suggest that genetic susceptibility increases the likelihood of developing focal epilepsy. Our findings of linking consanguinity to HS, may emphasize the same notion.

On the contrary, Striano et al\textsuperscript{19} reported clinical and genetic findings from 15 Italian families with FMTLE. The clinical and genetic findings were heterogeneous and could be linked to the studied loci or mutations.

We also observed an association between the history of FS and HS, found in 19.5% of the HS group and 11% of the control group. It is important to point out that sodium channel mutations lead to a homogenous phenotype of FS that is associated with HS. Colosimo et al\textsuperscript{20} and Scheffer et al\textsuperscript{21} recently demonstrated these mutations (SCN1A or SCN1B). Colosimo et al\textsuperscript{20} illustrated that out of 13 affected family members, 2 exhibited HS. Both cases showed focal complex or nocturnal secondary generalized tonic-clonic seizures. Scheffer et al\textsuperscript{21} performed SCN1B analysis on 402 individuals, only one of whom exhibited HS. This favors the hypothesis of a common genetic basis for TLE and FS, with or without HS.

In this study, we found that 65% of the patients who underwent anterior mesial temporal lobe resection had an excellent surgical outcome and became seizure-free after the surgery.\textsuperscript{22} The rate of seizure freedom is similar to what is reported in the literature for this type of epilepsy surgery.\textsuperscript{33,24}

**Study limitations.** This study was conducted in only one tertiary epilepsy center. Hence, our sample size was relatively small. A larger sample size, with patients from multiple centers, may provide higher statistical credibility to the results.

In conclusion, this study demonstrates a potential association between consanguinity and HS, which is a contributing factor to this disorder. A more extensive national cohort study is needed to further confirm this association.

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