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Short Communication

Abnormal glucose tolerance, white blood cell count, and telomere length in newly diagnosed, antidepressant-naïve patients with depression

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ABSTRACT

Chronic mood disorders have been associated with a shortened telomere, a marker of increased mortality rate and aging, and impaired cellular immunity. However, treatment may confound these relationships. We examined the relationship of glucose tolerance, white blood cell count and telomere length to depression in newly diagnosed, antidepressant-naïve patients. Subjects with major depression ($n = 15$), and matched healthy control subjects ($n = 70$) underwent a two-hour oral glucose tolerance test and evaluation of blood cell count and telomere content. The depression group had significantly higher two-hour glucose concentrations and a lower lymphocyte count than control subjects (respective means [SD] for two-hour glucose were 125.0 mg/dL [67.9] vs 84.6 [25.6] ($p < .001$); for lymphocyte count 2.1×10^9/L [0.6] vs 2.5×10^9/L [0.7] $p = .028$). Telomere content was significantly shortened in the depression group (87.9 [7.6]) compared to control subjects (101.0 [14.3]; $p < 0.01$). Abnormal glucose tolerance, lymphopenia and a shortened telomere are present early in the course of depression independently of the confounding effect of antidepressant treatment, supporting the concept of major depression as an accelerated aging disease.

1. Introduction

Depression will be the second contributor to the global burden of disease by 2020, according to the World health organization (WHO). The burden of depression is due not only to psychiatric disability but also to the associated comorbidity with physical diseases. The pathophysiology underlying the comorbidity remains unclear although several mechanisms have been implicated. As an etiological explanation, the association between mood disorders, cardiovascular diseases and immune disturbances has received considerable attention (Blume et al., 2011; Brown et al., 2009; Marano et al., 2009) suggesting that both systems might contribute to the increased mortality associated with mood disorders (Lippi et al., 2009).

Diabetes mellitus has been studied as a key factor contributing to the relationship between depression and increased cardiovascular disease. Epidemiological studies show that patients with diabetes have an increased risk of developing major depression (Egede, 2005), an association first described in 1969 (Mueller et al., 1969). The prevalence of depression among patients with type 2 diabetes mellitus is twice that of the general population (Nichols and Brown, 2003), with an estimated prevalence of depression in diabetic patients of 11–15% (Anderson et al., 2001). A meta-analysis suggested that a depressed adults have a 37% increased risk of developing type 2 diabetes (Knol et al., 2006) while another study showed a 23% increased risk of developing type 2 diabetes mellitus in depressed young adults (Brown et al., 2005; Knol et al., 2007). The mechanism of the association between depression and diabetes is still unknown, although the physiological reaction to the psychological stress associated with diabetes cannot completely explain the association (Grandinetti et al., 2000). In addition, potential confounding factors that are associated with weight gain and impaired glycemic control, such as body mass index and

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antidepressant treatment, must be taken into account (Derijks et al., 2008).

Immune disturbances have been described in patients with depression. Both immune activation and immune suppression (Blume et al., 2011) through an impaired cellular immunity function (increased inflammatory markers, neutrophilia and lymphopenia) have been described to underlie a major depressive episode. As stated before with diabetes and depression, the mechanism of association is unknown, although lymphopenia and a reduced lymphocyte proliferative response to mitogen have been confirmed in a review in depression suggesting an immune suppression related with an increased mortality. On the same line of evidence depression is associated with decreases in the number and percentage of lymphocytes (Zorrilla et al., 2001).

Another possible marker of morbidity in depression that has received considerable attention in mood disorders is telomere length. Telomere length has been linked to increased senescence in patients with depressed mood (Wolkowitz et al., 2010). The telomere is a nucleoprotein complex at the end of mammalian chromosomes that maintains chromosomal integrity and consists of double-stranded 5′-TTAGGG-3′ repeats. A shortened telomere has been linked to post-stroke mortality, dementia, cognitive decline (Martin-Ruiz et al., 2006), all-cause mortality in people above age 60 (Cawthon et al., 2003), type 1 diabetes (Balasubramanyam et al., 2007), type 2 diabetes (Adaikalakoteswari et al., 2007), and cardiovascular disease (Obana et al., 2003). Patients with major depressive disorder have been found to have a shorter telomere length (Lung et al., 2007; Wolkowitz et al., 2011), a marker of increased mortality rate and aging (Fitzpatrick et al., 2007) associated with oxidative and inflammatory stress. However, the subjects studied were not treatment-naïve, raising the question of whether this association was confounded by antidepressant treatment.

In an effort to clarify the pathophysiology of major depressive episodes, we tested the hypothesis that patients with major depression have cardiovascular and immune disturbances, and a shortened telomere. In order to avoid confounding by antidepressant medication side effects, we examined this relationship in newly diagnosed, antidepressant-naïve patients.

2. Materials and methods

2.1. Subjects

Patients with a major depressive disorder without psychotic features were recruited at the time of their first lifetime contact with psychiatric services for a depression. They came to clinical contact in a general academic hospital (Hospital Clinic of Barcelona). The catchment area for the hospital, Esquerra Eixample, is a relatively homogeneous middle class/upper middle class neighborhood in the center of Barcelona. These patients were enrolled if they had never previously received antidepressant or mood-stabilizing medications. They were allowed to receive anti-anxiety medication (lorazepam) the night before blood was drawn, to a maximum of 3 mg, but not on the day of the blood sampling and oral glucose tolerance test (GTT). Healthy control subjects were recruited using advertisements. All subjects came from a larger study of diabetes in neuropsychiatric disorders (Kirkpatrick et al., 2009).

Additional inclusion and exclusion criteria for all subjects were (1) age from 18 to 64 years, (2) no history of diabetes or other serious medical or neurological condition associated with glucose intolerance or insulin resistance (e.g., Cushing disease), (3) not taking a medication associated with insulin resistance (hydrochlorothiazide, furosemide, ethacrynic acid, metolazone, chlorthalidone, beta blockers, glucocorticoids, phenytoin, nicotinic acid, cyclosporine, pentamidine, or narcotics), and (4) no history of cocaine use in the previous 30 days. For control subjects, additional exclusion criteria were (1) no lifetime diagnosis of psychosis (associated with glucose intolerance; (Fernandez-Egea et al., 2009a) or major depressive disorder, (2) no current diagnosis of adjustment disorder, and (3) had not previously received psychotropic medication.

All subjects gave written informed consent for participation in the study, which was conducted with the oversight of the investigators' institutional review boards.

2.2. Assessments

All subjects were interviewed using the Spanish translation of the Structured Clinical Interview (SCID). The patients had no other history of Axis I disorder besides major depression. They were antidepressant-naïve, but no further information regarding past depressive symptoms was obtained. No subject with acute medical illness was included. For control subjects, additional exclusion criteria were (1) no lifetime diagnosis of psychosis (associated with glucose intolerance (Fernandez-Egea et al., 2009a); or major depressive disorder, (2) no current diagnosis of adjustment disorder, and (3) had not previously received psychotropic medication.

They were also administered the Dartmouth Assessment of Lifestyle Inventory (DALI), which quantifies substance abuse (Rosenberg et al., 1998), including a measure of smoking status (mean number of cigarettes per day). All subjects were given a 2-h 75 g oral glucose tolerance test which began between 8 and 9 AM after an overnight fast. Cortisol was sampled between 8 and 9 AM prior to ingesting glucose for the GTT. Height and weight, while wearing underwear and without shoes, were recorded between the blood samplings. Body mass index (BMI) was calculated using the formula (weight [kg]/height $[m]^2$). Further details on the GTT have been provided previously (Fernandez-Egea et al., 2009a).

Telomere DNA content (TC) was measured in blood leukocytes as previously described (Fernandez-Egea et al., 2009b). TC is directly proportional to telomere length measured by Southern blot ($r = 0.904$), can be measured with as little as 5 ng of genomic DNA, is insensitive to fragmentation of the DNA to <1 kb in length, and can be performed with DNA isolated from fresh, frozen, and paraffin-embedded tissues (Fordyce et al., 2006). Briefly, known DNA masses were UV cross-linked to a membrane, hybridized with telomere-specific oligonucleotides, end-labeled with fluorescein, and then detected with an alkaline phosphatase–conjugated antifluorescein antibody that produces light when incubated with CDP-Star substrate. Blots were exposed to Hyper film, digitized by scanning, and the telomere hybridization signals were measured.TC for each sample is reported as a percentage of the median chemiluminescent signal from 6 replicate determinations of each patient DNA relative to the chemiluminescent signal in the same amount of a reference DNA standard (placental DNA) measured in parallel. The laboratory determining TC was blind to the subject's clinical diagnosis. Cortisol was measured using an immunoassay (ADVIA Centaur; Siemens Healthcare). The coefficient of variation was 6.5%. Glucose was measured by an Advia 2400 Analyzer (Siemens, Barcelona Spain), using glucose oxidase reagents from the same manufacturer. Intra assay reliability expressed as coefficient of variation were lower than 3.2% for low values and lower than 2.8% for higher values.

2.3. Statistical analysis

The two matched groups were compared using the non-paired Student's *t*-test, or the χ^2 test for comparisons of proportions. Significance was defined as $p < 0.05$ for all statistical tests, and these were performed using SPSS version 17.0 for Windows.