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Co-occurrence of major depression or suicide attempt with migraine with aura and risk for unprovoked seizure

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Abstract

We hypothesized and found that the co-occurrence of migraine with aura (MA) with major depression (MD) or with suicide attempt (SA) increases the risk for developing unprovoked seizure more than these conditions alone. Number of conditions showed a linear relationship to seizure risk. This may reflect a new condition cluster defined by MA, MD, SA and unprovoked seizures. Identifying the biological underpinnings this cluster may affect clinical diagnosis and treatment.

Keywords

Unprovoked seizure; epilepsy; depression; migraine; case-control study

1.1 Introduction

Epilepsy is associated with major depression, suicide, suicide attempt, and migraine. Major depression (Hesdorffer, Hauser et al. 2000;Hesdorffer, Hauser et al. 2005), suicide attempt (Hesdorffer, Hauser et al. 2005) and migraine, particularly migraine with aura (MA) (Ludvigsson, Hesdorffer et al. 2006) have each been associated with an increased risk for developing epilepsy. Completed suicide (Rafnsson, Olafsson et al. 2001) is known to occur more than expected in people with epilepsy. Likewise, the relationship between MA and depression (Breslau, Schultz et al. 2000) is bidirectional and suicide attempt (Breslau, Schultz et al. 2000) is associated with prevalent MA. Combined, these associations suggest a common underlying genetic or acquired brain dysfunction.

The potential for a common brain dysfunction underlying each of these associations suggests the hypothesis that the risk for developing epilepsy is greater in people with a history of both

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MA and depression or both MA and suicide attempt than in those with only one of these disorders. Additionally, a dose-response relationship might exist between the number of risk factors and risk for seizures.

1.2 Methods

Our methods have been described in detail elsewhere (Hesdorffer, Hauser et al. 2005;Ludvigsson, Hesdorffer et al. 2006). Briefly, a nationwide surveillance system (Hesdorffer, Hauser et al. 2005;Ludvigsson, Hesdorffer et al. 2006) was established in Iceland to identify individuals with first unprovoked seizure and newly diagnosed epilepsy between December 1, 1995 and February 28, 1999. Informed consent was obtained over the telephone from the subject or, in the case of a minor, from the parent. This report is limited to cases and controls aged 10 years and older.

1.2.1 Cases—Once a potential case was identified, the occurrence of an incident seizure disorder was verified from medical records. Unprovoked seizure was defined as a seizure without an identified proximate precipitant, e.g., fever, head trauma, central nervous system infection (1993). Epilepsy was defined as at least two unprovoked seizures regardless of seizure type. Cases in this analysis included any subject, aged 10 years or older (81.2% participation).

1.2.2 Controls—Age-matched controls were selected from the population registry as the next two same sex births (excluding siblings of the case), who were alive, resided in Iceland at the time of the index seizure, and had no history of unprovoked seizure before the date of the case's incident seizure (the index date). As with cases, controls were restricted to those 10 years of age or older (79.6% participation).

Measures and Assessments

1.2.3 Psychiatric Assessment—A structured telephone interview was administered to make a DSM-IV diagnosis of major depression occurring prior to the date of the cases' incident unprovoked seizure or epilepsy. We used Icelandic translations of both the lifetime module of the Diagnostic Interview Schedule for Children version four (Shaffer, Fisher et al. 2000) and a standardized interview based on the Structured Clinical Interview for DSM (First MB 1999). Only major depression prior to the first unprovoked seizure was considered; cases and controls were coded as not having major depression if age at major depression onset was concurrent with first unprovoked seizure (N=4 cases) or with age at the index date (N=7 controls). Past suicide attempt was categorized as present or absent based upon the question in the standardized psychiatric instruments.

1.2.4 Migraine Assessment—The diagnosis of migraine headache was derived from a structured interview (2004). We considered recurrent migrainous headache, rather than a minimum of 5 episodes, based upon a probable migraine cohort, which showed that only 0.7% otherwise fulfilling migraine criteria experienced less than 5 episodes (Patel, Bigal et al. 2004). Visual symptoms (zigzag lines, heat waves, blurry vision or loss of vision), the most common aura (2004), were the only symptoms we explored for MA. Cases without visual symptoms were classified as migraine without aura (MO).

1.2.5 Alcohol intake—Alcohol intake, a potential confounder for the relationship between suicide attempt and unprovoked seizure, is associated both with completed suicide and with epilepsy. Frequency and amount of alcohol intake by decade was used to calculate cumulative alcohol intake antecedent to the episode of suicide attempt or the index date for those individuals reporting no suicide attempt.

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1.2.6 Neurological Assessment—Three study neurologists (WAH, PL, EO) reviewed all information, including results of neuroimaging and electroencephalography, to classify cases by seizure type and etiology (1993).

1.2.7 IRB—The study was reviewed and approved by the Icelandic Data Protection Commission (Tolvunefnd rikisins), the Ethics committee of the Chief Medical Officer of Iceland, the Medical Ethics Board of the National University Hospital of Iceland (Landspitalinn), the Institutional Review Board at Columbia University, and the Review Board of the National Institutes of Health (OPRR).

1.2.8 Statistical analysis—Student's t-test compared continuous variables and the chi-squared statistic compared categorical variables; only two-tailed tests were performed. Data were analyzed with SAS (SAS Institute, Inc., Cary, NC) using conditional logistic regression for matched sets, adjusting for the matching variables, age and gender. We evaluated whether the increased risk of unprovoked seizure observed with major depression differed according to the presence or absence of MA; and likewise whether unprovoked seizure risk differed with suicide attempt and MA. We also examined whether the number of conditions was associated with increased risk for seizures.

1.3 Results

Three hundred twenty-four cases and 647 controls were 10 years of age or older and half were male (median age for cases was 34.0 years and 33.5 years for controls). Most cases were identified at their epilepsy diagnosis (57.7%). Partial-onset seizures occurred in 36.4% of cases and most had unknown etiology. Major depression mainly occurred in the absence of migraine (59.0% in cases, 70.8% in controls) as did suicide attempt (52.4% in cases, 66.7% in controls). MA accounted for 71.4% of migraine in cases and 46.7% in controls (p=0.005).

Among controls, the lifetime prevalence of MA was 7.6% and the lifetime prevalence of depression was 7.4%. In accordance with prior studies (9), major depression was 2.1-fold more common in controls with MA than in those without MA (14.3% vs. 6.9%, p=0.06). MA, major depression and suicide attempt together occurred in 6 cases and 2 controls.

1.3.1 Major depression and MA

The risk for developing an unprovoked seizure was increased more in the presence of both MA and major depression, then in the presence of either condition alone (Table 1). The pattern of results was similar in subanalyses of children, adults, females, generalized seizures, and seizures of unknown cause (data not shown).

1.3.2 Suicide attempt and MA

The risk for developing an unprovoked seizure was increased most in the presence of both MA and suicide attempt, and was greater than the increased risk associated with suicide attempt alone or with MA alone. Adjustment for cumulative alcohol intake and major depression did not change the results. A similar pattern was seen in subanalyses conducted in adults and in children, although few suicide attempts occurred in children.

1.3.3 Number of conditions

Three conditions considered were major depression, suicide attempt and MA. The risk of an unprovoked seizure was increased 2.0-fold with any one condition (95% CI=1.4-3.0), 4.9-fold with any two conditions (95% CI=1.7-13.9), and 6.7 with all three conditions (95% CI=1.3-33.4). The test for linear trend was statistically significant.

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1.3.4 Associations in cases and in controls

Further analyses were conducted separately in cases and in controls to examine the association between depression and/or suicide attempt and MA. Depression and/or suicide attempt was associated with a non-significant 2.1-fold increase in MA among controls (95% CI=0.9-5.1) and with a significant 3.3-fold increase in MA for cases (95% CI=1.7-6.5).

1.4 Discussion

We found that the co-occurrence of major depression and MA increased the risk of unprovoked seizure by more than the risk associated with either major depression or MA alone. Similar finding were seen for suicide attempt and MA, even after adjustment for major depression and alcohol consumption. The apparent dose-response relationship between the degree of underlying brain dysfunction indexed by the joint occurrence of one or more than one of these conditions is compatible with the inference that combinations of major depression, suicidality, MA and seizure constitute a cluster of conditions not hitherto described. It is possible also that the manifest relations between these conditions reflect a causal pathway where one brain dysfunction (e.g., manifested by major depression) engenders other brain dysfunctions (e.g, manifested by MA and unprovoked seizure).

The population-based design, the standardized diagnoses of major depression and MA, and the high participation rates in cases and controls give credence to our results. Moreover, data from other population studies on the lifetime prevalence of MA, major depression, and suicide attempt support the validity of this information reported in our controls (Russell, Rasmussen et al. 1996;Weissman, Bland et al. 1996;Weissman, Bland et al. 1999).

We considered several potential weaknesses of our study. A tendency of subjects to report symptoms is an unlikely explanation for our findings, since the association was specific for MA and not for MO (results not shown). Interviewer bias is also unlikely since interviewers were unaware both of our hypotheses and of the diagnostic criteria for the conditions studied. Misclassification of MA as seizures or vice-versa was unlikely: most cases were under the care of one of the co-authors (EO, PL) who excluded this possibility.

Further work is needed to elucidate whether the associations reported in the current study is due a common antecedent factor such as a channelopathy or a polymorphism in genes associated with serotonin or norepinephrine. Identification of factors underlying these associations may have profound implications for clinical diagnosis and treatment of these common conditions.

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Table 1

Association between migraine with aura, major depression, suicide attempt and incident unprovoked seizures in Icelandic children and adults aged 10 years and over

	N (%) Cases (N =324)	N (%) Controls (N =647)	Adjusted OR (95% CI)
MA and major depression			
MA without major depression	45 (13.9%)	42 (6.5%)	2.5 (1.6-3.9)
Major depression without MA	24 (7.4%)	41 (6.3%)	1. 4 (0.8-2.4)
MA and major depression	15 (4.60%)	7 (1.1%)	4.6 (1.9-11.4)
Neither MA or depression	240 (74.1%)	557 (86.1%)	1.0 (Referent)
MA and suicide attempt			
MA without suicide attempt	51 (15.7%)	47 (7.3%)	2.4 (1.5-3.9)
Suicide attempt without MA	12 (3.7%)	7 (1.1%)	4.7 (1.7-13.0)
MA and suicide attempt	9 (2.8%)	2 (0.3%)	7.9 (1.7-37.3)
Neither MA or suicide attempt	252 (77.8%)	591 (91.3%)	1.0 (Referent)

MA: Migraine with aura

OR: Odds ratio

95% CI: 95% confidence interval