Treatises on psychiatric disorders as risk factors of somatic disorders and risk factors of suicide

Thesis

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Introduction

Epidemiological evidences suggest a frequent comorbidity between mood- and cardiovascular disorders (CVD). A bidirectional association between mood disorders and CVD has been proven. Namely, mood disorders pose a risk for the development of CVD (in addition their presence is associated with an unfavourable outcome of established CVD). On the other side, the pravelence of major (and minor) depression among patients after major CV events is much more higher than the corresponding prevalence rate in the general population. Numerous investigations about the possible etiological background of the frequent comorbidity between mood- and cardiovascular disorders have been conducted to date. One part of the investigations have focused on the mechanisms behind the mood disorder → CVD association, while others have dealt with the mechanisms behind the CVD → mood disorder association. A third direction of investigations supposed the existence of a common (e.g. genetic) root for the two conditions. Although, several theories have been proposed to explain the amplified risk of cardiovascular disease in patients with depression (i.e. decreased heart rate variability and baroreceptor sensitivity in depression; the role of hemoconcentration and platelet hyperactivity or overactivity of the HPA-axis in depression etc.) the exact biological mechanisms by which depression may increase the risk of cardiovascular events have not been completely elucidated so far. In addition, we can not exlude the possibility that psychotropics for the treatment of mood disorders (e.g. antidepressants; mood stabilizers, antipsychotics) may also elevate the risk of CVD. Adult bone marrow contains a subtype of progenitor cells that has the capacity to migrate to the circulation and to differentiate into mature endothelial cells. This cell population, endothelial progenitor cells (EPCs) has the ability to multiply and show marked proliferative capacity and resistance to stress. EPCs appears to be involved in both the maintenance of vascular integrity and postnatal vasculogenesis. Since their identification by Asahara et al. (1997), several studies have shown reduced numbers and/or impaired function of EPCs in a variety of cardiovascular risk states, including diabetes mellitus, hypercholesterolemia, hypertension, chronic renal failure, rheumatoid arthritis and smoking. Alternatively, cardiovascular protective factors such as exercise training, statin therapy, angiotensin II receptor antagonists and peroxisome proliferator activated receptor agonists are known to increase EPC number and function. Furthermore, longitudinal studies have found that the reduced number and/or functional activity of circulating EPCs are associated with increased risk of the development and the unfavourable outcome of CVDs. It is worthy of note that the majority of (pre)clinical investigations have found that EPC therapy is effective in the treatment of major cardiovascular events (AMI, stroke, limb ichemia). In our first investigation we hypothesized that major depression – as an independent risk factor for CVD – may be associated with an altered (decreased) number of bone marrow derived EPCs.

In our second investigation we tried to find the answer to the question whether season of birth (SOB) is associated with the risk of completed suicide. The quest of suicide risk factors is one of the most intensively developing issue of psychiatric epidemiology. From a global perspective suicide is the tenth leading cause of mortality (in several countries suicide is the third leading cause of death in the 15-34 year old population). Hungarian suicide rate is the highest in the world averaged over the last century. Suicide is a multicausal behavior in which both environmental and genetic factors are known to be involved. Accordingly, several sociological and biological theories try to explain the background of this complex phenomenon. However, results are not always unambiguous a number of *psycho-socio-cultural* and *economical* factors (i.e. religiosity; marital status; peculiar personality characteristics [hostility, aggressive/impulsive traits] and sexual orientations [homosexualism and bisexualism]; physical - especially sexual - abuse in childhood; working in some

occupational categories [i.e. physicians, dentists, veterinary surgeons, pharmacists, farmers]; economic crises; income inequivality; employment status etc.) may influence the risk of suicidal behavior. *Anthropometric/physiological* variables (i.e. body-mass index; height; respiratory functions; sleep duration; cholesterol level; ethnic belonging) may be also associated with suicidal behavior. In addition, numerous *pathological conditions* (i.e. psychiatric and substance use disorders [SUD i.e. alcohol use disorders; smoking; sedative/hypnotic/anxyolitic dependence; opiate dependence; heavy marihuana use etc.]; potentially fatal somatic disorders [e.g. malignant disorders]; COPD and asthma; etc.) are capable to modify the risk of suicidal behavior. As well, the *genetic determination* of suicide (that - interestingly - only partially overlaps with the genetic determination of mood disorders) and the *neurochemical correlates* of suicidal behavior are strongly demonstrated. „*Other*" factors (i.e. spring-summer time; first days of the week; changes in the psychiatric care system; antidepressant treatment; handgun ownership; incarceration etc.) may also influence the risk of suicidal behavior. Although, several suicide risk factors are known (see above), we are not able to appraise exactly the probability of such events in the clinical practice. In the last few decades, a number of interesting results have appeared about the associations between SOB and many physiological and pathological aspects of human life. First and foremost it has been consistently shown in several samples from different countries that SOB is associated with lifespan. Furthermore, the variability in some human features (e.g. handedness, reproductive lifespan and fertility, sleep patterns) is also influenced by SOB. Other results also suggest that SOB is associated with the altered risk of a variety of non-malignant (i.e. multiple sclerosis; narcolepsia, celiac disease) and malignant somatic disorders. The association between SOB and risks of some psychiatrical disorders (e.g. schizophrenia, anorexia nervosa) are also seems to be proved. At the same time, results about the relationship between SOB and risk of the development of other mental disorders (i.e. affective disorders) are not so convincing. There are only a few studies about the association between SOB and the risk of completed suicide. In addition, these provided somewhat inconsistent results and some of them also suffered from methodological shortcomings (mainly small sample sizes).

Aims

I. Investigation

As I discussed in the "Introduction", the decreased number and/or functional activity of EPCs are associated with elevated risk of CVDs (so we can consider the number of circulating EPCs as a marker of cardiovascular health). At the same time, EPCs are actors in the regeneration of injured vascular wall. Because depression is characterized by increased cardiovascular morbidity and mortality that cannot be explained by traditional cardiovascular risk factors alone and depressive disorders were found to be associated with dysfunction of the immune system and the bone marrow, we hypothesized that depression influences the number of bone marrow derived EPCs as well. In order to test this hypothesis we compared the number of EPCs in the peripherial circulation of patients with a current episode of major depression and control individuals, as well.

II. Investigation

The possible association between SOB and the risk of completed suicide were studied only in a few investigations previously. Furthermore, these investigations provided ambiguous results and some of them also suffered from methodological shortcomings. Considering that the Hungarian Central Statistical Office possess routinely collected data about months of births and suicide-related deaths in regard to long periods and the whole

hungarian population we decided to investigate the above association in a large population with adequate statistical methods.

Methods

I. Investigation

Thirty-three in- and outpatients diagnosed with a DSM-IV based major depressive episode in two psychiatric centers participated in the study (National Institute of Psychiatry and Neurology, Budapest; Central Hospital of the Hungarian Army, Budapest). During participant enrollment, complete physical and laboratory evaluations were carried out. Since virtually all known cardiovascular risk factors and major cardiovascular events have major impact on the number of circulating EPCs only patients (and controls) without CV risk factors and/or CV events in their medical history were enrolled into the study. Accordingly, patients with elevated levels of fasting blood-glucose, creatinine, urea nitrogen or liver functions, or with hypertension, BMI higher than 30 kg/m^2, elevated cholesterol or triglyceride levels, or with signs of infection (subfebrile temperature, fever, elevated white blood cell number or erythrocyte sedimentation rate) were excluded from the study. Moreover, cardiovascular risk factors (diabetes mellitus, hypertension, hypercholesterolemia, hypertriglyceridemia, renal failure) and cardiovascular diseases (acute myocardial infarction, arterial obstructive syndromes of limbs, ischemic stroke) in the medical history of the patients were also criteria for exclusion. Data about the smoking habits (smoking status and intensity, defined as self-reported average number of cigarettes smoked daily) of patients and healthy controls were collected as well. Based on smoking behavior, the following categories were used: 'non-smokers' (ex- and never smokers) and 'current smokers'. We have also excluded those individuals who had an other Axis-I psychiatric diagnosis than major depressive episode at the time of the investigation (or who had other diagnosis than unipolar depression or bipolar disorder in their medical history). The control group included 16 individuals matched for age, gender and smoking status. Smoker and non-smoker subgroups of patients and controls were also matched for age. Exclusion criteria for control persons were the same as those for patients with depression. Healthy controls had no previous or current episode(s) of major depression.

We have collected venous blood samples from all patients and control subjects. From the blood samples we have quantified the content of circulating EPCs in the peripherial blood by flow cytometric analysis (CD34+/VEGFR2+ and CD133+/VEGFR2+ cells were considered as "mature" and "immature" EPCs, respectively) and the levels of VEGF and TNF-α by ELISA and CRP by turbidimetric immunoassay. The quantification of EPCs was made on the day of the blood sample taking. The length of the time period between the assessment of depressive symptoms and the blood sample taking (with the 9-item Beck Depression Inventory) was maximum two days. The study was approved by the Local Ethical Committees of the National Institute of Psychiatry and Neurology, Budapest, and of the Central Hospital of the Hungarian Army, Budapest. All subjects gave their informed consent.

Continuous variables were compared with Student's t-test. The differences among more than two groups were analyzed with analysis of variance (ANOVA) and Scheffe's post hoc method. Continuous data were compared with Mann–Whitney U-test if the sample distribution was asymmetrical. Categorical data were compared using Fishers' exact probability and χ^2-tests. Linear regressions were analyzed using the simple regression model. Correlations of EPC and cytokine levels were determined using Spearman's rank correlation test. Differences were considered significant when $p < 0.05$. All statistical analyses were carried out using Statistica 7.0 (StatSoft Inc., Tulsa, OK, USA) software program.

II. Investigation

The sources of the data were the Birth Statistics and the Death Register of the Hungarian Central Statistical Office. We used the following variables from the Death Register: cause of death, gender, and birth date (month, year) of the deceased. We used the Birth Statistics to gain data about the number of monthly births in the period examined (from the years 1930 to 1969). Accordingly, we gathered data about all individuals who were born in this 40-year period in Hungary regarding their month of birth and gender. We also gathered data about all individuals who died by suicide over a 39-year period (1970–2008) in Hungary regarding their month of birth and gender. An individual whose International Classification of Diseases-8/9 (ICD-8/9) or ICD-10 code in the paragraph "cause of death" was one of the following was considered as a suicide completer: ICD-8/9: E950 to E959 and E980 to E989; ICD-10: X60 to X84 and Y10 to Y34. The total sample of suicide completers was divided by the method of suicide into a violent (ICD-8/9: E953–E958.7, E983–E988.7; ICD-10: X70–X83, Y20–Y32) and a nonviolent (ICD-8/9: E950–E952, E980–E982; ICD-10: X60–X69, Y10–Y19) subgroup. Due to the unreliable violence status (violent vs. nonviolent) of their suicide methods, we excluded suicide completers with the following diagnoses from the analyses aimed at investigating separately the relationship between SOB and risks of violent or nonviolent suicides: ICD-8/9: E958.8 and E958.9, E959, E988.8, E988.9, E989; ICD-10: X84, Y33, Y34. From the sample of participants (i.e., those who were born between 1930 and 1969), we excluded those individuals who were born in the years 1940 and 1943 because of missing data about their month of birth (during these 2 years, data gathering was insufficient because of the Second World War). In the first step of data processing, one time series was constructed from the number of monthly births of the total population between 1930 and 1939, 1941 and 1942, and 1944 and 1969. Another time series was constructed from the number of monthly births of suicide completers (who committed suicide between 1970 and 2008), who were born in the same period as the total population investigated (1930 –1939, 1941–1942, and 1944–1969). Next, we measured in all monthly birth cohorts the proportion of those individuals who died by suicide from 1970 to 2008. This process yielded the crude risk of suicide. However, it is important to note that because of the nature of our data, this crude risk of suicide is not equal to the real risk of suicide during a lifetime because the mortality period investigated (1970–2008) may only partially overlap with the total lifetime of individuals from the observed birth cohorts (in other words, implicitly, we do not have information about those participants who died by suicide either before 1970 or will die by suicide after 2008). These peculiarities of the time series do not render our analyses biased, as the extent of the missing data is similar in each monthly birth cohort. Our time series are sufficiently long (number of observed monthly birth cohorts = 456) to investigate properly our main research question about the effect of the SOB on the risk of suicide. In the second step of data processing, the changes in the crude risk of completed suicide were studied month by month. The crude risk of suicide was decomposed into four components: trend (T_t), season (S_t), cycle (C_t) and noise (I_t). Trend was determined as a 36-month moving mean and removed from the time series. Season was defined as the average percentage difference from the trend, which was characteristic to a given month (of birth) in the whole birth period investigated (1930–1969). Since we could not find any other cyclical component (4-, 8-, 18-, or 24-month-long ones), we omitted this component from the final model. In the third step of data processing, we examined using the one-way analysis of variance (ANOVA) module whether there was a statistically significant seasonal component. The level of significance chosen for analyses was $p = .05$. The explanatory variable in the model was the month of birth, while the dependent variable was the season. In the fourth step of data processing, we investigated whether the strength of the association between SOB and the risk of completed suicide varied with gender and/or the method of suicide (violent vs. nonviolent). To clarify these questions,

we performed similar analyses as discussed above on data from the given subpopulations. Data were managed using SPSS, version 15 (SPSS, Inc. Chicago, Illinois).

Results

I. Investigation

Patients and controls did not differed from each other in regard to their age, gender distribution, BMI, BUN, blood glucose, cholesterol and triglyceride levels, number of leukocytes and smoking habits (***Table I.***).

Table I. Baseline clinical characteristics and cytokine levels of patient and control groups

	Patients (n = *33*)	*Controls* (n = *16*)	P-*value*
Gender (female/male)	29/4 (88 vs 12%)	14/2 (88 vs12%)	0.98†
Age (years)	40.6 ± 10.6	40.3 ± 9.5	0.93*
BUN (mmol l^{-1})	4.26 ± 1.52	5.14 ± 1.18	0.055*
Body mass index (kg m^{-2})	23.3 ± 3.49	22.7 ± 4.1	0.61*
White blood cells (10^9 per liter)	7.27 ± 1.83	7.94 ± 1.48	0.18*
Blood glucose (mmol per liter)	4.75 ± 0.58	4.52 ± 0.75	0.31*
Total cholesterol (mmol per liter)	4.69 ± 0.82	5.11 ± 0.93	0.14*
Triglyceride (mmol per liter)	1.17 ± 0.5	0.89 ± 0.57	0.11*
hs-CRP (mg dl^{-1})	0.13 ± 0.06	0.11 ± 0.04	0.29*
TNF-α (pg ml^{-1})	2.68 ± 0.8	1.5 ± 0.46	0.03*#
VEGF (pg ml^{-1})	19.37 ± 3.83	17.35 ± 3.82	0.1
BDI score	38.6 ± 10.7	0.9 ± 1.44	< 0.01§#
Smoking status (current smoker/ nonsmoker)	19/14 (58 vs 42%)	10/6 (62.5 vs 37.5%)	0.74‖
Smoking amount in smoker subgroups (no. of cigarettes per day)	23.1 ± 11.7	15.3 ± 9.3	0.064*

Abbreviations: BDI, beck depression inventory; BUN, blood urea nitrogen; hs-CRP, high sensitivity C-reactive protein; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor.
Data are expressed as mean + s.d.
*Independent-samples *t*-test
†Fischer's exact test.
§Mann–Whitney's test.
‖ χ^2-test.
#Significant difference between patient and control groups.

In the patient population, both the levels of mature (CD34+/VEGFR2+) and immature (CD133+/VEGFR2+) EPCs per milliliter of PB were significantly lower than those in the group of healthy controls ($p < 0.01$ for both comparisons; ***Figure I.***). There was a statistically significant inverse relationship between EPC levels and BDI scores ($p < 0.01$ in cases of both EPC phenotypes) independent of the phenotypes of EPCs.

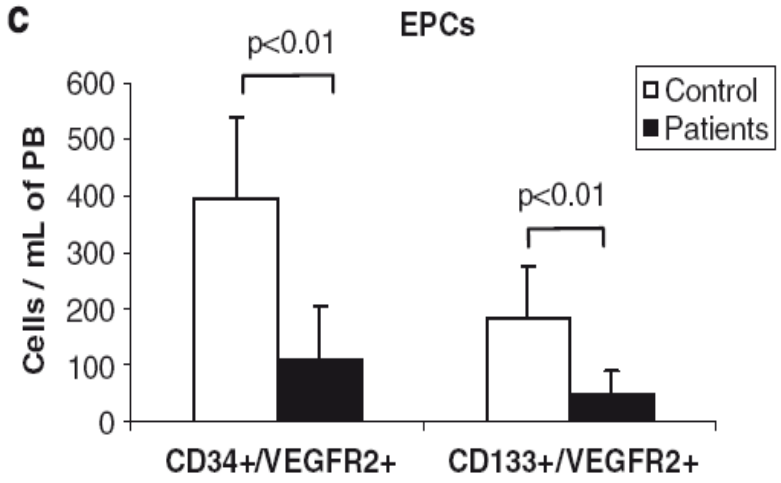

Figure I. Circulating EPC levels in healthy controls (n = 16) and patients with depression (n = 33).

Assessment of EPC numbers using CD34/VEGFR2 labeling indicated a significant decrease among smokers compared to non-smokers in both control and patient groups (p-values are < 0.01 and < 0.001, respectively; ***Figure II/a***). Quantification of EPCs by CD133/VEGFR2 labeling also revealed that the EPC level in the control population was significantly lower in smokers as compared with non-smokers ($p < 0.01$; ***Figure II/b***). Although a similar tendency was observed, the difference in CD133+/VEGFR2+ EPC levels between smokers and non-smokers remained statistically insignificant in the patient population ($p = 0.34$; ***Figure II/b***). When smoker controls were compared with smoker patients and non-smoker controls with non-smoker patients, both the CD34+/VEGFR2+ (***Figure II/a***) and the CD133+/VEGFR2+ (***Figure II/b***) EPC levels were significantly lower in the patient groups.

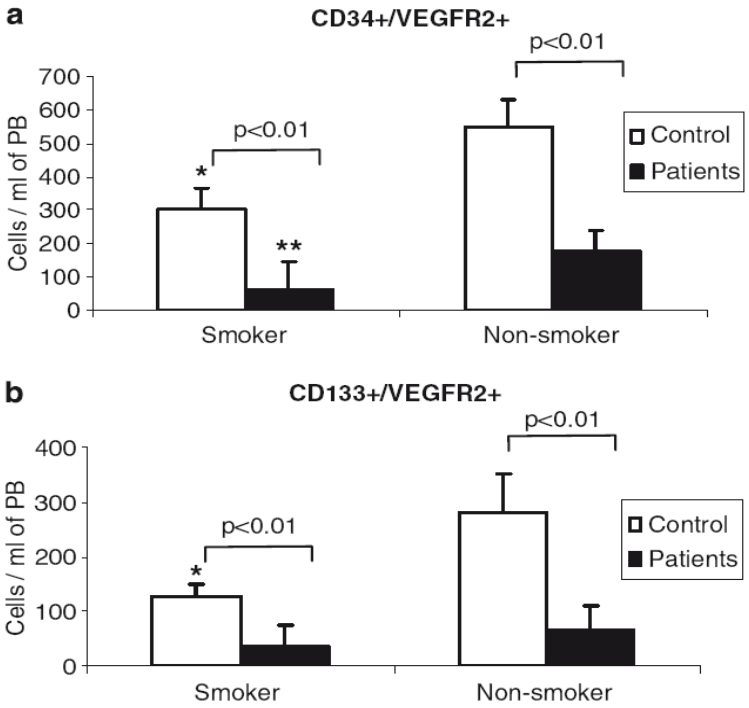

Figure II. Comparison of the numbers of mature (CD34+/VEGFR2+) and immature (CD133+/VEGFR2+) circulating EPCs in smoker vs. non-smoker subgroups of patient and control groups.

TNF-α levels of patients were significantly elevated as compared with those of healthy controls ($p = 0.03$, ***Table I.***) and, moreover, a statistically significant inverse correlation was observed between TNF concentrations and EPC numbers ($p < 0.05$, data not shown). Although patients with depression tended to have higher CRP levels than healthy controls, the difference between the two groups remained insignificant ($p = 0.29$, ***Table I.***). No significant difference was detected in the plasma levels of the key vasculogenic molecule, VEGF, between controls and patients ($p = 0.1$, ***Table I.***).

II. Investigation

After data cleaning, there were 6,697,361 individuals who were born in the territory of today's Hungary during the 38 years investigated (1930 –1939, 1941–1942, and 1944–1969). Of these 6,697,361 individuals, 78,779 died by suicide between 1970 and 2008. We excluded those few subjects whose months of birth were missing from the registers ($n = 39$). Finally, the number of those individuals who were born during the periods investigated and who died by suicide between 1970 and 2008 and all of whose data were available for further analysis was 78,740 (male: 60,890; female: 17,850). The numbers of violent and nonviolent suicides were 58,546 and 19,178, respectively. The violence status of suicide (violent vs. nonviolent)

was uncertain in 1016 cases, so we omitted these cases from the analyses aimed at investigating separately the relationship between SOB and risks of violent versus nonviolent suicides. In accordance with previous results, in our sample the proportion of violent suicides among all suicides was higher in male subjects than in female subjects (80% vs. 54%). Hanging was the most prevalent method in the violent group (81%) (***Table II***.).

Table II. Baseline Characteristics of the Whole Investigated Population and the Subpopulations of Suicide Completers and the Characterization of the Relationships Between SOB and the Risk of Completed Suicide in These Groups

	Number of Cases (*n*)	Crude Risk of Completed Suicide	*F*	Significance Level of *F*	Eta^2	Birth Periods Associated with Risk of Suicide	
						Increased	Decreased
All Suicides	78,740	.0116	16.04	$p < .001$	.28	April–August	October–January; March
Suicides Using Violent Method	58,546	.0086	10.08	$p < .001$	.20	May–August	December, March
Suicides Using Nonviolent Method	19,178	.0028	6.53	$p < .001$	.14	May–August	October; December–January
Male Suicides	60,890	.0174	12.23	$p < .001$	.23	May–August	October–December; March
Male Suicides Using Violent Method	48,892	.0140	8.79	$p < .001$	.18	May–August	October–December; March
Male Suicides Using Nonviolent Method	11,202	.0032	4.58	$p < .001$	.10	May; July–August	October–December
Female Suicides	17,850	.0054	5.06	$p < .001$	.11	April; June–July	October; January
Female Suicides Using Violent Method	9,654	.0029	2.55	$p = .004$	.06	April; July	October–November
Female Suicides Using Nonviolent Method	7,976	.0024	3.35	$p < .001$	.08	April	January
Suicides by Hanging	47,481	.0066	7.25	$p < .001$	.15	April; June–August	December, March

Statistics from the one-way analysis of variance models.
SOB, season of birth.

Our results demonstrated that there is a statistically significant association between the month of birth and the risk of completed suicide. This relationship was found in the total population and in all subpopulations investigated (i.e., male subjects, female subjects; suicide completers using violent methods, suicide completers using nonviolent methods; male suicide completers using violent methods, male suicide completers using nonviolentmethods; female suicide completers using violent methods, female suicide completers using nonviolent methods). Quantitatively, in the whole population investigated, those who were born in the highest risk period (July) have an approximately 13.8% (95% CI: 9.1%–18.6%) higher risk of dying by suicide than those who were born in the lowest risk period (December) (***Figure III.***). Another important finding of our study is that the above association is more definitive among male subjects than among female subjects.

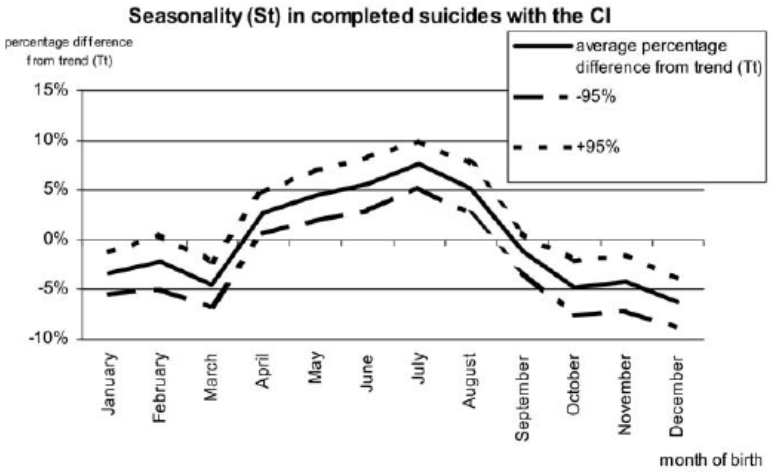

Figure III. The effect of season of birth on the risk of completed suicide in the whole population investigated. CI, confidence interval.

Discussion

I. Investigation

However, although an association between mood disorders and susceptibility to cardiovascular events has been discovered by several researchers, and altered circulating EPC levels have been reported in various conditions associated with vascular diseases, prior to the date of our investigation no studies have attempted to evaluate the significance of EPCs in patients with major depression. Therefore, we investigated the significance of EPC numbers in our study sample by using flow cytometry and found a significant decrease in both mature (CD34+/VEGFR2+) and immature (CD133+/VEGFR2+) circulating EPC numbers in depressed patients versus healthy controls, and moreover, a statistically significant inverse relationship between EPC counts and the severity of depression independent of EPC phenotypes (as assessed by BDI scores). We also found a significant decrease in EPC counts among smokers, regardless of the population category (patients or controls). These findings accord with the results of previous papers, in which smoking was demonstrated to decrease circulating EPC numbers. We have also quantified the levels of some molecules (TNF-α, VEGF, CRP) with presumptive effects on the number of circulating EPCs. Our results were in a good accordance with the findings of previous studies. We found normal VEGF levels in our patient population. Consequently, the possibility of insufficient bone marrow stimulation by VEGF in depression is not supported by the current results. The levels of TNF-α were significantly higher in patients when compared with the levels of healthy controls and, moreover, TNF-α levels inversely correlated with EPC counts. Since previous studies have demonstrated that TNF-α reduces the number of EPCs, our findings suggested to us that TNF-α might promote EPC number reduction in depressed patients.

In the three years - since our paper was published - only a few studies investigated the possible role of EPCs in the mediation of mood disorders associated elevated cardiovascular risk. In one of these, authors tested the hypothesis whether the presence of depressive symptoms (assessed with the "Depression Anxiety Stress Scales" (DASS)) in subjects (N=129) without significant CVD is associated with the altered number of circulating EPC. The numbers of circulating EPCs were determined by flow cytometry. Authors found that in healthy subjects, the presence of high depression scores were associated with depletion of circulating EPCs. Another study found that type D personality may also be associated with a significantly decreased number of circulating EPCs in patients with chronic heart failure (type D personality – a joint tendency toward negative affectivity and social inhibition – is frequent in patients with CVD and its presence - similarly to major depression - is associated with poor prognosis). Results of a third study also supported our findings. In this study authors found that the number of circulating EPCs was in an inverse relationship with the level of psychosocial stress (the association was especially strong in the 36-46 years old population).

Our investigation had some methodological shortcomings. First, virtually all individuals of the patient group received psychotropic medication. Since the effects of these agents on the number of circulating EPCs are not known we can not exclude the possibility that not only depression 'per se' but the pharmacological treatment of it also influences the number of EPCs. Second, the cross-sectional nature of our investigation hinders us to give answers to the next questions: 1, whether the EPC number abnormalities are state- or trait-dependent phenomena in affective disorders; 2, whether antidepressive treatments are associated with alterations in EPC numbers. Third, as it is known physical exercise is associated with the elevation of EPCs; as we did not measure the levels of physical activity in patient and control individuals, we were not able to take into consideration the effect of presumptive differences in the physical activity of the two groups. In our opinion the majority of these shortcomings would be overcome by the use of an animal model of depression (for

example the “olfactory bulbectomy” model in rodents). In this model we would be able to measure the number of circulating EPCs before and after the initiation of depression. Furthermore, the effects of antidepressants and physical activity on the number of EPCs would be also estimable (both in depressed and non-depressed (sham-operated) animals). Another direction of research would be the screening of effects of other - than pharmacological – treatment modalities of depression (electroconvulsive therapy, sleep deprivation, light therapy etc.) on the number of EPCs. In this wise, we would be able to investigate the effects of depression and the effects of different therapeutic modalities on the number of circulating EPCs, separately.

Finally, our results also suggest that individuals should be screened for depression in future studies investigating EPC number and function in patient populations with cardiovascular risk factors (diabetes mellitus, chronic renal failure, smoking, rheumatoid arthritis) or with definitive cardiovascular diseases (myocardial infarction, stroke). It is especially crucial that the depression be considered an independent variable in such studies because depression is so highly comorbid with these cardiovascular conditions and diseases.

II. Investigation

In our second investigation we found a significant association between season of birth and the risk of completed suicide. The number of suicide completers in our study greatly exceeds the number of suicide completers in any previous studies. Our results about the elevated risk of completed suicide among those who were born in the spring-summer period of the year (compared with those who were born in the autumn-winter period of the year) are in good agreement with the majority of results of the few relevant previous papers. The relative differences in the risks of completed suicide between the high-risk and the low-risk birth periods in our sample from Hungary are slightly smaller than those found in England, Wales, and Scotland (14% vs. 18%, respectively). A possible explanation of this difference could be that the strength of the relationship between SOB and suicide risk may be affected by latitude (i.e., the strength of the relationship increases with increasing latitude) (Hungary is located at lower latitudes [N46°–N49°] than England, Wales, and Scotland [N50°–N59°]). In our sample those who were born in the period from April to August have a higher risk of killing themselves by hanging than those who were born in the period from October to March. This finding is also in partial accordance with previous results (these suggest that hanging is more likely among those who were born in the period from winter to early summer).

What kind of biologically plausible mechanisms can explain our findings? The association between SOB and the risk of suicide behavior is probably best explained on a neurobiological basis. Some studies have found that 5-hydroxyindoleacetic acid (5-HIAA) levels in the cerebrospinal fluid (CSF) from both infants and adults vary with the SOB. Adult individuals who were born from February to July had lower levels of CSF 5-HIAA than those who were born from August to January (in newborns the pattern was somewhat different: 5-HIAA levels were lower among those who were born from November to April compared to those who were born from May to October). Considering that low levels of CSF 5-HIAA were found among suicides compared with nonsuicidal control subjects and this also predicts future suicide attempts and completions, the conclusion can be drawn that low levels of 5-HIAA may be a link between SOB and suicidal behavior. The complex interactions between SOB, mood disorders, and serotonin (5-HT) metabolism are further supported by the following facts: 1) about 90% of suicide victims have at least one current Axis I psychiatric disorder, most commonly a major depressive episode (which is, as is well known, associated with decreased CSF 5-HIAA levels); 2) in the majority of studies, the pattern of the association between SOB and the risk of major psychiatric disorders was similar to the pattern of the association between SOB and the risk of suicide (i.e., the high-risk birth period in regard to

suicide and the high-risk birth period in regard to main Axis I psychiatric disorders overlap each other during the spring); and 3) the high-risk period for suicidal behavior overlaps with the high-risk period for decompensation of mood disorders. In addition, some seasonal changes in the elements of the serotonergic system (i.e., 5-HT transporter density in the brain or platelet 5-HT2a receptor binding) are also described that may further nuance the above complex interaction between SOB, intra-annual decompensation of mood disorders, suicide, and the serotoninergic system. According to the results of investigations with both direct (measuring levels of transmitter metabolites [homovanillic acid and 3-methoxy-4-hydroxyphenylglycol] in the CSF) and indirect (measuring levels of personality dimensions—i.e., novelty seeking or circadian typology [morningness-eveningness]—that also refer to changes in the activity of the dopaminergic system) methods, activities of other neurotransmitter (dopaminergic and norepinephrine) systems also show consistent relationships with SOB. In conclusion, the above results suggest a very complex interaction between SOB and various transmitter (serotoninergic, dopaminergic, norepinephrine) systems that are strongly involved in suicide behavior.

In conclusion in our second investigation we found that SOB is strongly associated with the risk of completed suicide. If our results will be confirmed in independent samples, then these have important implications for suicide prevention: spring-summer born individuals (particularly those who have psychiatric and/or psychosocial suicide risk factors), especially during the spring/early summer high-risk period for suicide, should receive more attention in this respect.

Candidate's publications related to thesis

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IF: 15.049

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