IMMUNOLOGICAL PREDICTORS OF BRUCELLOSIS CHRONICITY IN WOMEN OF REPRODUCTIVE AGE

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Abstract. Brucellosis is a zoonotic infection characterized by the ability of Brucella spp. The development of chronic disease is associated with complex interactions between bacterial persistence, cellular immunity, cytokine regulation and host genetic factors. In women of reproductive age, these mechanisms are of particular interest because hormonal and immunological changes, especially during pregnancy, may influence the course and consequences of infection. The available evidence indicates that impaired Th1-mediated cellular immunity, altered interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α) responses, increased regulatory cytokine activity, and T-cell exhaustion may contribute to bacterial persistence. Polymorphisms in cytokine-related genes, including IL-4, IL-18, IL-10, TNF-α and TGF-β, have also been associated with susceptibility to brucellosis.

Keywords: brucellosis, chronic infection, women of reproductive age, cellular immunity, cytokines, Th1/Th2 balance, IFN-γ, TNF-α, IL-10.

Introduction. Brucellosis is a zoonotic bacterial infection caused by microorganisms of the genus Brucella. It remains an important public health problem in endemic regions and may present as an acute febrile illness, a prolonged infection or a chronic relapsing condition. The ability of Brucella to

survive and multiply within macrophages is a major factor contributing to persistence and disease progression [1,2].

Cellular immunity, particularly the Th1-mediated response, plays a central role in controlling intracellular Brucella. When this response becomes insufficient or dysregulated, bacterial persistence and prolonged inflammatory stimulation may occur [1,3]. Women of reproductive age represent a clinically important population. Pregnancy involves physiological changes in immune regulation, while infection during gestation may affect the maternal–fetal interface and increase the risk of adverse obstetric outcomes. Nevertheless, the specific immunological predictors of chronic brucellosis in non-pregnant and pregnant women remain insufficiently investigated [4].

Materials and Methods. A narrative review of scientific literature was conducted using PubMed, PubMed Central and other accessible academic sources. The search included combinations of the terms brucellosis, chronic brucellosis, immune response, cytokines, Th1, Th2, IFN-γ, TNF-α, IL-10, genetic polymorphism, women of reproductive age, and pregnancy. The immune response to Brucella involves innate and adaptive mechanisms. Following entry into the organism, bacteria are recognized by macrophages and other antigen-presenting cells. However, Brucella can modify intracellular signaling pathways, interfere with phagolysosomal maturation and establish intracellular replication niches [1,2]. The Th1 immune response is particularly important in controlling intracellular infection. Activated CD4+ T lymphocytes produce IFN-γ, which stimulates macrophage antimicrobial activity. TNF-α also contributes to inflammatory activation and coordination of cellular immune responses. An adequate balance of these mechanisms is essential for controlling bacterial replication [3].

Recent single-cell analysis by Wang et al. Demonstrated differences in immune-cell profiles across acute, subacute and chronic stages of brucellosis. Chronic

disease was associated with a dysregulated Th1 response, reduced IFN-γ-related activity and signs of T-cell and natural killer (NK)-cell exhaustion [5].

Cytokine Profiles as Potential Predictors. Cytokines regulate the intensity and direction of the immune response and may provide valuable information about disease progression. Among the most studied mediators in brucellosis are IFN-γ, TNF-α, interleukin-2 (IL-2), IL-4, IL-6, IL-10 and transforming growth factor-beta (TGF-β). IFN-γ and TNF-α are associated with protective cellular immunity and macrophage activation. Reduced or inadequate Th1 activity may compromise intracellular bacterial clearance. In contrast, IL-10 and TGF-β have immunoregulatory properties and may limit excessive inflammation. However, excessive regulatory activity may also weaken effective antimicrobial responses and contribute to bacterial persistence [2,3].

The review by Priyanka et al. Emphasizes that the outcome of Brucella infection depends on the coordinated balance between Th1- and Th2-associated cytokines. Disruption of this balance may influence susceptibility, disease progression and the development of persistent infection [3].

A study investigating IL-36, IL-37 and IL-38 in patients with acute and chronic brucellosis also identified differences in the concentrations of these cytokines between disease groups. Higher IL-37 and IL-38 levels were observed in chronic cases compared with acute cases, suggesting that members of the IL-1 cytokine family may be involved in the transition toward chronic disease [6].

Immunogenetic Factors. Individual genetic differences may influence susceptibility to Brucella infection and the effectiveness of immune responses. Polymorphisms in genes encoding cytokines and their receptors may modify cytokine production, inflammatory regulation and the ability to control intracellular pathogens. A systematic review and meta-analysis by Zafari et al. Identified associations between brucellosis susceptibility and several cytokine gene polymorphisms. Variants involving IL-4 (rs2243250) and IL-18 (rs1946519)

were associated with increased susceptibility, whereas selected polymorphisms in IFN-γ, TNF-α, IL-10 and TGF-β genes demonstrated potentially protective associations [7].

Specific Considerations in Women of Reproductive Age. The immune system of women undergoes physiological modulation in response to hormonal fluctuations and reproductive status. Pregnancy is characterized by a dynamic balance between inflammatory and regulatory immune mechanisms, particularly at the maternal–fetal interface. These changes may influence the clinical consequences of Brucella infection. Zavattieri et al. Reviewed the immune responses potentially involved in Brucella-associated gestational complications. Their findings indicate that Brucella can invade placental and decidual cells and stimulate the production of pro-inflammatory mediators, including TNF-α, IL-6 and IL-8.[4].

Clinical Significance and Future Perspectives

The identification of immunological predictors may improve risk stratification and follow-up of patients with brucellosis. A comprehensive research approach could include the assessment of:

- Cellular immunity: CD4+ and CD8+ T lymphocytes, NK cells and selected T-cell exhaustion markers.

- Cytokine profiles: IFN-γ, TNF-α, IL-2, IL-4, IL-6, IL-10 and TGF-β.

- Immunogenetic factors: selected polymorphisms in cytokine-related genes.

- Clinical parameters: disease duration, recurrence, focal complications and treatment response.

Conclusion. The development of chronic brucellosis is associated with complex interactions between intracellular bacterial persistence and dysregulation of host immune responses. Impaired Th1-mediated immunity, altered IFN-γ and TNF-α

activity, regulatory cytokine imbalance, T-cell exhaustion and genetic susceptibility represent promising areas for biomarker research. In women of reproductive age, reproductive and pregnancy-related immune changes should also be considered.

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