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Clinical risk factors in SUDEP

A nationwide population-based case-control study

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Study objective and summary result

This study tested the hypothesis that specific clinical characteristics are associated with increased risks of sudden unexplained death in epilepsy (SUDEP). The results indicated that experiencing generalized tonic-clonic seizures (GTCS) and living alone are risk factors for SUDEP.

What is known and what this paper adds

Past studies have identified factors such as GTCS and lack of nighttime supervision as risk factors for SUDEP, but these past studies had serious methodologic shortcomings. This investigation provides further evidence for GTCS and lack of nighttime supervision being risk factors for SUDEP.

Participants and setting

The investigators accessed the Swedish National Patient Register (SNPR) to obtain data from 255 individuals who died of probable or definite SUDEP between July 2006 and December 2011. For each SUDEP case, the investigators randomly selected 5 same-sex patients with epilepsy who were alive on the decedant's date of death.

Design, size, and duration

The study data were obtained from the SNPR and medical records. These data included the patients' living conditions and various demographic and clinical variables. Conditional logistic regression models were used to identify risk factors for SUDEP, and attributable proportion calculations were used to analyze potential interactions between risk factors.

Primary outcome measures

The primary outcomes were the risk factors for SUDEP.

Main results and the role of chance

The risk factors for SUDEP included experiencing GTCS within the previous year (odds ratio [OR], 26.81; 95% confidence interval [CI], 14.86–48.38), experiencing nocturnal GTCS within the previous year (OR, 15.31; 95% CI, 9.57–24.47), and living alone (OR, 5.01; 95% CI, 2.93–8.57). Experiencing GTCS and not sharing a bedroom was strongly associated with SUDEP (OR, 67.10; 95% CI, 29.66–151.88).

Table Associations between GTCS frequencies and the risk of SUDEP

No. of GTCS events in the previous 12 months	OR (95% CI) for SUDEP
0	Reference condition
1–3	22.14 (12.74–38.46)
4–10	31.87 (15.95–63.67)
>10	29.70 (15.04–58.63)

Bias, confounding, and other reasons for caution

The personnel who extracted data from medical records were not blinded to outcomes.

Generalizability to other populations

The present study's focus on Sweden may limit the generalizability of the results.

Study funding/potential competing interests

This study was funded by Stockholm County Council, GlaxoSmithKline, and Citizens United for Research in Epilepsy. Some authors report receiving personal fees and honoraria from healthcare companies; receiving research support from Uppsala County Council, the European Union, various foundations, and healthcare companies; and serving as an associate editor for *Epileptic Disorders*. Go to Neurology.org/N for full disclosures.

A draft of the short-form article was written by M. Dalefield, a writer with Editage, a division of Cactus Communications. The corresponding author(s) of the full-length article and the journal editors edited and approved the final version.

Disputes & Debates: Editors' Choice

Steven Galetta, MD, FAAN, Section Editor

Editors' note: Menarche, pregnancies, and breastfeeding do not modify long-term prognosis in multiple sclerosis

In the article, "Menarche, pregnancies, and breastfeeding do not modify long-term prognosis in multiple sclerosis," Zuluaga et al. reported that age at menarche, pregnancy before or after the diagnosis of clinically isolated syndrome (CIS), and breastfeeding did not substantially modify the risk of progressing to clinically definite multiple sclerosis (CDMS) or disability accrual per the Expanded Disability Status Scale (EDSS) in a cohort of 501 female participants with CIS. In response, Drs. Jokubaitis and Dobson argued that the patients with CDMS should be examined separately for the EDSS outcomes because a substantial proportion of the overall cohort did not have a second clinical attack and did not meet either the McDonald 2010 or Barkhof criteria for MS. They seek additional details regarding the propensity score–matched score analysis because a smaller number of matched pairs could limit the generalizability of the results. In addition, they noted that the analyses for the association of pregnancy and breastfeeding on time to EDSS 3.0 were not adjusted for relapse and that the differences between exclusive breastfeeding and mixed feeding strategies merit further exploration in prospective studies. They also argue that the harmful effects of suspending disease-modifying treatments (DMTs) in those with aggressive disease who become pregnant should be considered. Responding to these comments, Drs. Tintoré et al. noted that they built the model for time to EDSS 3.0 over the CDMS subcohort, in addition to providing further details of the propensity score–matched analyses. They reported additional analyses for the adjusted hazard ratio for pregnancy (but not for breastfeeding) on considering the annualized relapse rate over the first 3 and 5 years of disease and acknowledged that additional details of breastfeeding were unavailable. Regarding the problem of suspending DMTs in pregnant patients, they noted that they are analyzing a subgroup of women treated with natalizumab or fingolimod. As greater numbers of young women become eligible for DMTs with more inclusive revisions of the McDonald criteria, neurologists are likely to encounter challenging questions about the association of pregnancies and breastfeeding with MS disease activity, and the attendant DMT-related dilemmas, in their practice.

Aravind Ganesh, MD, DPhil, and Steven Galetta, MD
Neurology® 2020;94:455. doi:10.1212/WNL.0000000000009064

Reader response: Menarche, pregnancies, and breastfeeding do not modify long-term prognosis in multiple sclerosis

Vilija G. Jokubaitis (Melbourne) and Ruth Dobson (London)
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We read with interest the article by Zuluaga et al.,[1] which used the uniquely valuable Barcelona CIS (clinically isolated syndrome) cohort.[2] However, evolving multiple sclerosis (MS) diagnostic and treatment landscapes must be taken into account when using this cohort to inform current practice.

Of those included in the analysis,[1] 47% did not have a second clinical attack, 39% did not meet the McDonald 2010 criteria, and 32% did not meet the Barkhof criteria for the diagnosis of MS. This

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raises questions about cohort baseline heterogeneity because 2 of the primary outcome measures are confirmed Expanded Disability Status Scale (EDSS) 3.0 or 6.0. There is an argument in favor of examining the clinically definite multiple sclerosis (CDMS) cohort separately to the non-CDMS cohort.

Regarding the propensity score-matched analyses, we are interested to know the matching strategy used, how many matched pairs were included in this analysis, the matching ratio, the median follow-up duration, and censoring strategy. Only 142 respondents had pregnancies after a CIS[1]; it is thus possible that fewer than 142 matched pairs were included, limiting the generalizability of these results.

It appears that the analyses of the impact of pregnancy and breastfeeding on time to EDSS 3.0 were not adjusted for relapse. Relapse, particularly early in the disease phase, and relapse recovery are among the strongest predictors of future disability accumulation.[3,4]

Breastfeeding was studied as both a dichotomous variable (breastfeeding vs not) and a time-dependent event.[1] However, exclusive breastfeeding may be protective in a way that mixed feeding is not.[5] A truly prospective design is required to address the subtleties of this question.

The authors concluded that MS prognosis is not significantly affected by pregnancy once all other variables are considered.[1] However, in the current era of highly active disease-modifying treatment (DMT) use, pregnancy does not occur in isolation. The potentially harmful effects of suspending DMT in those with aggressive disease must be taken into account when discussing family planning in MS. We look forward to future studies to help answer the questions that this study raises, which is of prime importance to women with MS.

1. Zuluaga MI, Otero-Romero S, Rovira A, et al. Menarche, pregnancies, and breastfeeding do not modify long-term prognosis in multiple sclerosis. Neurology 2019;92:e1507–e1516.
2. Tintore M, Rovira À, Río J, et al. Defining high, medium and low impact prognostic factors for developing multiple sclerosis. Brain 2015; 138:1863–1874.
3. Bermel RA, You X, Foulds P, et al. Predictors of long-term outcome in multiple sclerosis patients treated with interferon β. Ann Neurol 2013;73:95–103.
4. Jokubaitis VG, Spelman T, Kalincik T, et al. Predictors of long-term disability accrual in relapse-onset multiple sclerosis. Ann Neurol 2016;80:89–100.
5. Hellwig K, Rockhoff M, Herbstritt S, et al. Exclusive breastfeeding and the effect on postpartum multiple sclerosis relapses. JAMA Neurol 2015;72:1132–1138.

Author response: Menarche, pregnancies, and breastfeeding do not modify long-term prognosis in multiple sclerosis

Mar Tintoré (Barcelona, Spain), Santiago Perez-Hoyos (Barcelona, Spain), and Susana Otero-Romero (Barcelona, Spain)

Neurology® 2020;94:456–457. doi:10.1212/WNL.0000000000009065

We thank Drs. Jokubaitis and Dobson for the comment on our article.[1]

We built the model for the time to Expanded Disability Status Scale (EDSS) 3.0 over the clinically definite multiple sclerosis (CDMS) subcohort. The adjusted hazard ratio (aHR [CI 95%]) associated to pregnancy is aHR = 1.26, CI 95% (0.62, 2.59).

Regarding the propensity score–matched analyses, we decided to perform inverse probability (IP) weighting to create the new pseudocohort to minimize the association between covariates and pregnancy status. Thus, no matching was performed, but we assigned IP weights to each of the patients in the cohort. The probability of being pregnant at any time, given the set of

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covariates, was estimated via a logistic regression adjusted for age at clinically isolated syndrome (CIS), topography of the CIS, oligoclonal bands (OB), number of T2 baseline lesions, treatment status (as time dependent), number of T2 lesions at first year, and CDMS (as time dependent).

We totally agree with the issue noted about not adjusting for relapse in the analyses of impact of pregnancy and breastfeeding on time to EDSS 3.0. Incorporating relapses in the adjusted model is key to predict disability. The adjusted hazard ratio for pregnancy, considering the annualized relapse rate over the first 3 years of disease, is aHR = 1.15, CI 95% (0.56, 2.36). When computing the annualized relapse rate within the first 5 years of disease, we obtain an aHR = 1.45, CI 95% (0.70, 3.02). A further step that we are exploring for this analysis is to include relapses as a time-varying event with the aim of approaching in a more realistic way the dynamic nature of the disease. We also agree that future research must focus on more precise modalities of breastfeeding, such as mixed or exclusive breastfeeding. Unfortunately, this information was missing in our study.[1]

In the era of high-efficacy drugs, suspending disease-modifying treatments may be harmful for patients with aggressive multiple sclerosis. To answer the questions our study raised, we are in the process of independently analyzing a subgroup of pregnant women treated with natalizumab or fingolimod.

1. Zuluaga MI, Otero-Romero S, Rovira A, et al. Menarche, pregnancies, and breastfeeding do not modify long-term prognosis in multiple sclerosis. Neurology 2019;92:e1507–e1516.

Editors' note: Teaching NeuroImages: A rare case of Jacobsen syndrome with global diffuse hypomyelination of brain

In the article "Teaching NeuroImages: A rare case of Jacobsen syndrome with global diffuse hypomyelination of brain," Patel et al. presented MRI fluid-attenuated inversion recovery (FLAIR) images at 18 months and 3 years of age in a boy with Jacobsen syndrome due to an 11q23-11q24 deletion. The images showed improvement in white matter abnormalities, which were termed hypomyelination by the authors. In response, Wolf et al. argued that hypomyelination is a permanent myelin deficit and is associated with a less hyperintense T2 white matter signal than is seen in this patient. They noted that the patient's deletion encompasses HEPACAM, a gene for which haploinsufficiency is associated with leukodystrophy that improves with time. They noted that the case is representative of limitations in extant classifications of leukodystrophies as either hypomyelinating or demyelinating. Responding to these comments, Patel et al. agreed that HEPACAM loss of function may account for some of the imaging abnormalities in Jacobsen syndrome but noted that macrocephaly and cysts (classical findings with HEPACAM mutations) are not typically seen in this syndrome. They noted that the original neuroradiologist interpretation termed the findings as global diffuse hypomyelination. This exchange highlights current uncertainties in the terminology surrounding the white matter abnormalities, particularly in the pediatric population.

Aravind Ganesh, MD, DPhil, and Steven Galetta, MD
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Reader response: Teaching NeuroImages: A rare case of Jacobsen syndrome with global diffuse hypomyelination of brain

Nicole I. Wolf (Amsterdam) and Marjo S. van der Knaap (Amsterdam)
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With interest we read the report by Patel et al.[1] concerning a patient with Jacobsen syndrome due to an 11q23–11q24 deletion and MRI evidence for leukodystrophy with improvement at a follow-up, substantiated by FLAIR images. The authors claimed that these abnormalities represent hypomyelination. Hypomyelination is defined as a significant and permanent myelin deficit.[2] Its MRI appearance is characterized by a diffusely hyperintense T2 white matter (WM) signal, which is less high than the signal in other leukodystrophies[2,3] and certainly less high than the WM signal in the patient discussed here,[1] who has strongly T2-hyperintense WM signal abnormalities.

The chromosomal deletion encompasses *HEPACAM*. Heterozygous and biallelic mutations in this gene cause megalencephalic leukodystrophy with subcortical cysts (MLC), a vacuolating leukodystrophy with macrocephaly. In dominant *HEPACAM* mutations, the leukodystrophy improves over time.[4] In Jacobsen syndrome, *HEPACAM* haploinsufficiency was earlier assumed to cause leukodystrophy.[5]

Why did the authors classify their case as hypomyelination? Many neurologists still categorize leukodystrophies in hypomyelinating and demyelinating disorders.[3] Perhaps the MRI improvement, not compatible with a demyelinating (progressive) disorder, prompted them to label this leukodystrophy hypomyelination? This case nicely illustrated that not all leukodystrophies are progressive and that there are more leukodystrophy categories beyond hypomyelination and demyelination.[3]

1. Patel H, Kumar A, Raymond G, Mainali G. Teaching NeuroImages: a rare case of Jacobsen syndrome with global diffuse hypomyelination of brain. Neurology 2019;92:e1665–e1666.
2. Pouwels PJ, Vanderver A, Bernard G, et al. Hypomyelinating leukodystrophies: translational research progress and prospects. Ann Neurol 2014;76:5–19.
3. van der Knaap MS, Schiffmann R, Mochel F, Wolf NI. Diagnosis, prognosis and treatment of the leukodystrophies. Lancet Neurol 2019;18:962–972.
4. van der Knaap MS, Boor I, Estévez R. Megalencephalic leukoencephalopathy with subcortical cysts: chronic white matter oedema due to a defect in brain ion and water homoeostasis. Lancet Neurol 2012;11:973–985.
5. Yamamoto T, Shimada S, Shimojima K, et al. Leukoencephalopathy associated with 11q24 deletion involving the gene encoding hepatic and glial cell adhesion molecule in two patients. Eur J Med Genet 2015;58:492–496.

Author response: Teaching NeuroImages: A rare case of Jacobsen syndrome with global diffuse hypomyelination of brain

Himadri Patel (Hershey, PA), Ashutosh Kumar (Hershey, PA), Gerald Raymond (Hershey, PA), and Gayatra Mainali (Hershey, PA)
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We thank Drs. Wolfe and Van der Knaap for their insightful comment, on our Teaching NeuroImages study,[1] and clarification of their precise definition of hypomyelinating disorders. We agree that HEPACAM loss of function may account for some of the issue in imaging in Jacobsen syndrome, but it does not appear to be the entire explanation, given the lack of macrocephaly or cysts in most patients reported. Regarding the hypomyelination classification, this was derived from the original radiology report, interpreted

Author disclosures are available upon request (journal@neurology.org).

by the neuroradiologist, as a global diffuse hypomyelination with mild diffuse brain atrophy. Further longitudinal studies would certainly be of interest.

1. Patel H, Kumar A, Raymond G, Mainali G. Teaching NeuroImages: a rare case of Jacobsen syndrome with global diffuse hypomyelination of brain. Neurology 2019;92:e1665–e1666.

CORRECTIONS

Clinical and neural responses to cognitive behavioral therapy for functional tremor

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In the article "Clinical and neural responses to cognitive behavioral therapy for functional tremor" by Espay et al.,[1] the full author's name should have appeared throughout as W. Curt LaFrance, Jr. The authors regret the error.

Reference

1. Espay AJ, Ries S, Maloney T, et al. Clinical and neural responses to cognitive behavioral therapy for functional tremor. Neurology 2019;93:e1787–e1798.

Clinical risk factors in SUDEP

A nationwide population-based case-control study

Neurology® 2020;94:459. doi:10.1212/WNL.0000000000009154

In the article "Clinical risk factors in SUDEP: A nationwide population-based case-control study" by Sveinsson et al.,[1] the bottom box in figure 1 should read "n = 255" and the fifth box down on the right should read "Controls." The editorial staff regret the errors.

Reference

1. Sveinsson O, Andersson T, Mattsson P, Carlsson S, Tomson T. Clinical risk factors in SUDEP: a nationwide population-based case-control study. Neurology 2020;94:e419–e429.

Genetic determinants of disease severity in the myotonic dystrophy type 1 OPTIMISTIC cohort

Neurology® 2020;94:459. doi:10.1212/WNL.0000000000008715

In the article "Genetic determinants of disease severity in the myotonic dystrophy type 1 OPTIMISTIC cohort" by Cumming et al.,[1] the study funding section should have read "Study funded by European Union's Seventh Framework Programme (FP7/2007–2013) under grant agreement number 305697 (the OPTIMISTIC project), the Wellcome Centre for Mitochondrial Research (ref 203105/Z/16/Z)), and donations to the DGM group from the Myotonic Dystrophy Support Group. The funders had no role in the study design, data collection, analysis, interpretation of data, writing the report, or decisions regarding when to submit publications." The authors regret the error.

Reference

1. Cumming SA, Jimenez-Moreno C, Okkersen K, et al. Genetic determinants of disease severity in the myotonic dystrophy type 1 OPTIMISTIC cohort. Neurology 2019;93:e995–e1009.

Author disclosures are available upon request (journal@neurology.org).