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Original Article

Serum serotonin in rheumatoid arthritis patients: Relation to rheumatoid factor positivity, clinical manifestations and fibromyalgia

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ABSTRACT

Aim of the work: To estimate serum level of serotonin in rheumatoid arthritis (RA) patients and study its relation with various clinical data, radiographic scores and fibromyalgia.

Patients and methods: This study involved eighty RA patients divided equally according to rheumatoid factor (RF) positivity. Modified Health Assessment Questionnaire, disease activity score in 28-joints (DAS 28), visual analogue scale of pain, Short Form Health Survey for mental and physical health, fibromyalgia questionnaire, RA Articular Damage score and radiological joint damage by van der Heijde modification were assessed. Serum level for serotonin was measured for all patients.

Results: The mean age of seronegative patients was 41.7 ± 10.7 years; 36 females and 4 males and of seropositive (44.9 ± 12.9 years and were 34 females and 6 males). Serum serotonin level was high in RA patients compared to control (129.8 ± 99.1 ng/ml vs 79.6 ± 54.5 ng/ml respectively, $p = 0.001$). Serum serotonin was higher in seropositive than seronegative (155.9 ± 93.2 vs 101.5 ± 99.4 ng/ml respectively, $p = 0.007$). Fibromyalgia syndrome (FMS) was associated with a significant lower serotonin level in both groups ($p < 0.005$). High serotonin level was associated with combined disease modifying antirheumatic drugs ($p = 0.04$) in seronegative patients. A lower serotonin level was associated with corticosteroids administration and dry eye ($p = 0.03$, $p = 0.004$ respectively) in seropositive cases. A significant correlation was present between serotonin level with erythrocyte sedimentation rate, vitality energy and mental health ($r = 0.4$, $p < 0.05$) in seropositive patients.

Conclusion: Serum serotonin level was high in RA, especially in seropositive patients. It demonstrated central antidepressant and peripheral pro-inflammatory role. The SSRI could be of benefit only in RA with FMS.

1. Introduction

Rheumatoid Arthritis (RA) is a chronic disease that can lead to pain, joint destruction, loss of function, and poor quality of life [1]. In RA the association between fatigue and pain had been well established [2]. Fatigue can be influenced by numerous factors, such as inflammation, pain, disability, and psychosocial factors (mood, beliefs, behavior) [3]. Rheumatoid factors (RFs) are predictors of more severe disease forms and higher tendency to develop extra-articular manifestations [4]. It has been shown that a progressive decrease in the RF levels parallels the decrease of clinical activity in patients treated with traditional disease modifying anti-rheumatic drugs (DMARDs) or biologic agents [5]. The magnitude of symptoms may not necessarily correlate with the severity of the underlying disease and symptoms may persist even when disease exacerbations have apparently settled [6]. Fibromyalgia can occur secondary to many inflammatory conditions and the frequency in Egyptian RA patients was estimated to be 14% [7] with a possible association to vitamin D deficiency [8]. It is of paramount importance to identifying secondary FMS in RA because unrecognized FMS can result in heightened disease activity scores and thus over treatment of RA or, in some cases, the cessation of therapies due to a perceived lack of efficacy [9].

Serotonin or 5-hydroxytryptamine (5-HT) is a neurotransmitter that has an important role in brain homeostasis. It is surprising that only 1% of 5-HT in the human body is found in the CNS. The remaining 99% is found in other body compartments such as the gastrointestinal tract and immune tissues [10]. It is thought to be a contributor to feelings of well-being and happiness [11]. Serotonin plays a key role in bone

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metabolism, osteoporosis [12] and innate immune response [13]. It has been proposed as a T-cell, [14] B lymphocytes modulator [15]. While the serotonin system regulates the hypothalamic pituitary adrenal (HPA) axis, corticosteroids have been found to regulate the serotonin system via serotonin synthesis and the various serotonin receptors [16].

Serotonin has long been regarded as a mediator of inflammation and has in different models demonstrated a pro-inflammatory effect. The 5-HT2A receptor has been shown to be a mediator of serotonin-induced pain and inflammation in rats. The magnitude of arthritis has also been shown to be limited by blockade of 5-HT2A receptors [17]. The release of serotonin from platelets is, at least in some cases, greater in patients with active or more severe RA disease. Furthermore, seropositive RA patients were found to have a higher serum and plasma levels of 5-HT than the healthy individuals and higher plasma levels than the seronegative patients [18]. Genetic variations in 5-HT receptors associated with RA have been reported [12].

In this study we aimed to estimate level of serum serotonin in RA patients and find its relation with RF positivity, various clinical manifestations, laboratory investigations, scores and fibromyalgia.

2. Patients and methods

Eighty patients fulfilling the 2010 ACR-EULAR classification criteria for RA [19] were recruited for the study, they were divided into two equal groups according to the RF positivity; 40 RF negative (Group I) and 40 RF positive (Group II) from the Rheumatology and Rehabilitation Department, Faculty of Medicine, Cairo University between September 2014 and July 2016 .Exclusion criteria were any patients with thyroid disease, diabetes mellitus, hepatitis C, patients on selective serotonin reuptake inhibitor (SSRI), selective serotonin norepinephrine reuptake inhibitors (SSNRI), Tricyclic anti depressants, anti-migraine, anticonvulsants, anti Parkinsonian agents, any kind of antipsychotics, opioids, tramadol and antiviral drugs. The study was approved by the Ethics Committee of Faculty of Medicine, Cairo University Hospitals. All patients gave their informed consent to participate in the study. Eighty age and sex matched apparently healthy subjects were taken as control. Patients were thoroughly examined. Pain was evaluated by visual analogue scale (VAS) [20]. The disease activity in RA patients was assessed using the disease activity score (DAS28) [21]. Screening of fibromyalgia syndrome (FMS) was done by using the 2010 ACR criteria [22], RA Articular Damage Score (RAAD) score was used for defining articular damage by physical examination [23]. The functional status was assessed according to the Modified Health Assessment Questionnaire (MHAQ) [24] and Short Form Health Survey (SF36) questionnaire for mental and physical health [25]. Plain x-rays (postero-anterior view) on the hands and feet were obtained for all patients using the modified van der Heijde score [26].

Blood specimens were collected after an overnight fasting analyzed for complete blood count (CBC), erythrocyte sedimentation rate (ESR) by the Westergren method, C-Reactive protein (CRP) was calibrated by Nephelometry method and Rheumatoid Factor (RF) was assayed with a quantitative immunonephelometry test (Behring, Marburg, Germany). RF was considered positive when the concentration was higher than the cut-off value of the kit (15 IU/ml). The liver and kidney function tests were considered.

The quantitative detection of serotonin in serum levels was performed using a commercially available enzyme linked immunosorbent assay (ELISA) kit provided by DRG Instrument, Gmb H, Germany, following the manufacture recommendations.

Statistical analysis: The statistical program SPSS version 15 was used for statistical analysis. Results were expressed as mean (± standard deviation), or number (percentage). Student's *t*-test was used to compare continuous variables between patients and controls, and between subgroups of RA patients (RF positive and negative). The chi-square test for the categorical variables was performed when appropriate. The correlations between variables were presented as the Spearman's correlation coefficient (rho). The level of statistical significance was < 0.05 (2-tailed).

3. Results

Eighty RA patients were recruited into two groups each composed of 40; group I (RF negative), with mean age of 41.7 ± 10.7 years, they were 36 (90%) females and 4 (10%) males and group II (RF positive) with mean age 44.9 ± 12.9 years, they were 34 (85%) females and 6 (15%) males. There were not significant difference between the two groups as regard the clinical parameters, the presence of FMS, SF36, DAS28, MHAQ, the X-ray scoring method and laboratory investigations including ESR, CRP, hemoglobin, total leucocytic count, platelet, transaminases and creatinine. Serum serotonin level was significantly higher in RA patients than control (79.6 ± 54.5 ng/ml) ($p = 0.001$), it was higher in group II than group I and control as shown in Fig. 1. Serotonin level was significantly lower in patient with a secondary FMS compared to those without in both groups as shown in Table 1. In group I, high serotonin level was demonstrated in patients receiving combined DMARDs *vs* patients receiving one DMARD (170.6 ± 137.7 ng/ml vs 86.8 ± 84.9 ng/ml respectively, $p = 0.04$). In group II a low serotonin level was demonstrated in RA patients with dry eye *vs* without (74.5 ± 59.5 ng/ml vs 176.2 ± 89.5 ng/ml respectively, $p = 0.004$). Also serotonin level was lower in RA patients receiving corticosteroids *vs* non receiver (128.7 ± 91.3 ng.ml *vs* 182.9 ± 89.2 ng/ml, $p = 0.03$). Table 2 shows the correlation of the serotonin level with the SF36 questionnaires, MHAQ and ESR. In group II serum serotonin level significantly correlated with ESR ($p = 0.003$, $r = 0.4$), vitality ($p = 0.005$, $r = 0.4$) and mental health ($p = 0.003$, $r = 0.4$).

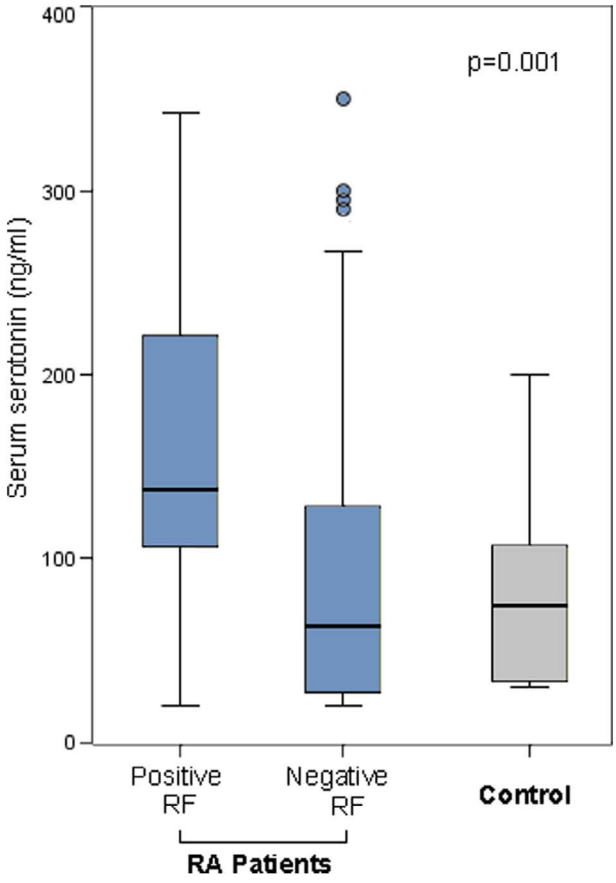

Fig. 1. Serum serotonin level among different groups of rheumatoid arthritis patients and control.