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Elevation of tumor necrosis factor alpha levels is associated with restless legs symptoms in clinically depressed patients

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ABSTRACT

Background: Restless legs syndrome is a sensorimotor disorder associated with several mental illnesses particularly depression.

Methods: A cross-sectional study of primary care patients. The prevalence of restless legs symptoms was studied in 706 patients with depressive symptoms and 426 controls without a psychiatric diagnosis by using a structured questionnaire. The depressive symptoms were evaluated with the BDI and the psychiatric diagnosis was confirmed by means of a diagnostic interview (M.I.N.I.). The subjects with elevated depressive symptoms were divided into two groups subjects with depressive symptoms with and without clinical depression.

Results: The prevalence of restless legs symptoms was 24.8% in the controls, 50.0% in the patients with clinical depression and 42.4% in the patients with depressive symptoms. CRP value was significantly higher ($p = .003$) in the clinically depressed patients than in the other groups. There was a higher concentration of TNF-α in the subjects with restless legs symptoms (7.4 ng/l ± 3.2) compared with the subjects without symptoms (6.7 ng/l ± 2.3)($p < .001$). There was a significant difference in the TNF-α levels between the subjects with and without restless legs symptoms in the depression group ($p < .001$) and among the patients with depressive symptoms but no a depression diagnosis ($p = .022$). In these groups, restless legs symptoms were associated with elevated levels of TNF-α.

Conclusions: TNF-α level was associated with restless legs symptoms only among subjects with depressive symptoms whether they had clinical depression or not. We suggest that TNF-α could be an underlying factor between restless legs symptoms and comorbidities.

1. Introduction

Restless legs syndrome is a common sensorimotor disorder. Restless legs symptoms are characterized by an unpleasant sensation in the legs that appears at rest in the evening or during the night, but daytime symptoms are not exclude. In addition, patients suffer from an urge to move their legs and moving or stretching the legs relieves the symptoms [1,2]. In previous studies, the prevalence of restless legs syndrome has been between 4% and 29% [3]. Among primary care patients, the prevalence has been found to be 24% to 25% [4,5]. Knowledge about the pathophysiology of restless legs syndrome and clinical experience have increased during the last decade, but the exact pathophysiology is still obscure [6].

Several different theories on the cause of restless legs syndrome have been suggested, such as deficient dopaminergic neurotransmission, iron deficiency, hormones, genetics, peripheral hypoxia, neuroinflammation and a lack of folate [7–12]. A lack of iron metabolism is more about the central nervous system than the peripheral parts, it affects dopaminergic function, thereby disturbing monoamine neurotransmitter synthesis [9]. For its part this could explicate the presences of depressive symptoms alongside of restless legs symptoms [13]. There are numerous studies on the relationship between depressed mood or depression and restless legs syndrome [14,15]. The fundamental causes that binds depression and restless legs symptoms together is unresolved.

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Notwithstanding, the relationship between tumor necrosis factor alpha (TNF- α) and depression is intricate. The activity of TNF-α is possibly linked to several other diseases such as psoriasis, rheumatoid arthritis and inflammatory bowel disease [16–18]. TNF-α is a member of a superfamily of proteins and it is most accurately a pleiotropic cytokine. TNF-α is a crucial factor intrinsic to the immune system's proinflmmatory actions. Many divergent cells, e.g., activated macrophages, monocytes, T-cells, lymphocytes and astrocytes, have the capacity for produce TNF- α [17]. Major theories that have linked TNF- α and depression together are revision on the hypothalamic-pituitary-adrenal-axis, genetic polymorphisms and changes in serotonin and dopamine transporters [19]. According to former studies, especially elevated levels of TNF-α have not had a conclusive link to depression [20–24], but this connection invariably exists [25,26]. The relation between TNF-α and restless legs syndrome has proved to be insignificant [27].

Previously, a commonly used inflammation marker— C reactive-protein (CRP)— activates the synthesis of interleukin-6 and TNF-α and most of all is associated with bacterial inflammation, tissue injury or stress but CRP has been found to be connected to depression [28,29]. The relationship between CRP and restless legs syndrome was negligible in a previous study [30]. However, another study suggested that systemic low-grade inflammation might play a role in restless legs symptoms [27]. Thus, inflammation could be one factor linking restless legs symptoms to depression. A relationship between depression, restless legs symptoms and inflammation markers, including CRP and TNF-α, has not been studied before at lenght thus the relationship required more searching.

Aims

Due to non-existent data on the correlation between TNF-α, restless legs symptoms and a diagnosis or symptoms of depression, we decided to study this relationship in a geographically defined sample of patients with depressive symptoms with and without clinical depression and population-based control subjects without a psychiatric diagnosis. We hypothesized that TNF-α may have a role in the elevated presentation of restless legs symptoms among depressed subjects.

2. Material and methods

New patients aged 35 years or older who went themselves or were referred by a general practitioner to a depression nurse case manager in 2008–2009 due to depressive symptoms and a score of least 10 in the 21-item Beck's Depression Inventory (BDI) were enlisted in this study. Altogether 706 patients were involved. The study (the Finnish Depression and Metabolic Syndrome in Adults study, FDMSA) was conducted in municipalities belonging to the Central Finland Hospital District, with a catchment area of 274,000 residents. Notification was based on written and oral patient information and written consent was obtained before any study procedures. The study protocol was approved by the Ethics Committee of the Central Finland Hospital District. The FDMSA -study has been reported in previous studies [31–35].

Random sampling was used to select a group of 426 middle-aged (> 35 years) persons as controls from among residents in the participating municipalities. Concurrently with the patient recruitment in 2008–2009, an age, sex and community stratified random sample representing the population in the study region was taken by Statistics of Finland (http://www.stat.fi). Statistics of Finland is independent organization under the Ministry of Finance and manages the data from administrative registers in Finland. All the subjects in the control group had a BDI score below 10 and no psychiatric diagnosis or current depressive symptoms and they used no psychoactive medications. A total of 27 subjects in the study groups did not answer the question about restless legs symptoms. To eschew misrepresented results, the data do not include subjects ($N = 78$) c-reactive protein (CRP) values over 30 mg/l or TNF-α values over 50 ng/l, ensuring that microbe based contamination would not excessively impact the results [36,37].

All the participants filled in a standard questionnaire form containing questions about previously diagnosed somatic disorders and use of medications, including antidepressants and hormone replacement therapy in females. Data on current smoking, years of education, use of alcohol (number of drinks per week) and leisure-time physical activity (number of 30-min exercise sessions) were also collected. Leisure-time physical activity was determined with the question:" How often do you do physical activity at least half on hour so that you are out of breath and sweating?" then answers were classified as low (0–2 sessions per month), moderate (1–2 sessions per week), or high (three or more sessions per week) [35].

The depressive symptoms were evalueted with the 21-item Beck's Depression Inventory (BDI) [38], which was completed by the participants. The psychiatric diagnosis was confirmed with a diagnostic interview (Mini-International Neuropsychiatric Interview; M.I.N.I. [39]) conducted by a trained study nurse [40]. Out of the whole study population, 439 subjects had a BDI score of 10 or higher and a diagnosis of depression determined with the diagnostic interview (M.I.N.I.) [39,41,42].

Restless legs symptoms were detected with a structured and tested question that takes into account the core characteristics of restless legs syndrome discomfort: an urge to move the legs, primarily during rest or inactivity, and partial or total relief with movement, with the presence or worsening of discomfort exclusively in the evening or at night. According to a previous validation study, the questionnaire had 100% sensitivity and 96.8% specificity. Moreover, the likelihood ratio for a positive result (LR + =31,25) adverted to the positive test had a conclusive elevate in the probability of restless legs syndrome [43].

The blood sample collection procedure happened in the health centre's laboratories by educated nurse and in an outpatient setting. Glucose and lipid level determinations were based on fasting blood samples drawn between 8 and 11 o'clock after 12 h of fasting. TNF-α was determined from freezed samples and cocentration was analyzed using an Immulite 1000 immunoassay analyzer (Siemens Healthcare Diagnostics Products Ltd., Gwynedd, UK). Serum total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides and plasma glucose were analyzed using Modular Analytics SWA (Hitachi High-Technologies Corporation, Tokyo, Japan).

2.1. Statistical analysis

Statistical comparisons between the groups was done by analysis of variance (ANOVA), Kruskal-Wallis test, Chi-Square test or Fisher-Freeman-Halton test, when appropriate. When adjusted models were used, analysis of covariance (ANCOVA) was applied; the models included age, smoking, alcohol use, body mass index and physical activity as covariates. In the case of violation of the assumptions (e.g. non-normality), a bootstrap-type method was used (10,000 replications) to estimate standard error. The normality of variables was evaluated by the Shapiro-Wilk W test. All the analyses were performed using STATA 15.0.

3. Results

A total of 1027 subjects, comprising the patients and controls, participated in our study; (33.0%) men and 688 (67.0%) women. Of these subjects, 396 were controls with no psychiatric diagnosis, 243 were patients with depressive symptoms without a depression diagnosis and 388 patients had received a depression diagnosis. All the subjects with elevated depressive symptoms and the clinically depressed patients had higher triglyceride levels, lower leisure time physical activity and higher body mass index (BMI) than the controls. Furthermore, the prevalence of current smoking was higher in the patient groups than in the controls. The clinically depressed patients had a significally higher