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GENETICS

Clinical and Genetic Risk Factors for Suicide under the Influence of Alcohol in a Polish Sample

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Abstract — Aims: Despite the large number of suicides that occur with intoxication, little is known about the unique predictors of suicide after alcohol consumption. The goal of this study was to examine clinical and genetic risk factors for alcohol-related suicide. **Methods:** Data on 162 suicide victims were obtained from post-mortem examinations, police and prosecution inquiries, autopsy protocols and available medical records. Four single nucleotide polymorphisms in the central serotonin system and the renin–angiotensin system related genes previously found to be associated with suicide, alcohol dependence or depression were genotyped. **Results:** The strongest predictor of suicide under the influence of alcohol was alcohol dependence (OR = 4.63). Those who did not drink alcohol before suicide were more likely to have a diagnosis of major depressive disorder in their medical record and more often had the TT genotype of the tryptophan hydroxylase 2 gene. **Conclusions:** Suicide under the influence of alcohol is strongly connected with alcohol dependence. The *TPH2* gene may play an important role in suicide vulnerability especially in individuals who did not drink alcohol before suicide.

INTRODUCTION

Worldwide, suicide is a major public health problem accounting for almost one million deaths annually (World Health Organization, 1996; US Department of Health and Human Services, 2000). Over the past 5 years, the world annual rate of suicide has remained relatively stable at approximately 16 deaths per 100,000—a rate higher than is currently seen in the United States of 10.8 deaths per 100,000 (National Center for Injury Prevention and Control, 2008). The suicide rates in Poland dramatically increased during the last 50 years: from 5.7 per 100,000 in 1955 to 15.8 in 2005 (World Health Organization, 2007). The rate among males in Poland is much higher than that among females (27.8/100,000 versus 4.8/100,000, respectively), which is comparable with gender suicide ratios worldwide: 3:1 to 7.5:1 (World Health Organization, 2007; Komenda Glowna Policji, 2008).

Alcohol use is consistently linked to greater risk of suicidal thoughts, non-fatal suicide attempts and suicide mortality. For example, when comparing across countries, a strong association exists between per capita alcohol consumption and suicide mortality (Ramstedt, 2001). Additionally, alcohol dependence is one of the most significant risk factors for suicide. Estimates of lifetime risk of suicide in those with alcohol dependence indicate that anywhere from 4.2 to 15% (Harris and Barraclough, 1997; Inskip *et al*., 1998) of those with alcohol dependence will ultimately die by suicide. Postmortem studies show that 20–35% of those who died by suicide had alcohol use disorders (Conwell *et al*., 1996; Pirkola *et al*., 2000). Individuals with alcohol dependence have a 60–120 times higher suicide risk than the non-psychiatry ill population (Sher, 2006).

Consistent with the data on alcohol dependence, alcohol use at the time of suicide is common. Among all suicide victims, a high proportion (10–54%) have a positive blood alcohol concentration (BAC) at the time of death (Bilban and Skibin, 2005; Centers for Disease Control and Prevention, 2006). For example, a study performed on a Polish sample revealed that, among suicide attempters, 30% had positive BACs, whereas only 6% were alcohol dependent (Kołaciński *et al*., 1997).

Although many suicides occur under the influence of alcohol, the unique risk factors for suicide after alcohol consumption are poorly understood and likely include a broad set of risk factors in addition to a diagnosis of alcohol dependence. Beyond the psychosocial risk factors that are typically linked to higher levels of alcohol use (previous suicidal behaviors, mood disorders and other psychiatric comorbidities) (Brady, 2006), it is also important to examine unique genetic characteristics that might be linked to suicide while intoxicated.

A number of prior genetic studies have demonstrated that suicidal behaviors are genetically transmitted independent from other psychiatric disorders (Mann, 2003). Central serotonin system dysfunction, in particular, seems to play an important role in this vulnerability (Mann *et al*., 1996; Corrêa *et al*., 2000). Serotonin-related genes are also associated with alcohol dependence and affective disorders (Parsian and Cloninger, 2001; Zill *et al*., 2004a; Lazary *et al*., 2008). Additional research has linked increased risk of suicide with the hypothalamic–pituitary–adrenal axis (Mann, 2003) and the renin–angiotensin system dysregulation (Hishimoto *et al*., 2006; Saavedra *et al*., 2006). It is possible that these factors, known for moderating stress response, may be particularly important in increasing suicide risk during periods of intoxication when other compensatory strategies may be impaired. To the best of our knowledge, prior work has not directly examined the link between specific genetic factors and the unique risk of suicide while intoxicated.

The aim of this study was to examine the clinical and genetic risk factors for alcohol-related suicide. We hypothesized that genetic markers of dysfunction in these biological systems could be specifically related to suicide under the influence of alcohol. The genes of interest were tryptophan hydroxylase-1 gene (*TPH1*) (Parsian and Cloninger, 2001; Bellivier *et al*., 2004), tryptophan hydroxylase-2 gene (*TPH2*) (Lopez de Lara

et al., 2007), serotonin transporter gene (*SLC6A4*) (Mann *et al.*, 2000; Lazary *et al.*, 2008) and angiotensyn-converting enzyme gene (*ACE*) (Baghai *et al.*, 2002; Hishimoto *et al.*, 2006; Fudalej *et al.*, 2009). These were selected because of their previously established relationship with vulnerability to suicide, alcohol dependence and/or affective disorders.

MATERIALS AND METHODS

Subjects

This study was based on a sample of 162 Caucasian suicide victims recruited in the Department of Forensic Medicine at the Medical University of Warsaw. Suicide victims represent all suicides autopsied from April 2005 to October 2006 with sufficient quality DNA available. Only cases with confirmed suicide as a cause of death by police and prosecutor's inquiries and post-mortem examinations were included. Signs of decomposition that made genotyping impossible were also exclusion criteria. In this study, only one individual was excluded due to decomposition of genetic material. ICD-10 criteria were used to classify suicides. The resulting sample consisted of 114 male subjects (70.4%) and 48 female subjects (29.6%), with an average age of 43.0 ± 16.52. Almost all of the sample (97.5%) had committed violent suicide: hanging (71.6%), jumping from height (14.1%), penetrating lesions (4.9%), shooting (3.7%), and lying under a train (3.1%). Only four persons died after drug intoxication (2.5%). Additionally, coexisting serious somatic diseases and alcohol or other psychoactive substances presence in the blood were examined. BACs greater than zero were considered to be positive. For the purposes of conducting sensitivity analyses, urine samples were also examined.

Prior medical records, when available, were searched to identify a lifetime history of psychiatric disorders and previous suicide behaviors. In the present study, over 30% (33.3%, $n = 54$) of suicide victims had previously undergone psychiatric treatment. The most common diagnoses were: alcohol dependence ($n = 28$), major depressive disorder ($n = 17$), personality disorders ($n = 8$), anxiety disorders ($n = 8$) drug dependence ($n = 4$), schizophrenia ($n = 2$) and dementia ($n = 2$). Depressive symptoms that occurred only during periods of heavy drinking among alcohol-dependent individuals ($n = 10$) or depressive episodes that, according to the medical records, should be considered as alcohol induced ($n = 3$) were not analyzed as a major depression.

To perform DNA analyses, blood samples were taken from the suicide victims. This study was approved by the Ethics Committee of the Medical University of Warsaw.

Genotyping

Genomic DNA was isolated from peripheral blood leukocytes by proteinase K digestion followed by organic extraction from blood samples. The selected intron 7 polymorphism A218C of *TPH1* gene (Nielsen *et al.*, 1997) and the intron 8 polymorphism (rs1386483) of *TPH 2* (Walitza *et al.*, 2005) were genotyped by the PCR-RFLP (polymerase chain reaction–restriction fragment length polymorphism) method. The following primers were designed for the *TPH1* polymorphism: (5′→3′): ATT AAA TAA ATT AGC ACA TGT GAA GCA TCT (forward); (5′→3′): TTT CCC CCA CTG GAA TAC AA (reverse) and for the *TPH2* polymorphism: (5′→3′): TGT AGC TGG CTC TGA ACG TGT ATT TTG CA (forward); (5′→3′): TGA ATT AGG AAA ATC AGC CAA AGG CAC A (reverse).

The *ACE I/D* polymorphism was genotyped using the modified method of Odawara *et al.* (1997) as described previously (Fudalej *et al.*, 2009). Briefly, DNA was amplified by PCR with two *I/D* flanking primers: sense primer (5′→3′) CTG GAG AGC CAC TCC CAT CCT TTC T and antisense primer (5′→3′) GAT GTG GCC ATC ACA TTC GTC AGA T generating fragments of 192 bp and 479 bp in the presence of the *D* and *I* allele, respectively. In order to control for a mistyping of the ID as DD genotype, all DD samples were re-genotyped using a second PCR with insertion-specific primers: sense primer (5′→3′) TGG GAC CAC AGC GCC CGC CAC TAC and antisense primer (5′→3′) TCG CCA GCC CTC CCA TGC CCA TAA.

The 44 bp insertion/deletion polymorphism in the promoter region of serotonin transporter gene (serotonin-transporter-linked polymorphic region; 5-HTTLPR) (Mann *et al.*, 2000) was amplified by PCR using primers: (5′→3′): GGC GTT GCC GCT CTG AAT GC (forward); (5′→3′): GAG GGA CTG AGC TGG ACA ACC AC-3 (reverse).

Detailed information on PCR conditions can be obtained on request. All PCR products were separated by electrophoresis in 2% agarose gels and visualized with ethidium bromide.

Statistics

All analyses were performed using SPSS 15.0 for Windows. Differences between suicide victims with positive and negative BACs at the time of death were examined using chi-square tests or Fisher's exact tests for categorical variables and two-sample *t*-tests for continuous variables.

Genotyping results were tested for the Hardy–Weinberg equilibrium. A series of analyses were conducted in order to determine whether the selected polymorphisms in the four genes were associated with suicide under the influence of alcohol. The analysis of the model of inheritance was conducted using logistic regression. We considered three models of inheritence according to all of the chosen polymorphisms: recessive, codominant and dominant. Fit of these models was analyzed by calculating $\Delta L = 2(L_f - L_m)$ where L_f and L_m are $-\log$ likelihood of the full genotype model and a given model, respectively. The ΔL statistics has a χ^2 distribution with one degree of freedom (Hosmer *et al.*, 1997).

Finally, we completed a multivariable logistic regression to assess the predictors of suicide under the influence of alcohol. This model included those clinical and genetic variables that were previously found to be significantly associated with alcohol-positive suicide.

RESULTS

Almost 40% (39.5%, $n = 64$) of all suicide victims died while intoxicated: 43% ($n = 49$) of men and 31.3% ($n = 15$) of women. The average BAC in this group was 0.17 g/dL ± 0.09 and did not differ between genders.

When comparing the two groups of suicide victims with a positive or negative BAC at the time of death, we did not find any significant differences with regard to age, sex, prior suicide

Table 1. Characteristic of suicide victims

Characteristics: *n* (%)	All subjects ($n = 162$)	Alcohol negative $n = 98$ (60.5)	Alcohol positive $n = 64$ (39.5)	χ^2 or t	P
Gender (male)	114 (70.4)	65 (66.35)	49 (76.6)	1.94	0.16
Age at death in years, mean (standard deviation)	43 ± 16.5	44 ± 17.8	42 ± 13.9	0.50	0.62
Any prior suicide attempt(s)	17 (10.5)	11 (11.2)	6 (9.7)	0.14	0.71
Any prior self-injuries	30 (19.2)	14 (14.9)	16 (25.8)	2.86	0.91
Any serious somatic disease	60 (37.0)	32 (32.7)	28 (43.9)	2.04	0.15
Any prior history of major depression	17 (10.5)	15 (15.3)	2 (3.1)	6.12	0.013
Any prior history of alcohol dependence	28 (17.3)	9 (9.2)	19 (29.7)	11.38	0.001
Method of suicide					
Hanging	116 (71.6)	67 (68.4)	49 (76.6)	1.28	0.25
Jumping from a height	23 (14.2)	15 (15.3)	8 (12.5)	0.25	0.62
Others	23 (14.2)	16 (16.3)	7 (10.9)	0.93	0.34

Table 2. Genotype frequencies among analyzed polymorphisms in relationship to the alcohol blood concentration when committing suicide

Genetic Marker *n* (%)	All subjects $n = 162$	Alcohol negative $n = 98$ (60.5)	Alcohol positive $n = 64$ (39.5)
TPH1			
AA	30 (20.8)	20 (23.5)	10 (16.9)
AC	62 (43.0)	30 (35.3)	32 (54.2)
CC	52 (36.2)	35 (41.2)	17 (28.9)
TPH2[a]			
TT	25 (17.5)	20 (23.0)	5 (8.9)
CT	67 (46.8)	35 (40.2)	32 (57.1)
CC	51 (35.7)	32 (36.8)	19 (34.0)
SLC6A4			
SS	28 (19.3)	20 (23.0)	8 (13.8)
SL	57 (39.3)	35 (40.2)	22 (38.0)
LL	60 (41.4)	32 (36.8)	28 (48.2)
ACE			
II	43 (28.7)	25 (27.8)	18 (30.0)
ID	77 (51.3)	49 (54.4)	28 (46.7)
DD	30 (20.0)	16 (17.8)	14 (23.3)

[a] $\chi^2 = 5.04$; $P = 0.025$; OR = 0.33, 95%CI (0.12; 0.93).

attempts, self-injuries, evidence of serious somatic diseases and method of suicide (see Table 1). However, those who committed suicide after alcohol consumption were more likely to suffer from alcohol dependence (OR = 4.18; 95%CI: 1.75–9.97; $\chi^2 = 11.38$; $P = 0.001$) and less likely to have a history of major depressive disorder (OR = 0.18; 95%CI: 0.04–0.81; $\chi^2 = 6.12$; $P = 0.013$).

The genotype distributions of all selected polymorphisms were in agreement with the Hardy–Weinberg equilibrium. No significant differences in genotype distributions between alcohol-positive and -negative suicide victims groups were detected when analyzing *TPH1*, *SLC6A4* and *ACE* gene polymorphisms (Table 2). However, we found an association between the selected polymorphism (rs1386483) of *TPH2* and alcohol-related suicide phenotype under the recessive model of inheritence, which had the best fit ($\chi^2 = 1.31$, $P = 0.25$). The TT genotype was less likely to occur among those who drank alcohol before they died ($\chi^2 = 5.04$, $P = 0.025$, OR = 0.33, 95%CI: 0.12–0.93) than in the group of suicide victims without alcohol present in their blood.

A logistic regression was performed to assess the predictors of suicide under the influence of alcohol. Only variables that were previously found to be associated with this subtype of suicide behavior were included in this model. The overall model was statistically significant ($\chi^2 = 18.44$, $P < 0.0001$). The strongest predictor of suicide under the influence of alcohol was alcohol dependence, recording OR = 4.63 (95%CI: 1.65–12.93, $P = 0.004$). Even after controlling for a diagnosis of alcohol dependence and depression, those who had the TT genotype were almost four times less likely to commit suicide after alcohol consumption (OR = 0.27, 95%CI: 0.09–0.83, $P = 0.022$).

DISCUSSION

Suicide under the influence of alcohol was common (39.5%) in individuals autopsied in the Department of Forensic Medicine at the Medical University of Warsaw from April 2005 to October 2006. This finding is consistent with previously reported worldwide rates of alcohol use at the time of suicide (Bilban and Skibin, 2005; Binczycka-Anholcer, 2006). According to the WHO, 20% of suicides in the world occur while individuals are intoxicated (World Health Organization, 2002). Police statistics in Poland reveal a similar percentage (22.2%) of alcohol-positive suicides (Komenda Glowna Policji, 2008). However, this previously published rate may underestimate the true number of individuals intoxicated at the time of suicide because not all suicide victims in Poland are examined for BACs. When autopsies are carried out in Forensic Departments, such as was done in the present study, all individuals are tested for BACs. Other researchers from a number of European countries who recruited samples from Forensic Departments reported overall rates of alcohol-positive suicides that were broadly similar to our findings (Ohberg *et al*., 1996; Crombie *et al*., 1998; Bilban and Skibin, 2005; Binczycka-Anholcer, 2006). These findings indicate that clinicians should pay close attention to suicidal thoughts and attempts that occur while being intoxicated and should be aware of the elevated risk for suicide in those who misuse alcohol.

One consistent finding across all studies of alcohol use and suicide is that men are more likely to have a positive BAC at the time of death than women. In the present study, the rates of alcohol-positive suicides were 43% in men and 31.3% in women. The rate of alcohol-positive suicide in women in the present sample is somewhat higher than the rates reported in Finland (19.6%) (Ohberg *et al*., 1996) and Slovenia (18.3%) (Bilban and Skibin, 2005), and slightly lower than the rate found in Scotland (37%) (Crombie *et al*., 1998). In a similar Polish sample, Binczycka-Anholcer (2006) found that 47.5% of men and 36.0% of women who committed suicide had a positive

BAC at the time of death. These consistent gender differences in rates of positive BACs at the time of death by suicide may be due to several different factors. First, this finding may simply reflect the fact that alcohol use disorders are more common in men than women. Additionally, some other mechanism (such as differential levels of impulsivity) could explain why acute intoxication is particularly problematic in terms of suicide risk in men as compared to women.

Binczycka-Anholcer (2006) also reported that, among women, the range of BAC was between 0.15 g/dL and 0.20 g/dL. The average BAC in our sample was also relatively high and did not differ between genders. Thus, the typical individual with alcohol-positive suicide in this sample was intoxicated at a rate over eight times the legal limit for operating a motor vehicle in Poland.

The primary aim of this study was to describe the risk factors associated with suicide under the influence of alcohol. Among the available clinical characteristics, only alcohol dependence and major depression were correlated with suicide while intoxicated. It is not surprising that alcohol dependence in our sample was related to increased probability of suicide after alcohol consumption. Alcohol-dependent individuals especially during a heavy drinking episode with possible alcohol-induced depressive syndromes are at increased risk for suicide.

Additionally, it was found that a history of major depression was associated with a lower likelihood of suicide following alcohol use. This finding is generally consistent with prior reports of a lower prevalence of psychiatric disorders (excluding alcohol dependence) in those who died by suicide under the influence of alcohol (Hayward *et al*., 1992; Hakko *et al*., 2005). Similarly, Preuss and colleges (Preuss *et al*., 2002) in a large naturalistic study of alcohol-dependent individuals reported that those with independent major depressive episodes were less likely to report alcohol consumption at the time of a suicide attempt than those with alcohol-induced depressive symptoms.

Thus, although both alcohol dependence and depression are risk factors for suicide (Harris and Barraclough, 1997; Inskip *et al*., 1998), they may be associated with different patterns of suicidal behaviors. For example, suicide in those with major depression may follow a longer period of suicidal ideation and planning for the suicide attempt. In the case of alcohol-related suicides, these may be more likely to be impulsive, poorly planned acts. This is consistent with James's (James, 1966) thesis that cognitive and emotional changes connected with alcohol consumption may lead to impulsive suicide. Similarly, Simon *et al*. (2001) found that alcohol use was more common prior to an impulsive suicide attempt (i.e., those that occur with less than 30 min of planning) although differences did not reach statistical significance. In the same study, depression was significantly less likely to have been diagnosed in those who made an impulsive attempt. Others have found that alcohol-dependent individuals are more likely to report impulsive suicide attempts (Modesto-Lowe *et al*., 2006; Zouk *et al*., 2006). More work is needed to better understand the association between pre-existing psychopathology, acute alcohol intoxication and suicide mortality. The most informative design would be the longitudinal study with more standardized measures of psychopathology, independent and alcohol-induced mood disorders, and suicidal thoughts and behaviors.

The present study makes the unique contribution of examining potential genetic characteristics associated with suicide after alcohol consumption. To analyze genetic predisposition to suicide under the influence of alcohol, we genotyped four polymorphism in four genes, which were reported as associated with vulnerability to suicide, alcohol dependence and/or depression. Among the genetic markers examined, only the *TPH2* polymorphism was significantly associated with alcohol-related suicide phenotype. The TT genotype was more frequent in the sober group of suicide victims. This genotype remained significantly associated with the lower likelihood of suicide under the influence of alcohol in a multivariable logistic regression model. This finding is broadly consistent with emerging research on the potential role of the central serotonin system in suicide vulnerability and suggests that this genetic predisposition may be stronger in those who are not intoxicated at the time of suicide.

Tryptophan hydroxylaze (TPH) is the rate-limiting enzyme of serotonin synthesis in the brain. The THP2 is a recently discovered, neuronal specific isoform of TPH that may play an important role in the regulation of central serotonin system activity. Research on the *TPH2* gene has found a link between *TPH2* and vulnerability to suicide (Zill *et al*., 2004b; Ke *et al*., 2006), depression (Zill *et al*., 2004a) and other mental disorders influenced by the central serotonin system dysfunction. As was mentioned above, those who did not drink before committing suicide were more likely to be previously diagnosed as depressed and more often had the TT genotype. This is consistent with the hypothesis that genetic variation in *TPH2* may lead to central serotonin system dysfunction causing vulnerability to suicide, especially among depressed individuals. We hypothesize that this particular genetic polymorphism in *TPH2* (rs1386483) is related to serotonin system dysfunction, which is consistent with previous findings on this polymorphism (Stoltenberg *et al*., 2006).

Those with a history of depression may have been more determined to die by suicide and less likely to make an impulsive suicide attempt. Many studies of the association between certain genetic factors and suicide combine both alcohol-related and non-alcohol-related suicides into a single outcome. The inclusion of both alcohol-related and non-alcohol-related suicides in a single analysis of genetic influences on suicide risk may decrease the potential to detect the impact of indicators of poor serotonin function on suicide. Future research on risk factors for suicide may want to separate out those with and without alcohol intoxication for a more precise indicator of specific suicide risk.

LIMITATIONS

There are several limitations to this study. First, the study sample was relatively small- the study had power of 0.8 do detect genotype differences associated with an OR higher than 2.5 or lower than 0.25. Thus, we cannot exclude that effect(s) of some other tested gene(s) may have been missed in our analysis. Psychiatric diagnoses were not available for all of the suicide victims. Also, the extent to which individuals met criteria for different psychiatric conditions at the time of suicide is unknown. Diagnoses were based on prior treatment records and some participants were not seen by treatment providers for

psychiatric reasons prior to suicide. This limitation can likely lead to an under-diagnosis of prior psychopathology and may have diminished our ability to detect the strength of association between different conditions and suicide under the influence of alcohol. Additionally, although efforts were made to avoid classifying alcohol-induced depression as a separate depressive disorder, this process was difficult due to the study design. It is likely that some individuals may have been misclassified as having major depressive disorder. This project focused on only four polymorphisms in four specific genes. A broader examination of additional genetic factors would likely identify other genetic characteristics associated with alcohol-related suicide. Further studies are needed to explore and better understand the risk factors for suicide after alcohol consumption.

CONCLUSIONS

To the best of our knowledge, this is the first study to analyze clinical and genetic risk factors for suicide in individuals under the influence of alcohol. On the basis of the findings presented here we can confirm that alcohol dependence is the strongest predictor for this behavior. Additionally, suicide after alcohol consumption is *less* likely to occur in those with prior depression and with the TT genotype in the *TPH2* gene polymorphism (rs1386483). We hypothesize that the TT genotype may lead to the central serotonin system dysfunction that can influence the predisposition to suicide with no preceding alcohol intoxication, especially among depressed individuals.

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