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Research Article

The Role of Long Pentraxin 3 and Nuclear Factor Kappa Beta in Vitiligo Occurrence and Disease Severity

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Objectives. To reveal the role of long pentraxin 3 (PTX3) and nuclear factor kappa beta (NF-kB) in vitiligo and their relationship with disease severity. *Materials and Methods*. The study groups consisted of a total of 54 patients, including 27 patients diagnosed with vitiligo and 27 healthy controls without any cutaneous disease. Patients with amelanotic, sharply demarcated, and chalk-white macular lesions were defined as vitiligo. The diagnosis of vitiligo was confirmed by Wood's lamp examination. No biopsies were taken from the lesions, and no additional laboratory testing was performed. Skin and hair pigmentations in lesions other than hands and feet were evaluated. Vitiligo grading was done using the largest macules overall. Spreading rates were evaluated in selected lesions with Wood's lamp. The long pentraxin 3 and NF-kB levels in serum samples of participants were measured by the ELISA method. *Results*. According to the Vitiligo European Task Force consensus 16 of 27, vitiligo patients were in the slow progressive phase, and 11 patients were in the active progressive phase. The serum PTX3 levels of the patients in the vitiligo group were found to be significantly higher than those of the control group (8.21 ± 2.11 ng/ml vs. 6.76 ± 1.90 ng/ml, $p < 0.03$). Similarly, the serum NF-kB levels of the patients in the vitiligo group were significantly higher than those of the patients in the control group (15.03 ± 3.45 ng/ml vs. 12.19 ± 4.20 ng/ml, $p < 0.01$). A positive and significant correlation was found between serum NF-kB and PTX3 ($r = 0.677$ and $p < 0.01$). PTX3 and NF-kB levels were significantly higher in patients in the active progressive phase than in patients in the slow progressive phase. PTX3 and NF-kB values in the active progressive phase tended to be higher than those detected when the disease was in the slow progressive phase. *Conclusions*. High serum PTX3 and NF-kB levels in vitiligo are evidence of impaired proinflammatory activity and innate and adaptive immunity.

1. Introduction

Vitiligo is an autoimmune skin disease with multifactorial etiology and characterized by depigmentation in the affected areas [1, 2]. The chain of autoimmune events that cause melanocyte loss is not clearly known. It is thought that there is melanocyte damage due to somatic, genetic, neuronal, degeneration, and adhesion defects occurring in the melanin-epidermal unit [1]. The close neighborhood of melanocytes with the dermis causes damage to melanocytes by the cytotoxic activity of melanin-specific immune cells that come to the region with vascular structures. In addition, inflammatory damage to keratinocytes leads to the adhesion of melanocytes to keratinocytes, resulting in melanocyte loss [3, 4].

Long pentraxin 3 (PTX3) is a multifunctional soluble pattern recognition molecule. It is a glycoprotein structure stabilized by disulfide bonds [5]. Octameric structure of PTX3 has a critical role in both the inflammatory reactions of the host and the regulation of innate immunity [6]. PTX3 has been shown to play a role in the emergence of some cutaneous lesions via CD4+ T helper cells [7]. It is not known whether PTX3 plays any role in the regulation of inflammatory response and host innate immunity. The following multifunctional properties of PTX3 overlap with the etiology of vitiligo: regulation of innate and inflammatory response, regulation of microvascularization and neoangiogenesis, remodulation of the extracellular matrix, and wound healing [1, 2, 7]. The autoimmune nature

of the disease and the properties of PTX3 make it a candidate for a potential biomarker in vitiligo. Since PTX3 is intensely stored in circulating macrophages and neutrophils and secreted when necessary, expression levels may vary in vitiligo. The proinflammatory response stimulates PTX3 synthesis in many cells. In particular, neutrophils are responsible for the initial and intense release of PTX3 at the site of inflammation [8]. Thanks to the secretion of PTX3 by different cell groups, a protective effect is provided against many microorganisms and viruses by regulating innate immunity and inflammatory response [7, 9]. While these positive effects due to PTX3 are realized, the prevention of tissue damage due to excessive inflammatory response is also done by PTX3 itself. The last mentioned feature gives PTX3 a molecular character that contributes to the wound healing process [10].

Nuclear factor kappa beta (NF-kB) is the main regulator of inflammatory reactions and its levels increase in many inflammatory diseases [11]. If the expression pattern of the proinflammatory glycoprotein PTX3 is correlated with NF-kB expression, the basic role of PTX3 in vitiligo can be revealed. In vitiligo, cellular inflammatory pathway hyperactivation may induce melanocyte loss due to defects in both innate and adaptive immunity [1]. α-MSH is an anti-inflammatory hormone involved in melanocyte growth and melanin production and exerts melanocyte protective effect by blocking TNFα-stimulated NF-kB activity [12]. Previous research suggests that TNFα contributes to depigmentation by stimulating NF-kB activation in vitiligo patients and that vitiligo treatment should be planned through inhibition of this pathway [13]. In addition to the defect in innate immune response, damage to the vascular endothelium, dermal neurons, and extracellular matrix due to proinflammatory cytokines causes melanocyte loss and depigmentation in vitiligo [1, 2, 13]. Considering its important roles in immunity, tissue repair, and regulation of inflammation, both PTX3 and NF-kB may play a role as an etiological culprit in the formation of skin lesions of vitiligo. This study was planned to compare the serum PTX3 and NF-kB concentrations in vitiligo patients and in healthy controls. The study also sought to examine the relationship between vitiligo severity, PTX3, and NF-kB levels.

2. Materials and Methods

The study groups consisted of a total of 54 patients, including 27 patients diagnosed with vitiligo and 27 healthy controls without any systemic or cutaneous disease. The study was initiated after obtaining local ethical approval and all participants provided informed consent. The study was conducted with strict compliance with the Helsinki Declaration criteria. Participants were selected from male and female patients, regardless of vitiligo type. Patients with both segmental vitiligo and nonsegmental vitiligo were included in the study. The diagnosis of vitiligo was made by two experienced dermatologists, who detected typical images of depigmented lesions on physical examination. Patients with amelanotic, sharply demarcated, and chalk-white macular lesions were defined as vitiligo. Care was taken to ensure that the lesions were totally amelanotic but not scaly. The criteria determined at the Vitiligo Global Issues Consensus Conference were taken into consideration for the diagnosis of vitiligo. This classification, revised in 2011, adopted the term "vitiligo" as an umbrella term for all forms of nonsegmental vitiligo, including mixed vitiligo [14].

No biopsies were taken from the lesions, and no additional laboratory testing was performed to confirm the diagnosis. In each case, the diagnosis of vitiligo was confirmed by Wood's lamp examination after physical examination. In wood *s* light examination, the lesion becomes more accentuated, and its whiteness becomes clearer and there is no blue white fluorescence. According to the Vitiligo European Task Force consensus, skin and hair pigmentations in lesions other than hands and feet were evaluated [15]. Vitiligo grading was done using the largest macules overall. A specific grading scale was used to detect vitiligo activity [16]. Spreading rates were evaluated in selected lesions with Wood's lamp. According to these criteria, 16 of 27 vitiligo patients were in the slow progressive phase, and 11 patients were in the active progressive phase. Participants in the control group were matched with the vitiligo group in terms of body mass index, age, and gender.

Chemical-induced leucoderma, cutaneous depigmentations due to topical or systemic drug use, inflammatory hypopigmentation, hypomelanoses secondary to neoplasms, depigmentation disorders due to idiopathic hypomelanosis, and congenital nevi were considered in the differential diagnosis. Those who had any of these were excluded from the study. Since the incidence of other autoimmune diseases in the presence of vitiligo increased, those with additional endocrine, systemic, or autoimmune disease were excluded from the study. Pregnant women, those with suspected pregnancy, and patients in the lactation period were not included in the study groups. Family history, medical history, age, and gender of both groups were recorded. Venous blood samples were taken from both groups for PTX3 and NF-kB measurement after an overnight fast. After the collected blood was centrifuged at 3,500 rpm for five minutes, the supernatants were separated and stored at −20°C until analysis.

2.1. ELISA Analysis of Serum Long PTX3 and NF-kB Levels. After the frozen supernatants were thawed under appropriate conditions, the long pentraxin 3 and NF-kB levels in serum samples were measured using human PTX3 or NF-kB (SunRed Biotechnology Company, Shanghai China) kits by the ELISA method and in accordance with kit procedures. Absorbance was read spectrophotometrically with the Bio-Tek ELx800 (Bio-Tek Instruments, USA) ELISA reader at 450 nm. Concentration was calculated for both biomarkers using the standard curve. The measuring range of the PTX-3 kit was 0.08–20 ng/mL, and the sensitivity was 0.051 ng/mL. On the other hand, the measurement range of the NF-kB kit was 0.15–40 ng/mL, and the sensitivity was 0.146 ng/mL.

2.2. Statistical Analysis. Analysis of each group was performed on IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA). The distribution of the

Table 1: Comparison of long PTX3, NF-kB, and demographic findings of both groups.

	Vitiligo ($n = 27$)	Control ($n = 27$)	p values
Age (years)	39.7 ± 4,11	38.5 ± 3.59	0.12
BMI (kg/m^2)	26.8 ± 5.30	26.1 ± 3.98	0.40
Gender (female or male)	F: 11 M: 16	F: 11 M: 16	0.35
Active progressive phase	11	—	NA
Slow progressive phase	16	—	NA
Long pentraxin 3 (ng/ml)	8.21 ± 2.11	6.76 ± 1.90	<0.03
NF-kB (ng/ml)	15.03 ± 3.45	12.19 ± 4.20	<0.01
	Active progressive	Slow progressive	
Long pentraxin 3 (ng/ml)	9.56 ± 3.20	7.10 ± 1.90	<0.01
NF-kB (ng/ml)	17.3 ± 3.09	11.9 ± 2.07	<0.01

Results are given as Mean ± SD. $p < .05$ was considered significant. NA: not applicable. BMI: body mass index.

data was determined by the Shapiro–Wilk test. Normally distributed variables were analyzed with the independent samples t-test. Non-normally distributed variables were analyzed with the Mann–Whitney U test. Pearson correlation coefficients were calculated to determine the relationships between PTX3, NF-kB, and other variables. Results are given as mean ± standard deviation. $p < 0.05$ was accepted as statistically significant.

3. Results

In addition to the demographic findings of the patients in both groups, the serum PTX3 and NF-kB levels are shown in detail in Table 1. Age, gender distribution, and body mass index data of both groups were recorded as similar. Sixteen of 27 patients in the vitiligo group were in the slow progressive phase. The remaining 11 patients were in the active progressive phase. The lesions showed focal, mucosal, acrofacial, and generalized distribution, as well as in some cases, unisegmental, bisegmental, or multisegmental distributions. Rarely, there were cases in which segmental and nonsegmental vitiligo were detected simultaneously. As clearly shown in Figure 1, the serum PTX3 levels of the patients in the vitiligo group were found to be significantly higher than those of the control group (8.21 ± 2.11 ng/ml vs. 6.76 ± 1.90 ng/ml, $p < 0.03$). Similarly, the serum NF-kB levels of the patients in the vitiligo group were significantly higher than those of the control group (15.03 ± 3.45 ng/ml vs. 12.19 ± 4.20 ng/ml, $p < 0.01$). The fact that both inflammatory markers are significantly higher in vitiligo patients than in controls is a finding that supports the proinflammatory etiology of vitiligo. The roles of PTX3 and NF-kB in inflammatory reactions were quite different from each other. As shown in Figure 2, the rate of NF-kB in the inflammatory reaction in the vitiligo group was approximately twice that of PTX3 (36% vs. 19%).

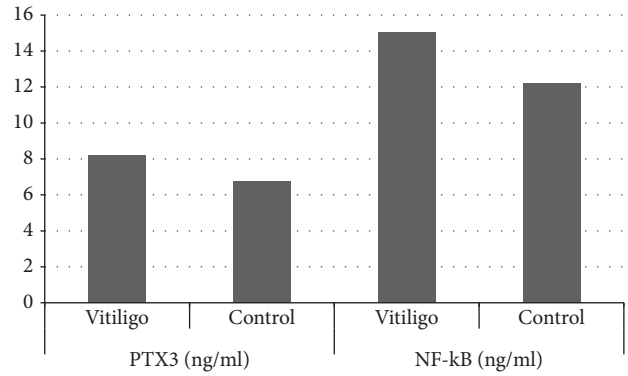

Figure 1: Graphical representation of long PTX3 and NF-kB concentrations of each group.

There was no significant correlation between serum PTX3, NF-kB values, and demographic data. Likewise, we did not detect a correlation between vitiligo type and PTX3 and NF-kB levels. However, a positive and significant correlation was found between serum NF-kB levels and long PTX3 ($r = 0.677$ and $p < 0.01$). When subgroup analysis was performed in terms of serum biomarkers according to the disease phase, PTX3 and NF-kB levels were significantly higher in patients in the active progressive phase than in patients in the slow progressive phase. PTX3 and NF-kB values detected while the disease was in the active progressive phase tended to be higher than those detected when the disease was in the slow progressive phase and those detected in the controls (Table 1 and Figure 2).

4. Discussion

Vitiligo is a multifactorial etiological disease that occurs as a result of the combined effect of autoimmune, biochemical, hormonal, environmental, innate, and adaptive immunological events in individuals with genetic predisposition [1, 2, 17]. However, the exact mechanisms that trigger vitiligo pathogenesis remain unclear despite many suspected etiological culprits [3]. The chain of reactions initiated by oxidative stress and proinflammatory molecules first leads to the loss of melanocytes by apoptosis and to a decrease in melanin production over time, resulting in white patches in the color of the skin. NF-kB is the main proinflammatory biomarker regulating intracellular inflammatory reactions [11]. NF-kB alone or in combination with other inflammatory molecules can initiate the vitiligo development process by causing both damages to the dendrites of melanocytes and melanocyte apoptosis [4, 13, 18]. PTX3, a glycoprotein involved in both inflammatory reactions and innate immunity [5, 6], has also been shown to play a role in the emergence of some cutaneous diseases [7]. PTX3 is believed to initiate the formation of skin lesions through T helper-mediated reactions [7]. However, there is no study investigating the possible relationship between PTX3 and the formation of vitiligo.

In the current study, we investigated how circulating NF-kB and PTX3 levels changed in vitiligo patients. We found that both proinflammatory molecules were significantly

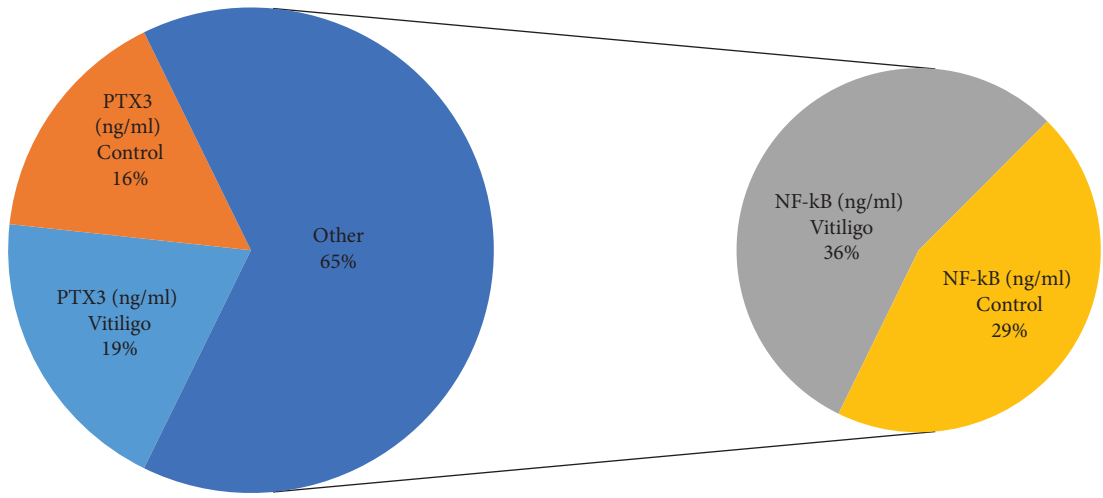

Figure 2: Graphical presentation of the role of PTX3 and NF-kB in inflammatory reactions in vitiligo and control groups. Although both molecules have a role in vitiligo-related inflammatory reactions, the role of NF-kB is approximately twice higher than that of long PTX3.

elevated in the sera of vitiligo patients compared to healthy controls. Isolated studies report a relationship between NF-kB overproduction and the formation of vitiligo [13, 18]. Studies indicate that NF-kB p65 levels are increased in biopsy samples taken from vitiligo lesions [18]. Another study suggested that melanin depigmentation in vitiligo was initiated via TNFα-stimulated NF-kB activity [13]. There are also translational study models showing that inhibition of NF-kB expression by different molecules prevents melanocyte loss [1, 18, 19]. Consistent with the last sentence, some studies showed that interleukin applications had a melanocyte protective effect through the NF-kB pathway [20]. Moreover, one study reported that increased activation of phosphatidylinositol 3-kinase/protein kinase B in vitiligo lesions disrupted NF-kB pathway functions and led to keratinocyte loss [21]. The last mentioned study suggests that the NF-kB pathway defect leads not only to melanocyte loss but also to the loss of keratinocytes through the apoptotic process [21].

The study showed that serum NF-kB levels of vitiligo patients increased significantly compared to healthy controls. Interestingly, the NF-kB levels of the participants in the active progressive phase of vitiligo showed a more significant increase than those of the participants in the slow progressive phase. This finding suggests that the increase in NF-kB contributes to disease progression and vice versa. In a study using an NF-kB inhibitor (Bay 11–7082), the prevention of melanocyte loss is supporting evidence that NF-kB contributes to the onset and/or progression of the disease [22]. The fact that we found a positive and significant correlation between serum NF-kB levels and PTX3 suggests that NF-kB plays a role in the etiopathogenesis of vitiligo in interaction with other proinflammatory cytokines. When the literature data and our results are evaluated together, the development or progression of vitiligo can be prevented with treatments aimed at inhibiting or modulating the NF-kB pathway. The fact that we did not detect a significant correlation between age, gender, and BMI levels and NF-kB expression suggests that this proinflammatory molecule is genetically regulated in vitiligo patients and may be associated with innate or adaptive immunity [19–22].

Although a relationship has been established between different cutaneous diseases and PTX3 [7, 23, 24], there are no clinical or experimental data on circulating PTX3 changes in vitiligo patients. PTX3 is a molecule whose synthesis and release are regulated by proinflammatory cytokines involved in innate and adaptive immunity. It increases the expression of interleukins, microorganism destruction products, and TNF-alpha PTX3 [25]. We showed that serum PTX3 levels were significantly increased in vitiligo patients compared to controls. There was a significant correlation between the disease stage and PTX3 expression. Patients in the active progressive phase had more significant PTX3 levels than those in the slow progressive phase. This finding suggests that PTX3 plays an important role in determining the phases of vitiligo. PTX3 may do this by triggering chronic low-grade inflammation [9]. As is known, PTX3 can cause low-grade inflammation by regulating the activation of classical and lectin-mediated complement pathways [25]. The positive correlation between PTX3 levels and NF-kB in vitiligo patients suggests that PTX3 acts together with other proinflammatory molecules in addition to the activation of the complement system.

Besides its proinflammatory effect, PTX3 may contribute to the formation of vitiligo by impairing innate immunity. Consistent with this, impaired humoral immunity has been reported in PTX3-deficient mice models [9]. Under normal conditions, PTX3 secreted from lactoferrin-positive neutrophil granules secondary to inflammation and immunogenic stimulation contributes to the regulation of adaptive and innate immunity [8]. It achieves this by ensuring the clearance of apoptotic cells. In support of this, increased serum PTX3 levels have been reported in childhood systemic lupus erythematosus [24]. The fact that the increase in PTX3 expression is proportional to vasculitis, and disease severity is evidence of the effect of this molecule on inflammatory reactions and immunity in diseases with a cutaneous component, such as lupus [24]. Similarly, increased PTX3 in

cutaneous leishmaniasis may contribute to the disruption of T helper-mediated immune cell response and the emergence of skin lesions [7]. Increased PTX3 levels have also been reported in psoriasis, a common disease characterized by inflammation and impaired T-cell response. It was also emphasized that PTX3 expression increased in proportion to the severity of psoriasis [23]. We showed for the first time a similar relationship between cutaneous diseases and PTX3 in vitiligo patients. In addition to a significant increase in serum PTX3 levels compared to healthy controls, we found a positive and significant relationship between PTX3 and disease severity. High circulating PTX3 levels in the vitiligo group may be a sign of both inflammatory response and impaired innate and adaptive immunity. Due to the important effect of PTX3 in determining the occurrence and severity of vitiligo, PTX3 and complement pathways may be a clue for new drug applications. By inhibiting PTX3 synthesis, the transition of the disease to the active progressive phase can be prevented, or the enlargement of the lesions can be limited.

The small number of participants, the collection of segmental and nonsegmental cases in a single pool, and the high mean age are the minor limitations of the study. Another limitation is that predictive value, specificity, and sensitivity of the investigated markers, and their diagnostic values were not investigated by regression analysis. Despite all the limitations, this is the first clinical study to show an increase in serum PTX3 in vitiligo. The relationship between serum PTX3 and NF-kB levels and disease progression in vitiligo was demonstrated for the first time in this study. With more extensive studies using PTX3 and NF-kB blockers with a larger number of participants, it may be possible to design a new drug that prevents the formation of vitiligo or slows its progression.

Data Availability

The data used in this study are available on request from the corresponding author.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Şule Gençoğlu conceptualized and designed the study and performed the data collection from outpatients. Zekiye Kanat conducted the data processing and drafted the manuscript, while Şule Gençoğlu supervised and reviewed the complete text. All authors read and approved the final version of the manuscript.

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