



Family Ties: Reproductive Decision Making Among Members of Multiplex Epilepsy Families

Epilepsy Currents
2021, Vol. 21(5) 344–345
© The Author(s) 2021
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/15357597211032047
journals.sagepub.com/home/epi
 SAGE

Keywords

familial epilepsy, epilepsy genetics, LGII, reproductive decision making, genetic attribution, epilepsy, pregnancy, inheritance

Reproductive Decision-Making In Families Containing Multiple Individuals With Epilepsy

Nakamura J, Sorge ST, Winawer MR, Phelan JC, Chung WK, Ottman R. *Epilepsia*. Epub Apr 4 2021. doi:10.1111/epi.16889

Objective: This study evaluated factors influencing reproductive decision-making in families containing multiple individuals with epilepsy. **Methods:** One hundred forty-nine adults with epilepsy and 149 adult biological relatives without epilepsy from families containing multiple affected individuals completed a self-administered questionnaire. Participants answered questions regarding their belief in a genetic cause of epilepsy (genetic attribution) and estimated risk of epilepsy in offspring of an affected person. Participants rated factors for their influence on their reproductive plans, with responses ranging from “much more likely” to “much less likely” to want to have a child. Those with epilepsy were asked, “Do you think you would have wanted more (or any) children if you had not had epilepsy?”. **Results:** Participants with epilepsy had fewer offspring than their unaffected relatives (mean = 1.2 vs 1.9, $P = .002$), and this difference persisted among persons who had been married. Estimates of risk of epilepsy in offspring of an affected parent were higher among participants with epilepsy than among relatives without epilepsy (mean = 27.2 vs 19.6, $P = .002$). Nineteen percent of participants with epilepsy responded that they would have wanted more children if they had not had epilepsy. Twenty-five percent of participants with epilepsy responded that “the chance of having a child with epilepsy” or “having epilepsy in your family” made them less likely to want to have a child. Having these genetic concerns was significantly associated with greater genetic attribution and estimated risk of epilepsy in offspring of an affected parent. **Significance:** People with epilepsy have fewer children than their biological relatives without epilepsy. Beliefs about genetic causes of epilepsy contribute to concerns and decisions to limit childbearing. These beliefs should be addressed in genetic counseling to ensure that true risks to offspring and reproductive options are well understood.

Commentary

When I began seeing women with epilepsy for pregnancy counseling, I thought I was fully prepared with an understanding of malformation rates, breastfeeding safety, and therapeutic drug monitoring. I was not prepared, however, for the frequent question “Is my child going to have epilepsy?” This is an important question for many prospective parents living with epilepsy. In the study that is the focus of this review, The Epilepsy Family Study at Columbia University (EFSCU) looked at how the perception of genetic risk influenced the decision to have children among members of multiplex epilepsy families.¹

The EFSCU has contributed greatly to our understanding of the epidemiology of epilepsy in families.² It has also led to the characterization of Autosomal Dominant Partial Epilepsy with Auditory Features (ADPEAF) and the discovery that pathogenic variants in LGII are responsible for this syndrome in about half of affected families.³ For the present study, the authors contacted 589 participants from the EFSCU and 49% responded. The results presented

were based on the survey responses of 298 participants from 94 different families with epilepsy. There were 149 survey respondents with epilepsy and 149 respondents who were biological relatives of PWE but did not have epilepsy themselves. Fifty-nine of the relatives were full siblings, whereas 90 (60%) were half-siblings or more distant relatives (aunts, uncles, cousins, nieces or nephews). Participants were recruited to the EFSCU between 1997 and 2006 and the survey was completed between 2013 and 2015. According to the authors, none of the survey respondents had definitive clinical genetic testing at the time of the survey. However, 20% of the families had a phenotype compatible with ADPEAF and 10.6% of the families had an LGII pathogenic variant identified through research genetic testing.

A principal finding of the study is that PWE reported having fewer children than did their unaffected relatives (1.2 vs 1.9, $P = .002$). The 2 groups were comparable in terms of age, sex, education, and marital status. Catholic religion did emerge as an important confounder in that it was associated with having more children and fewer PWE identified as Catholic. The authors



report that the difference was still significant when controlling for Catholic religion.

Among individuals with epilepsy, 25.9% indicated that the concern of a “chance of having a child with epilepsy” would make them “less likely to have a child.” In comparison, 18.6% of unaffected relatives that were not full siblings said the same, but only 11.1% of unaffected full-siblings indicated this concern would affect their reproductive decision making. Participants were also asked 2-3 questions about their belief that genetics contributed to epilepsy in their family and the likelihood that they themselves had a genetic mutation related to epilepsy. The answers to these questions determined their “genetic attribution” score. Across all participants, the genetic attribution score correlated with the likelihood that a “chance of having a child with epilepsy” would make them “less likely to have a child.”

Participants with epilepsy were also asked if they would have had more (or any) children if they had not had epilepsy themselves; 19% said “yes” to this question. However, for the roughly 1 in 5 PWE that indicated they would have had more children, this decision was not just about genetic risk. While PWE with an intermediate or high genetic attribution score were more likely to say “yes” to this question, the severity of a person’s epilepsy was also significantly associated with this decision. Twenty percent of participants indicated that the effect of epilepsy on their own ability to care for a child was a reason for having fewer children. Women with epilepsy (WWE) were much more likely than men to answer that they would have had more children had they not had epilepsy themselves (25.6% vs 9.7%, $P = .02$). The same survey also asked WWE separate questions about issues specific to epilepsy and 56% indicated that concerns about the effect of seizure medications and seizures on the fetal development was important in their reproductive decision making.

In summary, this study demonstrates that concerns about genetic risk can be one of several factors in complex reproductive decision making within multiplex epilepsy families. PWE are more likely to have these concerns than their unaffected family members and this may play a role in why these individuals have fewer children. As the authors themselves point out, one limitation of this study is that the majority of the participants were white, non-Hispanic and highly educated. This limits the generalizability of these findings to other individuals with epilepsy, other families, and other cultures. Further research into how epilepsy and genetic risk is perceived in other communities will be an important topic of future research. Additionally, this cohort may have represented families with milder epilepsy and fewer comorbidities (individuals with epilepsy had to be able to fill out the survey). The perception of epilepsy within a family with several high-functioning persons with well-controlled epilepsy (such as often in the case with LGII-related epilepsy) may be very different from that in a family with one or more members with epilepsy and associated intellectual disability or autism.

This is a study of patients with epilepsy in families with multiple affected individuals, thus it also may not be generalizable to PWE without any other affected family members. One might assume that an individual who is the only person in their family with epilepsy might rate their genetic risk as lower than those with multiplex families. However, this is sometimes not the case or a correct

assumption. A similar survey of PWE that did not focus on families with epilepsy, found comparable genetic attribution within a cohort of epilepsy clinic patients.⁴ In this study a higher percentage, 34%, of PWE indicated they would or would have had more children had they not had epilepsy. Concern about genetic risk to a child along with concerns about being able to care for a child were associated with the decision to have fewer children.

Counseling an individual with epilepsy about their risk of having a child with epilepsy is never a one-size-fits-all discussion. It requires careful attention to the possible etiologies of a patient’s epilepsy, their family history, and an understanding of related epidemiology and genetics. Addressing perceptions and stigma about epilepsy are also important. In the age of epilepsy genetic testing, it is tempting to think we can answer a patient’s questions about heritability with a genetic test. In some cases, identifying a pathogenic variant in an individual with epilepsy can help clarify the risk to offspring. It can certainly help answer this question for family members who test negative for the variant(s). In many cases, however, variable penetrance makes predictions difficult. Furthermore, genetic testing that does not reveal a cause for an individual’s epilepsy does not exclude a genetic etiology as many genetic causes of epilepsy have yet to be elucidated.

Compared to a generation ago, we have an increasing number of tools to assist in accurate counseling and prediction of an individual’s chances of having a child with epilepsy. This makes reproductive counseling both more complex and more individualized. Similarly, potential reproductive implications for the proband and family members need to be part of pre-test genetic counseling, even if the patient being tested is not considering having children at the time. Continued study of how individuals’ beliefs, values, culture, and perception of epilepsy affect their reproductive decision making will be important as we enter a new era of genetic medicine in epilepsy.

By Elizabeth E. Gerard 

ORCID iD

Elizabeth E. Gerard  <https://orcid.org/0000-0003-3062-8360>

References

1. Nakamura J, Sorge ST, Winawer MR, Phelan JC, Chung WK, Ottman R. Reproductive decision-making in families containing multiple individuals with epilepsy. *Epilepsia [online serial]*. Epub 2021 Apr 4. Accessed at: <https://onlinelibrary.wiley.com/doi/10.1111/epi.16889>.
2. Winawer MR, Rabinowitz D, Barker-Cummings C, et al. Evidence for distinct genetic influences on generalized and localization-related epilepsy. *Epilepsia [online serial]*. 2003;44:1176–1182. Accessed at: <http://www.ncbi.nlm.nih.gov/pubmed/1626268>.
3. Ottman R, Winawer MR, Kalachikov S, et al. LGII mutations in autosomal dominant partial epilepsy with auditory features. *Neurology*. 2004;62:1120–1126.
4. Helbig KL, Bernhardt BA, Conway LJ, Valverde KD, Helbig I, Sperling MR. Genetic risk perception and reproductive decision making among people with epilepsy. *Epilepsia*. 2010;51:1874–1877.