Prolactin, Another Important Player in the Mosaic of Autoimmunity

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As of today, more than 80 different autoimmune diseases have been described, in which an inappropriate immune reaction against diverse tissues and organs plays a critical role [1]. Although diverse factors such as environment, diet, genetic predisposition, smoking, sex hormones and other agents have been shown to be involved in autoimmunity, the pathogenesis of this heterogeneous group of diseases is still not completely understood [2]. The high prevalence of autoimmunity among females prompted an extensive investigation of gender and hormonal involvement in the pathogenesis of these diseases [3]. The great majority of reported studies focused on the complex interplay between estrogen, progesterone, testosterone, prolactin and autoimmunity [3,4].

A recent study by Aulestia and colleagues [5] aimed to assess the role of estradiol and prolactin in patients with systemic lupus erythematosus (SLE). Hormone association with the disease and disease activity was measured using the SLE disease activity index (SLEDAI) and BILAG. The study population included 60 women with SLE; their mean age was 37 ± 14 years. There was no statistically significant association between the diverse systems, organ involvement and hormonal levels, except for renal involvement which showed a positive interaction with estradiol levels. Neither was a statistically significant association found between estradiol, prolactin levels and disease activity in the immunological (anti-dsDNA, C3, C4) and hormonal (estradiol and prolactin) profiles. Supporting these findings, we also could not find, in a large cohort study, an association between high prolactin levels and SLE disease activity defined as SLEDAI and ECLAM [6]. Similar results were found in another study conducted by our group assessing the significance of hyperprolactinemia in SLE disease activity [7]. Moreover, no direct correlation was identified between prolactin levels and the clinical disease activity.

Interestingly, we found a higher prevalence of serositis, pleuritis, pericarditis, peritonitis, anemia, and proteinuria among hyperprolactinemic SLE patients [6]. Therefore, the lack of a positive correlation between prolactin and the common SLE disease activity scores is not necessarily incompatible with most findings in the literature [8,9]. Indeed, most of the studies have supported the pathogenic role of prolactin in autoimmune diseases and, in particular, SLE [8,9].

A recent cross-sectional study of 73 SLE patients assessed the correlation between prolactin levels and SLEDAI; 62 of the patients were evaluated before and after the treatment [10]. High levels of prolactin were identified in 19.4% of SLE patients but not in healthy controls. Additionally, a strong correlation has been reported between prolactin levels and SLE disease activity [10]. Another study reported significantly higher serum prolactin levels in 34 active SLE subjects (13.43 ± 5.65, $P < 0.01$) and 13 quiescent SLE subjects (11.86 ± 5.07, $P < 0.01$) compared with normal controls (7.38 ± 3.09) [11].

Prolactin is secreted from the pituitary gland and other organs and exerts numerous and diverse effects on the immune system [9]. The prolactin receptor is constitutively expressed on Treg and effector T (Teff) cells in SLE patients [12]. Moreover, the immunostimulatory effects of prolactin, such as the production of autoantibodies, are mediated by the decrease in negative selection among immature autoreative B cells [13].

In an animal model study, prolactin showed increased viability and decreased apoptosis of immature B cells from MRL/lpr mice induced by the cross-linking of B cell antigen receptor (BCR). Therefore, the maturation of self-reactive B cells is reinforced and contributes to the onset of SLE [14].

Dopamine is a neurotransmitter in the central nervous system. One of its many physiological functions [15] is the predominant role it plays in regulating prolactin by suppressing its secretion [15]. Several studies have been con-

ducted to evaluate the effect of dopamine agonists in the treatment of autoimmune disease through the decrease of prolactin levels [6,16]. Evaluating the implication of bromocriptine as a dopamine agonist in the treatment of SLE, Walker [17] found that bromocriptine is able to attenuate the course of SLE in NZBxNZW mice when the treatment was initiated before the appearance of clinical manifestations.

A very interesting case is that of a 22 year old SLE patient with disease duration of 3 years and stable on prednisone and hydroxychloroquine [16]. The patient was found to have a prolactinoma and recurrent granulomatous mastitis. Under treatment with prednisone, hydroxychloroquine and bromocriptine, she recovered and remained free of granulomatous mastitis relapse. In an experimental study investigating the effect of dopamine agonists on the development of SLE, bromocriptine had a suppressive effect on in vivo autoantibody production, as well as the disappearance of clinical and pathological manifestations of the disease [17]. Bromocriptine seems to be effective not only in SLE, since a similar effect was observed in mice with experimental antiphospholipid syndrome [18]. An open-label study has investigated the role of bromocriptine in the treatment of seven patients with active non-life-threatening SLE [19]. The patients were treated for 6 to 9 months and demonstrated a significant decrease in disease activity.

Interestingly, the effect of bromocriptine as preventive treatment for SLE postpartum flare has been reported. A recent study included 76 pregnant SLE patients randomly classified into two groups: treated (2.5 mg bromocriptine twice daily for 2 weeks after delivery) and control [20]. Treatment with bromocriptine led to decreased serum levels of prolactin and estradiol in the second week as well as a beneficial effect in preventing relapses of SLE disease during the postpartum period. Another randomized clinical trial to evaluate the efficacy of bromocriptine in preventing a flare of SLE in the postpartum period included 68 consecutive pregnant SLE patients [21]. It was also found in this study that the rate of postpartum relapse was lower in the treated than the control group [21].

In summary, the role of gender and prolactin in SLE is currently being further elucidated. Although several studies have reported controversial results, a large majority support the finding of an unfavorable effect of prolactin in SLE in terms of disease induction and activity. This is reinforced by reports not only on the pathogenic effect of prolactin in SLE animal models studies but also on the beneficial effect of dopamine agonists, mainly bromocriptine, as therapeutic agents. Therefore, treatment with bromocriptine may be considered in non-responsive SLE cases, especially in those with high prolactin levels, or as a preventive agent for postpartum flares in SLE.

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