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Short communication

The inflammatory marker GDF-15 is not independently associated with late-life depression

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ABSTRACT

Objectives: Growth differentiation factor-15 (GDF-15) is an inflammatory molecule that reacts to cell stress. Since major depression is associated with inflammation, we examined whether GDF-15 levels are elevated in patients with late-life depression.
Methods: Plasma GDF-15 levels were analyzed in 350 patients diagnosed with major depressive disorder in the last six months and 128 non-depressed controls from the Netherlands Study of Depression in Older persons (age ≥ 60 years). Major depressive disorder and age of onset were assessed with the Composite International Diagnostic Interview. Severity of depressive symptoms was measured with the Inventory of Depressive Symptoms (IDS-30). Multiple linear regression models were applied to study depression (diagnosis, onset age, severity, antidepressant drug use) as determinant of GDF-15 level, adjusted for demographic and clinical variables.
Results: Plasma GDF-15 levels were 22% higher in patients with major depression compared to controls. Within the depressed group, levels were higher in patients with older age of onset. GDF-15 levels showed a small, positive correlation to the levels of the inflammatory mediators IL-6 and C-reactive protein ($r = 0.23$, and 0.24, $p < 0.05$). This increase was independent from comorbidities, such as cardiovascular disease, rheumatism and diabetes, and anti-inflammatory drugs. However, this increase was dependent on lifestyle factors as smoking, physical activity and alcohol use. Within the depressed subgroup, neither depression severity or antidepressant drug use was associated with GDF-15 levels in the fully adjusted models.
Conclusion: The inflammatory factor GDF-15 does not seem to be an independent inflammatory marker for late-life major depressive disorder.

Introduction

Growth differentiation factor-15 (GDF-15), also known as macrophage inhibitory cytokine-1, is a member of the Tumor Growth Factor-beta (TGF-β) family of inflammatory proteins. GDF-15 is primarily expressed under conditions of inflammation and oxidative stress. Increased plasma levels of GDF-15 have been associated with, for instance, the presence and risk of cardiovascular diseases [1].

Interestingly, GDF-15 has also been related to neuroinflammation [2,3]. In view of this relation, we hypothesized that GDF-15 would be a good inflammatory biomarker for neurological diseases. Therefore, we performed a pilot study to examine the plasma GDF-15 levels of patients with Alzheimer's disease with those in cognitively intact controls. Interestingly, we found that plasma GDF-15 levels were only increased in patients with depressive symptoms, leading us to hypothesize that GDF-15 is a sensitive biomarker for inflammation in depression. The association between inflammation and depression has been studied repeatedly, with variable outcomes, which may be due to variability in the measured inflammatory mediators [4]. Most consistent associations with depression are found for the peripheral inflammatory markers interleukin-6 (IL 6), C-reactive protein (CRP) tumor necrosis factor alpha (TNF-α) [5,6].

This study examines the association between plasma GDF-15 levels and depressive disorder in a large cohort of formally diagnosed depressed and non-depressed older persons, and we studied the role of potential confounders.

Methods

Sample

Data were used from the Netherlands Study for Depression in Older persons (NESDO), a multi-site naturalistic prospective cohort study [7]. The NESDO study included 378 depressed and 132 non-depressed older adults. Inclusion criteria were an age of 60 years or above and for the

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patient group a past 6-month diagnosis of depression or dysthymia according to DSM-IV-R criteria [8] confirmed with the Composite International Diagnostic Interview (CIDI; WHO version 2.1; life time version). Participants with a clinical diagnosis of dementia, a psychotic or bipolar disorder, a Mini Mental State Examination-score (MMSE) under 18 (out of 30 points), or insufficient command of the Dutch language were excluded. Inclusion criteria for non-depressed controls were no lifetime diagnosis of depression (according to the CIDI), dementia or other serious psychiatric disorders, and good command of the Dutch language. The ethical review boards of the participating institutes have approved this study. All participants gave informed consent.

For this study participants were selected on the presence of a major depressive disorder (MDD) and availability of plasma (N = 350 patients, 128 non-depressed controls).

GDF-15 measurement in plasma

Blood samples were obtained in the morning between 8 and 9 am after an overnight fast, centrifuged at 1800 *g* for 15 min at room temperature. All plasma was immediately frozen at −80 °C at the Biobank of the Department of Clinical Chemistry VU University Medical Center. GDF-15 was analyzed on a novel automated assay on Abbott Architect, with a reported limit of detection of 10 pg/mL. Reagents were provided by Abbott. Assay linearity analysis was established by dilution of two samples in five increments up to 16-fold. To test inter-assay reproducibility, 7 samples were measured on 2 days, yielding a coefficient of variation of 4.9%. The intra-assay coefficient of variation was 3.8%, obtained by analysis of three plasma samples in 2–3 replicates, in three independent measurements. Recovery analysis was measured by three concentrations of spiked calibrator protein. The mean recovery was 109% (n = 29).

Other inflammation markers

High-sensitivity plasma levels of CRP were measured in duplicate by a immunoturbidimetric assay (Tina-quant CRPHS, Roche Diagnostics, Mannheim, Germany). Intra- and inter-assay coefficients of variation were 2% and 2%. Plasma IL-6 levels were measured in duplicate by a high sensitivity ELISA (PeliKine Compact™ ELISA, Sanquin, Amsterdam, The Netherlands). Intra- and inter-assay coefficients of variation were 8% and 12%. All samples had CRP and IL-6 levels above the lower limits of detection of the kits.

Depression characteristics

Age of onset was assessed with the CIDI, severity of depressive symptoms with the Inventory of Depressive Symptoms 30-item version (IDS-30; [9]).

Covariates

The selection of potential confounders of the association between GDF-15 and depression was based on previous literature [1,10] and included demographic data, such as age, gender, and educational level; clinical variables, such as specific chronic diseases and inflammatory drugs; and life style variables: smoking, alcohol intake, and physical activity. Chronic diseases were assessed by means of a well-validated, self-report questionnaire [11]. Medication use was assessed with drug container inspection of all drugs used in the past month and classified according to the World Health Organization Anatomical Therapeutic Chemical classification (ATC) (WHO, 2010). Inflammatory medication included corticosteroids, non-steroidal and other anti-inflammatory agents.

Finally, lifestyle characteristics, including smoking behavior (never, former and current), alcohol intake (number of drinks per week), and physical activity based on the International Physical Activity Questionnaire [12].

Statistics

First, differences between the MDD patients and the non-depressed controls were examined by means of independent t-tests or the Mann–Whitney test where appropriate for continuous variables, and chi-square tests for categorical variables. To study the association between GDF-15 and the other inflammation markers bivariate correlations were computed. To obtain normal distribution, GDF-15 was ln-transformed. To study whether GDF-15 levels were dependent from the age of onset of depression, we examined the association between age of onset groups (split on the median) and the lnGDF-15 levels by means of bivariate regression analyses.

We studied the adjusted and unadjusted association between MDD (independent variable) and lnGDF-15 (dependent variable) in linear regression models. For explorative reasons confounders were entered group wise in subsequent models. Subsequently, we repeated the analyses with the IDS scale (severity of depressive symptoms) as independent variable. Analyses were performed by IBM SPSS version 20. A p-value <0.05 was considered as statistically significant.

Results

Table 1 shows the descriptives of the sample. GDF-15 levels were significantly increased by 22% in patients with MDD. The GDF-15 levels were positively correlated to the cytokines IL-6 and CRP (r = 0.23, p < 0.01 for IL-6 and r = 0.24, p < 0.01 for CRP). The average levels of

Table 1
Characteristics of the controls and MDD patients.

	Controls (n = 128)	MDD patients (n = 350)	p
Demographic characteristics			
Gender (% female)	61.7	66	0.39
Mean age (SD)	70.0 (7.2)	70.5 (7.3)	0.49
Level of education			<0.001
Basic, %	7.0	20.3	
Intermediate, %	53.1	59.1	
High, %	39.8	20.6	
Depression characteristics			
Mean age at onset depression (SD)	–	48 (20.4)	
Depression severity (SD)	7.7 (6.4)	30.4 (13.1)	<0.001
Antidepressant drug use			
SSRI, %	0.8	26.9	<0.001
TCA, %	2.4	22.6	<0.001
Other, %	0	28.6	<0.001
Clinical characteristics			
Diabetes, %	18.0	13.2	0.19
Heart disease, %	21.1	22.3	0.77
Rheumatism, %	7.0	14.6	0.03
Stroke, %	2.3	11.2	0.003
Head injury, %	522.7	27.5	0.29
Anti-inflammatory drug use, %	25.0	39.1	0.004
Lifestyle characteristics			
IPAQ, MET-minutes/week, median (IR)	2507 (1406–4449)	1520 (536–3555)	<0.001
Smoking (%)			<0.001
Never	29.7	29.1	
Former	61.7	43.8	
Current	8.6	27.1	
Alcohol use, median no. of drinks per day (IR)	0.53 (0.15–1.18)	0.03 (0–1.18)	<0.001
Inflammatory markers			
GDF-15 (pg/mL), median (IR)	712.85 (584.7–1055.9)	868.6 (639.7–1189.9)	0.002
lnGDF-15 (SD)	6.68 (0.47)	6.81 (0.48)	0.006
IL-6 (pg/mL), median (IR)	0.59 (0.34–1.64)	0.50 (0.33–1.83)	0.07
CRP (pg/mL), median (IR)	1.58 (0.83–3.15)	1.87 (0.82–4.08)	0.35

SD: standard deviation; IPAQ: International Physical Activity Questionnaire; IR: interquartile range; MET: metabolic equivalent of task minutes (ratio of energy expenditure during activity compared to rest times the number of minutes performing the activity).