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ORIGINAL PAPER

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Increased risk of developing stroke for patients with major affective disorder

A registry study

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Abstract Only a few studies have evaluated depressive disorder as a risk factor for cerebrovascular disease. In a hospital discharge register with nation-wide coverage of all hospitals in Denmark we used linkage between the somatic and psychiatric registries to study comorbidity between affective disorders and cerebrovascular diseases in hospitalised patients.

The main finding of this study was that patients with depression severe enough to be hospitalised, seem to be at an increased risk of developing cerebrovascular disease. The hazard ratio of getting a diagnosis of stroke after initially having been discharged with a diagnosis of depression was found to be 1.22 (95 % Confidence Interval: 1.06–1.41). In the group of patients with manic/bipolar disorder no association was found concerning development of stroke.

In elderly with first time depression admitted to hospital, neurological disorders should be carefully evaluated and especially the risk of stroke should be considered.

Key words depression · affective disorder · stroke incidence · registries

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Introduction

In recent years there has been an increasing interest for risk factors for stroke. Only a few studies have evaluated depressive disorder as a risk factor for cerebrovascular disease (CVD). To the best of our knowledge, no research reports have investigated the risk of developing stroke in patients with depression as compared to the risk of patients with other medical illnesses.

Evaluating depressive symptoms as a risk factor for CVD has only been done in a few larger community studies. In a large-scale community sample (6676 adults at the initial evaluation), in Alameda County in California, depressive symptoms were evaluated as a risk factor for mortality of stroke. When adjusting for age, sex, and race, patients with depressive symptoms had an increased risk of mortality from stroke compared to patients with stroke but without depressive symptoms (hazard ratio 1.66; Confidence Interval (95 % CI): 1.16–2.39) [17].

In a community-based study in Amsterdam, The Netherlands, it was shown that major depressive syndromes in the elderly (age over 65 years) increased the risk of overall mortality in both men and women. The follow-up of death was ascertained from registers in a follow-up period of 6 years [33].

Based on evidence both on volumetric changes of specific brain structures [21] and vascular changes within white and grey matter [25], a hypothesis of *vascular depression* has emerged. This mainly applies as a predisposition explaining depressive syndromes in geriatric patients [2, 22]. Steffen and Krishnan [35] have taken it even further and proposed a DSM-IV [3] diagnostic classification for two new mood disorder subtypes, vascular depression and vascular mania. These classifications respectively include neuroimaging findings, which may include white or grey matter hyperintensities, as seen in MRI images, and fulfilling general criteria of depression or mania. Additionally proposed criteria were onset after 50 years of age, a lack of family

history of mood disorders, and a marked disability in instrumental or self-maintenance activities of daily living. These criteria would also include post-stroke depression [26, 35].

To the best of our knowledge the risk (or hazard ratio) of developing stroke in bipolar disorder has not previously been reported. But the relation between mania and stroke is most probably bi-directional, as described in a meta-analysis by Videbech [36]. In this review, all studies investigating bipolar disorder patients with MRI and with age matched control groups were located. White Matter Hyperintensities (WMH) across ten studies with comparable control groups were evaluated. A cross study odds ratio of the risk of finding WMH in patients with bipolar disorder was 3.29 (95% confidence interval 2.14 to 5.02) [36]. Evidence has accumulated over the years in favour of the hypothesis that non-symptomatic WMH represent a sub-clinical form of ischaemic brain damage [32]. It has been found in late onset mania (age over 50 years) that silent cerebral infarction was present in 65% [18]. Structural neuroimaging has been further reviewed in [36].

The aim of the present study was to estimate the risk of receiving a diagnosis of a cerebrovascular disease (ischemic or haemorrhagic stroke) on a subsequent discharge from hospital, for patients previously discharged with a diagnosis of affective disorder compared with a diagnosis of osteoarthritis.

Methods

In this report cerebrovascular disease was defined as a diagnosis of 'thrombosis cerebri' (ICD-8 code: 433.09–433.99) or 'embolia cerebri' (ICD-8 code: 434.09–434.99) and cerebral haemorrhage (ICD-8 code 430.00–431.99) and these diagnoses are in combination hereafter called 'stroke'. The risk of developing stroke after a first ever diagnosis of either depression or mania episode was compared with the risk of developing stroke after first ever diagnosis of osteoarthritis (ICD-8 code: 713.00–713.09). In further analyses, we adjusted for the effect of 'gender' and 'age of first discharge' and evaluated comorbid alcohol/drug abuse as potential confounders.

The data collection procedure and formation of the cohort have been described in depth elsewhere [28]. In brief, by linkage of public hospital registers in Denmark (The Danish Psychiatric Central Register (DPCR) [16], The Danish National Hospital Register (DNHR) [5], Danish Register of Causes of Death [24]) from 1977 to 1993, using ICD-8 diagnoses, two study cohorts were identified: patients with affective disorder episodes (mania and depression) and patients with osteoarthritis. The two patients groups were merged and the length of time to first admission with a diagnosis of stroke was estimated for each patient, censoring if death occurred, if other neurological diagnosis occurred, or if admission with stroke had not occurred before 31 December 1993. Because of delayed entry into the cohort, the follow-up period thus varied between 1 day and 17 years. Time to first diagnosis of stroke was estimated.

For the security of patients and safety of the patients' personal data, all patients were given code identification across all groups. The unique personal identification number (CPR number) was then deleted before the study base was released for data processing by the investigators [28].

Statistical analysis

Cox regression for proportional hazards was used for calculating the risk of receiving a diagnosis of stroke after a discharge with a diagnosis of either depression or manic episode and compared with the risk of a diagnosis of stroke after an initial control group diagnosis. Censoring was done when schizophrenia, other neurological diseases, death, or end of study period occurred. The assumption of proportional hazards in the Cox regression models was checked graphically as described by Andersen et al. [4].

Results

In total, 95,145 patients were discharged with a first time diagnosis of affective episode or osteoarthritis in the period from 1977 to 1993. Seventeen patients were excluded from further analysis due to miscoding (one patient had insufficient data and 16 had overlapping episodes of admission). The study sample thus included 95,128 patients: 13,748 patients with affective disorder episodes (2007 with mania and 11,741 with depression), and 81,380 patients with osteoarthritis. Characteristics of the two patient groups regarding gender and age at first discharge are presented in Table 1. From this table it appears that patients with an affective diagnosis were about ten years younger than patients with osteoarthritis (56.7, SD 16.5 versus 66.6 SD 13.4) but with a broad standard deviation, also reflecting the large number of patients. The broad standard deviations make it reasonable to analyse the cohorts in the same analysis. In a separate analysis, the group of 13,748 affective patients was divided into the 2007 patients with mania/circular episodes (code 296.19 and 296.39) and the 11,741 patients with depression (code 296.09 and 296.29). The risk

Table 1 Stroke. Characteristics of patients in the affective group and the control group

	Mania	Depression	Affective disor.	Osteoarthritis
Number of patients	2007	11741	13748	81380
Female gender (%)	53.2	67.3	65.2	60.3
Mean age at first discharge (years)	50.6	58	56.7	66.6
SD (years)	18.0	15.9	16.5	13.4
Proportion developing stroke (%)	1.3	1.9	1.8	1.9
Censoring due to schizophrenia (%)	2.26	0.81	1.02	0.02
Censoring other neurological (%)	3.6	5.6	5.3	2.6
Censoring due to death (%)	30.9	33.6	33.2	28.4
Proportion alcohol/drug abuse (%)	7.2	5.7	5.9	0.2

for patients in the mania group and the risk for patients in the depression group of subsequently being admitted with a discharge diagnosis of stroke were calculated.

Table 2 shows the result of the Cox regression models *adjusting* for differences in gender and age at first discharge entered in subsequent analyses. Age at first discharge was entered into the model as a categorical variable with ages 15 to 45 years as one interval and thereafter in ten-year intervals. This was the optimal distribution of ages (giving the Maximum Likelihood). In each diagnostic group (depression, mania and affective disorder) there are three Cox regression models.

The first regression model containing only the 'diagnostic group' is presented. The second Cox regression in each group includes correction for gender, and the third analysis in each diagnostic group includes correction for group, age, and gender in the same analysis. It is shown that correction for age is the most influential single factor to be corrected for. Additional Cox regression models with a diagnosis of substance abuse included, as a categorical covariate did not affect the results (not shown). Substance abuse was in this context defined as alcoholism (ICD-8, code: 303.09–303.99) and drug abuse (ICD-8, code: 304.09–304.99).

It can be seen in all the analyses that uncorrected for age the hazard ratios are below one, and corrected for age, the hazard ratios are higher than one. That is, patients with depression have a 1.22 (95% CI: 1.06–1.42) times increased risk of developing stroke compared to patients with osteoarthritis, when corrected for gender and age. The effect of a manic/bipolar episode did not reach statistical significance (Hazard rate = 1.02; 95% CI: 0.69–1.51). Patients with affective disorder have an estimated hazard rate of 1.19 (95% CI: 1.04–1.37).

In a separate analysis for "late onset" depression defined as age at first onset diagnosis of depression above 50 years gave similar results with a hazard rate of 1.17 (95% CI: 1.00–1.37) and a p-value of 0.047.

Table 2 The risk of developing stroke in patients with a diagnosis of affective disorder compared with osteoarthritis in Danish National Hospital cohorts. Divided by depression, mania and affective episodes. Adjusted for differences in 'age at first discharge', and gender in Cox regression models

Hazard Ratio (HR)	Osteoarthritis	(95% CI)	p-value
Depression			
Diagnostic Group	0.848	0.735–0.977	0.022
Diagnostic Group + gender	0.857	0.744–0.988	0.034
Diagnostic Group + gender + age	1.222	1.057–1.412	0.007
First depression after 50 years			
Diagnostic Group	0.993	0.851–1.158	0.927
Diagnostic Group + gender	1.011	0.866–1.180	0.891
Diagnostic Group + gender + age	1.171	1.002–1.369	0.047
Affective episode			
Diagnostic Group	0.803	0.702–0.918	0.001
Diagnostic Group + gender	0.809	0.707–0.926	0.002
Diagnostic Group + gender + age	1.192	1.039–1.368	0.012
Mania/bipolar episode			
Diagnostic Group	0.542	0.367–0.798	0.002
Diagnostic Group + gender	0.537	0.365–0.792	0.002
Diagnostic Group + gender + age	1.019	0.688–1.508	0.926

Discussion

The main finding of this study was that patients with depression severe enough to be hospitalised seem to be at an increased risk of developing stroke. In the group of patients with manic/bipolar disorder no association was found. Further analyses revealed that the increased risk for patients with depression of developing stroke was not related to the effect of alcohol/drug abuse.

Only a few studies have evaluated depressive disorder as a risk factor for stroke. To the best of our knowledge, no studies have investigated whether patients with manic disorder are at increased risk of developing stroke.

The results of this study are in accordance with results presented in most other studies recently published [12, 17, 29, 30, 33, 34, 37]. The general risk factors for cardiovascular disease and cerebrovascular diseases are somehow mutual but overall cerebrovascular disease occurs later in life than cardiovascular disease [9]. Everson et al. found an increased mortality from stroke in patients who had self-reported depressive symptoms, even after adjusting for known clinical and behavioural risk factors [17]. The limitation of the study was that no validated rating scales were used. Depression was assessed as: "more than five depressive symptoms" on a 'true' or 'false' checklist called Human Population Laboratory Depression Scale. This is probably not comparable to clinical depression. In comparison with our study the study was also limited to death of stroke (mortality) rather than evaluating morbidity. Another study used assessment of psychosocial factors as a predictor of stroke incidence in a community based cohort of 2812 elderly with an up to six years follow-up [11]. By itself depressive symptoms as measured with the Centre for Epidemiological Studies – Depression Scale (CES-D) were predictive of stroke incidence. After controlling for sociodemographic and health variables, no effect was detected. However, from this study it is not possible to generalise because the definition of stroke was rather broad including e. g. transient cerebral ischaemias and only depressive symptomatology was evaluated.

Recently, House concluded from a controlled trial including 448 hospitalised patients that mood symptoms on a self-reported rating scale may be associated with increased 12- and 24-month mortality after stroke, after adjustment for factors associated with stroke severity [23]. Together with other evidence, these results suggested that depressive symptoms are a risk factor for increased mortality from vascular disease [17].

Imaging techniques (PET scan and MRI) investigating patients with affective disorders have revealed functional and structural abnormalities (a subgenual prefrontal cortex abnormality) and suggested this as a marker of affective disorder [15]. Our results, from a dif-

ferent scientific field, lend support to the hypothesis of a neurobiological connection between depressive disorder and stroke in the elderly [20]. Whether recurrence of depressive episodes and other comorbid conditions have any influence on the risk of developing stroke remains to be investigated. In the light of recent published data it seems to be interesting [6, 10].

On the other hand, we did not find any association between bipolar/manic disorder and stroke.

Arthritis as control group

In the present study, patients with osteoarthritis have been chosen as a control group because osteoarthritis is a chronic and progressive disease without any known affection of brain function [19, 27]. Although it has only been scarcely investigated, the risk of developing depression in patients with osteoarthritis does not seem to be increased [13, 31].

The effect of treatment

In the observation period of this study, the standard regime of treatment in Denmark was tricyclic antidepressants (TCA) as medication in most hospitalised cases. It is not indicated anywhere in the literature that TCA should increase the risk of stroke [1, 14]. This would also seem unlikely since TCA have a tendency to lower the blood pressure in patients on this treatment. Selective Serotonin Reuptake Inhibitors (SSRIs) were introduced in the study period, but have also not been suspected of increasing the risk of stroke [7]. Non-steroid anti-inflammatory drugs (NSAID) are widely used in patients with osteoarthritis and could have reduced these patients' risk of developing stroke. We had no opportunity to investigate this problem in the present study since treatment was not listed in the registers in use. In the same way it was a drawback of this study that it was not possible to adjust for the effect of tobacco smoking, hypertension, alcohol consumption, and other "life-style" circumstances (e. g. Body Mass Index) since these covariables are not registered in the administrative public registers used in this study. Therefore it should be made clear that the results given here do not implicate a causal relation between depression and stroke but merely that a correlation was found between a first time diagnosis of depression after hospitalisation and an increased hazard ratio of stroke later in life.

In a validation study a positive predictive value of a register diagnosis of stroke in the DNHR was found to be 85 % [8].

Conclusion

The main finding of this study was that patients with depression severe enough to be hospitalised, seem to be at an increased risk of developing cerebrovascular disease. In the group of patients with manic/bipolar disorder no association was found.

In elderly with first time depression admitted to hospital, neurological disorders should be carefully evaluated and especially the risk of stroke should be considered.

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