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Epidermal growth factor and fibroblast growth factor-2 circulating levels in elderly with major depressive disorder

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ABSTRACT

Epidermal growth factor (EGF) and Fibroblast Growth Factor-2 (FGF-2) are growth factors involved neuronal growth and synaptic plasticity. These markers have been implicated in neuropsychiatric disorders, including major depression. However, no particular studies of EGF and FGF-2 have been conducted in older adults with major depressive disorder (MDD). In this study, we aim to investigate the plasma levels of EGF and FGF-2 in elderly with MDD. We included 89 older adults with MDD and 51 older (healthy control, HC) adults. The cognitive performance was evaluated by the Mattis Dementia Rating Scale (MDRS). The EGF and FGF-2 were measured by using multiplex assay for LUMINEX platform. There were also no significant differences between the patient group in terms of plasma levels of EGF and FGF-2 when compared to the HC group. There were not any significant correlations between plasma levels of EGF or FGF2 and MDRS total or individual scores in patient group and HC. There were significant correlations between plasma levels of EGF and FGF2 in both patient group and HC. Further study on plasma levels of EGF and FGF2 should be implemented in larger samples in elderly with MDD.

1. Introduction

Late-life depression (LLD) is one of the most common mental disorders in the elderly, with prevalence rates ranging from 1% to 5% (for major depressive episodes) (Byers et al., 2010). Its occurrence increases the risk of adverse health outcomes, including higher rates of medical morbidity (Vaccarino et al., 1999; He et al., 2014) increased risk of Alzheimer's disease and Vascular dementia (Wu et al., 2016; Ford-Perriss et al., 2001; Gomez-Pinilla et al., 1994) and higher risk of mortality (Vaccarino et al., 1999). Beyond disease, LLD has been linked to decreased health span, as measured by fewer years lived without frailty, significant functional impairments, elevated direct and indirect costs (Turner et al., 2006; Delgado-Rivera et al., 2009), Despite its frequency and public health relevance, the pathophysiological mechanisms that contributes to LLD are not well-established, but possibly involves the dysregulation of neurotrophic and other growth factors (Teixeira et al., 2010).

Epidermal growth factor (EGF) and the fibroblast growth factor (FGF) -2 are growth factors involved in neuronal growth and synaptic plasticity (Vaccarino et al., 1999; Wong et al., 2004). Few studies have evaluated the plasma levels of EGF and FGF in MDD, with inconsistent results. One study reported the plasma EGF levels were significantly lower in patients with MDD than HC (Tian et al., 2012), while Yavasci and collaborators did not find significant differences in serum EGF levels between MDD and control subjects (Yavasci et al., 2014). Two studies reported no significant differences of FGF-2 between patients with MDD and healthy control (HC) (Takebayashi et al., 2010; Kahl et al., 2009). He et al. (2014) reported significantly lower FGF-2 level in MDD patients compared to controls. In contrast, another study reported higher peripheral FGF-2 in MDD patients than in controls (Lu et al., 2013).

All published studies to date about the association between EGF and FGF-2 levels and MDD have focused on the younger adult population. Nonetheless, reduced neurotrophic support is also present in older

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adults with MDD (or late-life depression, LLD) (Diniz et al., 2010, 2013) and is a major driver of cognitive decline in this population (Diniz et al., 2014, 2016). However, there are no published studies that evaluate the association between EGF and FGF-2 and LLD. Our study aims, thus, to evaluate the association between EGF and FGF-2 plasma levels in LLD. Given the high heterogeneity of results in younger adults with MDD, we have no a priori hypothesis about the direction of the association of these biomarkers with LLD.

2. Methods

We included 89 older adults with MDD and 51 older adults with no past or current history of psychiatric disorders (healthy control, HC) in the current analysis. The presence of organic brain diseases, tumor or inflammatory diseases were exclusion criteria in this study. The patient had not received nor had clinical indication of ECT or TMS at the time of the assessment. The subjects were recruited and evaluated at the Geriatric Psychiatry Program, Faculty of Medicine, Federal University of Minas Gerais, Belo Horizonte, Brazil. The institutional Review Board of Faculty of Medicine, Federal University of Minas Gerais in Brazile approved this study and written informed consent was obtained from all subjects.

All subjects underwent a comprehensive psychiatric assessment. The diagnosis of major depressive episode (single or recurrent) was based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV, American Psychiatric Association, 1994). The severity of the depressive symptoms were evaluated by the Hamilton Depression Rating Scale, 21 items (HDRS). Patients diagnosed with Axis-1 or Axis-2 disorders other than MDD and patients diagnosed with depression or a psychotic disorder based on a general medical condition or substance use were excluded from the study. The Mattis Dementia Rating Scale (DRS) were used for assessment of cognitive function. The comparison group included older adults without history of major depression or other major psychiatric diagnosis. The study protocols were approved by the local Ethics Committee. All the subjects gave their written informed consent to participate in the study procedures before recruitment.

2.1. EGF and FGF-2 assay

Blood samples were taken from the patient and control groups from the antecubital vein after 12 h of fasting between 08:00 and 10:00 a.m. Plasma aliquots were stored at −80 °C freezer until laboratory analysis. The EGF and FGF-2 were assayed by a multiplex immunoassay with LUMIINEX according to the manufacturer instructions (Merck Millipore Corporation, Germany) in accordance with the manufacturer's instructions. All samples were analyzed in duplicate, and the laboratory analysis was done in a single run on the same day. A standard curve was created based on the following standard concentrations: blank, 3.2 pg/mL, 16 pg/mL, 80 pg/mL, 400 pg/mL, and 2,000 pg/mL. The analytical sensitivity of the assay is 0.7 pg/mL. The intra- and inter-assay coefficients of variation were 2.2% and 7.9%, respectively.

2.2. Statistical analysis

All data analysis was done using the SPSS v25 (SPSS Inc., Chicago, IL, USA). As the EGF and FGF-2 levels showed a non-normal distribution, we carried out non-parametric test to evaluate group differences in the levels of these biomarkers. We did Mann–Whitney *U* test to evaluate the effect of diagnosis (LLD vs controls) on the biomarkers levels. Spearman Correlation tests were done to evaluate the correlation between EGF, FGF-2, demographic variables, severity of depressive symptoms, and cognitive performance. Pearson Chi-square tests were used to evaluate differences in the frequency of sex and medical comorbidity between LLD and controls. Non adjusted statistical significance was defined as $p < 0.05$ (two-tailed). Given the large amount of comparisons and the risk of type I error, we also used the Bonferroni correction for adjusting the significance level in the analyses.

Table 1
Demographic and clinical characteristics, FGF-2 and EGF values according to diagnostic groups.

Variable	MDD (n = 89)	HC (n = 51)	Z or χ^2	P value
Age (Years)	72 (65–78)	71 (65–77)	$Z = -0.967$	0.333
Gender (Female/Male)	77/12	44/7	$\chi^2 = 0.078$	0.78
Education (Years)	4 (2–7)	10 (4–12)	$Z = -0.367$	<0.001
HDRS	20 (14–25)	1 (0–2)	$Z = -10.032$	< 0.001
GAD-7	10 (2.5–15)	0 (0–2)	$Z = -7.26$	< 0.001
Medical Comorbidities				
HTN (n)	68	37	$\chi^2 = 0.048$	0.827
DM-2 (n)	35	11	$\chi^2 = 3.434$	0.064
Obesity (n)	33	16	$\chi^2 = 0.015$	0.901
Antidepressant use (n)	64	0		
DRS Score	121 (112–132)	134 (128–140)	$Z = -5.166$	< 0.001
FGF-2 (μg/dL)	27.8 (1.8–92. 9)	35.7 (4.4–117.7)	$Z = -0.792$	0.428
EGF (μg/dL)	9.2 (2.6–26.3)	9.7 (3.9–39.7)	$Z = -0.873$	0.383

All values are shown as median (25th–75th percentile).
Abbreviations: HDRS: Hamilton Depression Rating Scale – 21 item; GAD-7: Generalized Anxiety Disorder – 7 item; HTN: arterial hypertension; DM-2: Diabetes Melito Type 2; DRS: Mattis Dementia Rating Scale; FGF-2: Fibroblast Growth Factor -2; EGF: Epithelial Growth Factor.

3. Results

The demographic and clinical data for all participants are shown in Table 1. LLD and controls showed no significant differences in most clinical and demographic variables, except that LLD subjects had a significantly less years of formal education compared to controls ($p < 0.001$). As expected, the LLD group showed worse scores on the DRS and higher levels of anxiety symptoms compared to the controls. Sixty-four (65%) LLD patients were under antidepressants treatment at the time of study inclusion. The most common antidepressant in this population was sertraline (78%), followed by venlafaxine (15%) and nortriptyline (5%), and others (2%).

There were no significant differences between the LLD and HC groups on plasma levels of EGF ($z = -0.873$, $p = 0.38$) or FGF-2 ($z = -0.792$, $p = 0.42$). Antidepressant use did not have a significant impact on plasma levels of EGF ($z = -0.483$, $p = 0.629$) or FGF-2 ($z = -0.156$, $p = 0.876$). In a sensitivity analysis, excluding those who were on antidepressants, there was no significant differences in EGF ($z = -0.177$, $p = 0.86$) or FGF-2 ($z = -0.800$, $p = 0.424$) between the LLD group and controls. Sex had no significant impact on EGF ($z = -0.121$, $p = 0.307$) or FGF-2 ($z = -0.249$, $p = 0.803$).

HDRS scores were not correlated with EGF (rho = 0.05, $p = 0.6$) or FGF-2 (rho = 0.01, $p = 0.9$) in the whole sample. GASD-7 scores showed no significant correlation with EGF (rho 0.5, $p = 0.6$) or FGF-2 level (0.02, $p = 0.85$). In contrast, DRS score was significantly correlated to plasma levels of FGF-2 in the whole sample (rho = 0.3, $p = 0.009$), but not with EGF levels (rho = 0.06, $p = 0.6$). However, the significance level of the correlation between FGF-2 and DRS scores did not survive the adjustment for multiple comparisons (Bonferroni corrected p-value = 0.008).

4. Discussion

To the best of our knowledge, the present study is the first to investigate the relationship between plasma EGF levels and FGF-2 levels and MDD in elderly. We also examined the correlation of EGF and FGF-2 levels with cognitive function and gender. Our findings indicated that

no significance of EGF levels and FGF-2 levels were found in elderly patients with MDD. There was no gender difference of EGF levels and FGF-2 levels in elderly patients with MDD, or there was no significant correlation between gender and plasma levels of EGF and FGF-2 in patients. Furthermore, there were not any significant correlations between plasma levels of EGF or FGF-2 and MDRS total or individual scores in patient group and the HC group. Above findings are in line with Yavasci's report regarding levels of EGF in MDD patients (2014, Takebayashi's report (2010) and Kahl's report (2009) regarding level of FGF-2 in MDD patients. Yavasci (2014) also did not suggest any correlations between plasma levels of EGF and sex, BMI, numbers of relapses or the duration of the disorders. Ikeda et al. (2008) did not demonstrate any association between levels of plasma EGF and age, sex, onset age of the disorder, smoking status or BMI.

MDD is considered to be a neuropsychiatric illness. The roles of FGF-2 include angiogenesis (Ford-Perriss et al., 2001) and neurogenesis (Gomez-Pinilla et al., 1994; Turner et al., 2006; Delgado-Rivera et al., 2009). It has been reported that FGF-2 is a key factor in the pathophysiology of mood disorders. One hypothesis is peripheral FGF-2 is the consequence of increased oxidative stress in MDD. One study has found peripheral FGF-2 levels in MDD patients significantly decreased after treatment (He et al., 2014). It is noted that patients in this study have received antidepressants with HDRS score indicated less depression after 8 weeks treatment. Therefore, it is hard to differentiate the decreased level of FGF-2 is due to direct effects of antidepressants or due to improved mood state. Our study did not detect significant difference of levels of FGF-2 in MDD patients and HC. Noteworthy, the level of FGF-2 was reported decreased with age (Yavasci et al., 2014), which may partially explain our finding regarding no significant differences were found between elderly patients with MDD and HC. Another study also pointed out that peripheral FGF-2 levels in patients with MDD are significantly decreased after treatment (He et al., 2014), which could be related to non-significant levels of FGF-2 in our elderly MDD patients as most of patients are currently receiving treatment.

None of previous studies have focused on elderly with MDD. Despite no significance of EGF levels and FGF-2 levels were found in MDD patients, these results are helpful in furthering our understanding of the role of EGF and FGF-2 in the pathophysiology of MDD and the involvement of FGF-2 and EGF in elderly with MDD.

5. Limitations and implications

There are limitations of this study. First, most patients are currently on medications. However, it is noteworthy that one report found no alterations in plasma EGF levels differences between the patients who were undergoing treatment and those who were drug naïve (Sohrabji, 2006). Second, majority of MDD patients in our study are females. It has reported level of EGF is affected by hormonal changes (Sohrabji, 2006). Our study did not find any difference in terms of EGF and FGF-2 blood level between male and female patients. Third, our sample size may have been underpowered to find significant differences on EGF and FGF-2 level in LLD. Larger samples are needed to be studied to determine the alteration of EGF and FGF-2 in depression especially in elderly. Last, we did not assesse subtypes of depression due to limited samples recruited in our study, which could affect the results as presented in our study.

6. Conclusions

In line with the previous studies, the present study demonstrated no significant differences between the patient group to the control group in terms of the plasma EGF and FGF-2 levels. We did not find any significant correlation between the plasma EGF and FGF-2 levels and age but EGF is affected by gender in the patient group. We also found HDRS score is correlated to plasma levels of FGF-2 in the patient group. Tian et al. (2012) speculated that decreased levels of EGF are a common phenotype in severe forms of psychiatric disorders, not the mild ones. Further studies with larger samples are needed to determine whether EGF and FGF-2 might be useful pathophysiological biological indicators of depression especially in elderly.

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Conflict of interest

The authors have no conflicts of interest to declare.

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