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Cerebrovascular reactivity in depressed patients without vascular risk factors ☆

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Abstract

Introduction: Cerebrovascular reactivity (CVR) seems to be gaining importance as a prognostic factor for stroke risk. CVR reflects the compensatory dilatory capacity of cerebral arterioles to a dilatory stimulus; this mechanism plays an important role in maintaining a constant cerebral blood flow. Evaluating factors that influence CVR will help prevention or early detection of cerebrovascular disease (CVD). In this study we aimed to measure the CVR in vascular-risk free depressed individuals so as to evaluate the effect depression has on CVR and hence its role as a stroke risk factor.
Methods: Using acetazolamid (ACZ) stimulation, CVR was assessed with a transcranial Doppler ultrasound in 25 non-smoking depressed patients (average age: 48.48 ± 14.40) and in 25 healthy non-smoking controls (average age: 46.76 ± 13.69) by calculating the difference between the maximal mean blood flow velocity at baseline and the maximal mean blood flow velocity after ACZ stimulation.
Results: Basal Cerebral Blood flow in Patients was 50.6 cm/s (SD: 11.6) versus controls 52.80 cm/s (SD: 12.70) whereas after stimulation maximal blood flow velocity was 72.64 cm/s (SD: 15.75) in patients versus 80.20 cm/s (SD: 18.43) in controls. In an analysis of covariance we found that cerebrovascular reactivity was significantly reduced in the vascular-risk free depressed sample. Age had a significant influence whereas gender did not.
Discussion: Major Depression appears to decrease cerebrovascular reactivity supporting the idea of increased risk for stroke in depressed patients. The mechanisms leading to this phenomenon and its subtle subgroup differences should be further investigated.

Keywords: Cerebrovascular reactivity; Depression; Vascular risk factor; Metabolic syndrome; Non-smokers

1. Introduction

The dilatory mechanism by which cerebral arterioles maintain a constant cerebral blood flow is reflected by the CVR. Since alterations in cerebral blood flow relate to stroke risk, CVR might play a role in stroke-risk prognosis. Evaluating the factors that influence CVR could help detect, or even prevent, early stages of cerebrovascular disease (CVD). In the following text we expose the sequence of ideas behind this study.

1.1. From depression to cerebrovascular disease and vice versa

Despite increasing evidence pointing towards a bidirectional relationship between depression and stroke, the relationship between these two entities has until now focused on depression as a consequence of stroke.

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Various interpretations of the etiological model relating cerebrovascular diseases and depression exist: a hierarchical, an interactive and a common etiological model. All of these are plausible, variable and not mutually exclusive (Ramasubbu, 2000). This study focuses on changes of CVR in major depression as a possible factor for increased stroke risk.

We considered, the growing evidence suggesting depression as stroke a risk factor. First, prospective epidemiologic studies found that patients suffering depressive episodes have a higher prevalence of stroke (Jonas and Mussolino, 2000; Larson et al., 2001; Ohira et al., 2001; Everson et al., 1998; Colantonio et al., 1992). According to the authors, these findings remained statistically significant after adjusting for body mass index, smoking habits, diabetes, cholesterol, gender, blood pressure, alcohol consumption, physical activity, race and education. (Jonas and Mussolino, 2000; Larson et al., 2001; Ohira et al., 2001; Everson et al., 1998; Simonsick et al., 1995). Secondly, more and more evidence suggests that depression influences vascular risk factors (Eaton et al., 1996; Jonas et al., 1997), stroke recovery (Parikh et al., 1990) and increases the risk of cerebrovascular disease in patients with vascular risk factors (Simonsick et al., 1995).

1.2. Cerebrovascular reactivity as an early indicator of cerebrovascular diseases?

It is suggested that perfusion imaging following vascular challenge tests, such as the CVR acetazolamide test (a carbonic anhydrase inhibitor), might provide a more sensitive measure of early CVD than structural MRI (Knop et al., 1992; Ringel Stein et al., 1992). The increase of blood flow velocity after stimulation with acetazolamide offers a reliable method for assessing CVR (Dahl et al., 1992).

CVR reflects the compensatory dilatory capacity of cerebral arterioles to a dilatory stimulus, which is important for maintaining constant cerebral blood flow. A normal CVR is of considerable importance for a physiological blood supply of the brain. The main factors modulating brain blood flow velocity are blood viscosity and vascular tone. Impaired autoregulation of vascular tone may contribute to increased risk of CVD.

Furthermore, an impaired CVR has been found to be associated with a higher risk of stroke (Yonas et al., 1993; Silvestrini et al., 1996; Molina et al., 1999).

Previous studies have shown a decreased vasodilatory capacity under various circumstances, for example in subjects with vascular risk factors such as long-term insulin-dependent diabetes (Fülesdi et al., 1997) or non-controlled hypertension.

1.3. From depression to cerebrovascular reactivity

However, the pathophysiologic mechanisms leading to this association between depression and stroke are not understood. We postulated that since CVR is a good indicator of stroke risk and depressed patients have a higher risk of stroke, depression might also lead to a reduced CVR and thus contribute to increased stroke risk.

We recently investigated a group of patients suffering from an acute depressive episode who were otherwise healthy and found a reduced CVR compared to the healthy control group (Neu et al., 2004). Due to the high prevalence of smokers among psychiatric patients, however, we had included smokers as well as non-smokers.

Several reasons led us to carry out the present study with non-smoking depressed patients and controls. First, long-term effects of smoking could still have influenced our previously published results since we did find a negative correlation between number of pack years and CVR. Second, addiction to nicotine could be stronger in depressed than in healthy people, however there is, to date, no objective way of quantifying this.

The present study evaluates our findings in a sample of non-smoking patients and controls without any vascular risk factors.

2. Materials and methods

2.1. Patients

Patients were recruited from in-patients at our university clinic. Inclusion criteria were major depression (of both unipolar or bipolar type disorders) as defined by DSM-IV (structured clinical interview for DSM-IV, axis I disorder (First et al., 1997)), ages 18–70 years (**48.48 ± 14.40**) and right-handedness. Pregnancy, the presence of any vascular risk factors or history of neurological, cardiac, vascular or other psychiatric diseases led to exclusion from the sample.

2.2. Controls

The control group was made up of individuals who responded to a newspaper advertisement. All individuals were drug-free, between 18 and 70 years old (**46.76 ± 13.69**), right-handed, without vascular risk factors or history of neurological, cardiac, vascular or psychiatric disorders. Although controls were not matched for age or gender their epidemiologic parameters did not differ significantly from the patient group.

2.3. General procedure

All patients and controls underwent a careful neurological and cardiologic examination, as well as ECG and blood chemistry tests. Clinical history was taken with particular attention to vascular risk factors. Any abnormalities in these examinations *led to exclusion.*

Based on standard definitions, the presence of vascular risk factors was determined. Cardiac arrhythmia, coronary heart disease, hypertension (systolic blood pressure values >130 mmHg and/or diastolic blood pressure >90 mmHg