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Does serum Gas6 level change in active uveitis?

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Abstract

Purpose: The aim of this study was to investigate serum Growth Arrest-Specific Protein 6 (Gas6) levels in the active and inactive periods of uveitis.

Material and methods: In this study, serum Gas6 levels were evaluated in 21 patients during active and inactive periods. After measuring serum Gas6 levels in the active phase, the serum Gas6 test was repeated in the inactive period. Commercial Enzyme-Linked Immunosorbent Assay (ELISA) kits (Gas6, WKEA Med Supplies Corporation, NY, USA) were used to measure Gas6 levels. Plasma concentrations were analyzed with an ELISA reader at 450 nm following the manufacturer's instructions.

Results: In the study, the mean age of 21 patients was 33 (7–62) years. The mean follow-up period was 30.05 ± 18.76 months. While the average Gas6 value measured during active uveitis attacks was 1.02 ± 0.39 ng/mL (range: 0.54–2.12), the Gas6 value during the passive period was 0.71 ± 0.23 ng/mL (range: 0.39–1.17). The Gas6 level during active uveitis attacks was significantly higher than during the passive period ($p = 0.04$).

Conclusion: The findings of this study suggest a notable elevation in serum Gas6 levels across all cases of active uveitis, irrespective of the underlying etiology, whether infectious or noninfectious. To successfully integrate serum Gas6 levels into the diagnostic and follow-up protocols for active uveitis, additional comprehensive investigations are imperative.

Plain language summary

Does a blood marker change during active eye inflammation

This study explored whether a protein called Gas6 in the blood changes during active and inactive phases of uveitis, a condition causing eye inflammation. Researchers measured Gas6 levels in 21 patients during both active inflammation and when the disease was inactive. The results showed that Gas6 levels were significantly higher during active uveitis than in the inactive phase. This increase was observed regardless of whether the inflammation was caused by an infection or another reason. These findings suggest that blood Gas6 levels could potentially help in diagnosing and monitoring active uveitis. However, more research is needed to confirm these results and determine how to use Gas6 measurements in clinical practice.

Keywords: active uveitis, Gas6, inactive uveitis

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Introduction

Uveitis is the inflammation of the uvea, which includes the iris, ciliary body, and choroid, as well as the inflammation of the vitreous or retina. It is an inflammatory condition in which cytokines, chemokines, as well as T and B cells are involved.[1]

Uveitis has various causes, including infectious diseases, inflammatory diseases, ophthalmologic entities, and drug-induced uveitis.[2] In addition, genetic predisposition and environmental factors play a significant role in uveitis. Many cases of idiopathic uveitis still have unknown causes, indicating that despite medical advances, the origins of the inflammation in these cases remain unidentified. Research in the field continues to explore these unknown factors and underlying mechanisms to improve understanding and develop more effective treatments.

Growth arrest-specific gene 6 (Gas6) was first discovered in 1988. This gene encodes a protein that plays a role in various biological processes such as cell growth, adhesion, and apoptosis. In addition, Gas6 has a significant role in cellular signal transduction, and as a result, it has been studied by many researchers.[3] Gas6 is a vitamin K-dependent protein expressed in various tissues such as vascular smooth muscle cells, bone marrow, capillary endothelial cells, and adipocytes.[4] Changes in serum Gas6 levels have been detected in a variety of pathologies, including autoimmune diseases, coagulopathies, cancer, and inflammation.[5] In addition, it has been reported that plasma Gas6 levels increase in certain inflammatory conditions such as septic shock and severe acute pancreatitis.[6,7] Despite uveitis being an inflammatory process, the changes in serum biomarkers during the active and quiescent phases of uveitis have not been sufficiently documented in the literature. In this study, the levels of Gas6 during active and inactive uveitis processes were investigated.

Material and methods

In this study, serum Gas6 levels were evaluated in 21 patients during active and inactive periods. After measuring serum Gas6 levels in the active phase, the serum Gas6 test was repeated in the inactive period. The plasma Gas6 concentration was measured using the ELISA technique in venous blood samples obtained from the patients. Blood samples were collected in pyrogen-free, EDTA-containing tubes, allowed to clot at +4°C for 1 h, and then centrifuged at 2000 revolutions per minute for 10 min. The obtained plasma was stored at −80 °C until analyzed. Commercial Enzyme-Linked Immunosorbent Assay (ELISA) kits (Gas6, WKEA Med Supplies Corporation, NY, USA) were used to measure Gas6 levels. Plasma concentrations were analyzed with an ELISA reader at 450 nm following the manufacturer's instructions.

The diagnosis of active and inactive uveitis was made by two ophthalmologists. The differential diagnoses of all patients were meticulously conducted in collaboration with the rheumatology, radiology, and infectious diseases departments. Periorbital pain, redness, photophobia, ciliary injection, cells in the anterior chamber, flare, Tyndall effect, keratic precipitates, and hypopyon were evaluated in favor of active anterior uveitis. The diagnosed uveitis was classified as anterior uveitis, intermediate uveitis, posterior uveitis, or pan uveitis. Active uveitis is defined based on the anatomical location within the eye: more than 0.5+ anterior chamber cells or 1+ flare indicates exacerbation in anterior uveitis, while the presence of more than 0.5+ vitreous cells characterizes intermediate uveitis. Active chorioretinal inflammation is considered diagnostic of posterior uveitis.

Statistical analysis

Categorical variables were described using frequency (n) and percentages (%). Statistical significance was assessed at the $p < 0.05$ level. The chi-square test was employed to examine differences between the active uveitis group and the inactive group. All statistical analyses were performed using MedCalc® Statistical Software version 19.7.2 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2021).

Results

In the study, the mean age of 21 patients was 33 (7–62) years. Eight of the patients were male (38.1%) and thirteen were female (61.9%). The mean follow-up period was 30.05 ± 18.76 months. A total of 11 patients (52.4%) were involved in both eyes, 9 patients (42.9%) were affected in the right eye, and 1 patient (4.8%) in the left eye. While the average Gas6 value measured during active uveitis attacks was 1.02 ± 0.39 ng/mL (95% CI: 0.54–2.12), the Gas6 value during the passive period was 0.71 ± 0.23 ng/mL (95% CI: 0.39–1.12). The Gas6 level during active uveitis attacks was significantly higher than during the passive period ($p = 0.04$) (Figure 1).

Among the patients, 5 had uveitis attributed to Fuchs' syndrome, 4 were diagnosed with uveitis

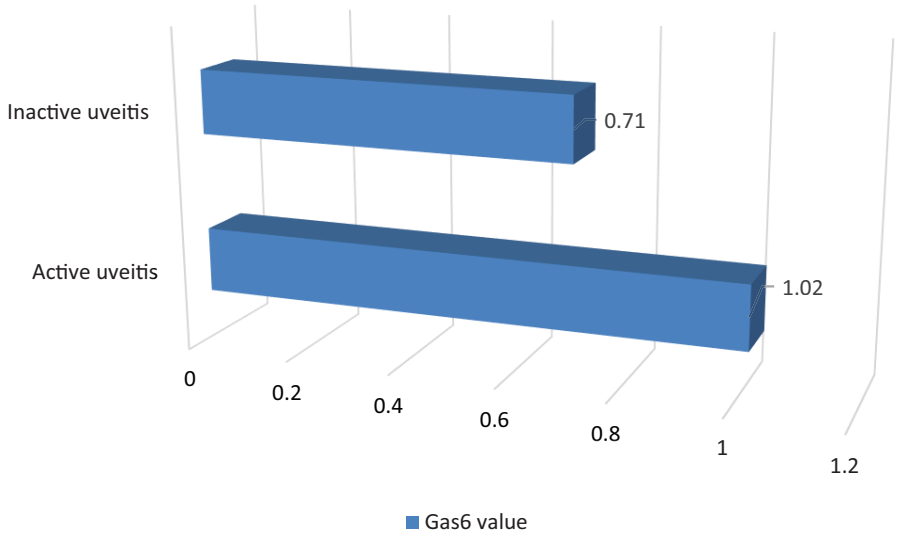

Figure 1. The Gas6 values observed during periods of active and inactive uveitis.
Gas6, growth arrest-specific protein 6.

related to Behçet's disease, 2 had uveitis associated with CMV infection, and 2 had uveitis linked to toxoplasma. The remaining 8 patients were considered to have idiopathic uveitis. Anatomically, there were 11 panuveitis, 8 anterior, and 2 intermediate cases. In this study, 4 (19.0%), 6 (28.6%), and 11 (52.4%) were categorized as acute, chronic, and recurrent, respectively.

Discussion

In the diagnosis and monitoring of uveitis, various markers and diagnostic tools may be employed. Distinguishing between active and passive phases in uveitis is crucial for effective treatment planning. In a study conducted by Karadağ et al.,[8] elevated serum levels of IL-6, IL-8, TNF-α, CRP, and heat shock protein 70 were identified in Behçet's patients during the active uveitis period. Dysregulation of Gas6 has been associated with various diseases, including autoimmune disorders and cancer. Gas6 is actively involved in the modulation of immune responses and inflammatory processes.[9] This study distinctly demonstrates that serum Gas6 levels are elevated during the active uveitis period in comparison to the inactive period, irrespective of whether the uveitis is infectious or noninfectious in nature.

Several studies have indicated that Gas6 levels also rise in inflammatory conditions such as pancreatitis, sepsis, and septic shock, suggesting that Gas6 functions as an acute-phase protein. The study conducted by Borgel et al.[10] revealed an increase in plasma Gas6 levels in severe sepsis, showing a correlation with the degree of organ dysfunction. The study by Ekman et al.[11] identified the Gas6 protein as a potential determinant of inflammation. On the other hand, Balogh et al.[12] emphasized that detecting excessive Gas6 secretion serves as a suitable marker for pathophysiological events. These findings collectively underscore the significance of Gas6 in inflammatory processes and its potential utility as a marker for assessing pathophysiological conditions. In this study, while four patients were diagnosed with infectious uveitis, none presented with sepsis, yet high Gas6 levels were detected in all these patients. It is worth noting that this study did not explore the correlation between any acute-phase reactant and Gas6 during the active uveitis period, which could be considered a limitation of this research.

Gas6 is a vitamin K-dependent protein that plays a role in the pathogenesis of autoimmune diseases. In a study conducted by Kim et al.[13] in patients with SLE, Gas6 levels were observed to be significantly higher than those in the control group. In contrast, another study reported that Gas6 levels in patients with SLE were not significantly different from those in the control group.[14] The study conducted by Wu and colleagues demonstrated an elevation in Gas6 levels in the serum

of SLE patients, particularly those with lupus nephritis or cutaneous vasculitis, suggesting its potential as a marker of disease activity.[15] In this study, while no patients had a definitive diagnosis of SLE, there were nine patients diagnosed with idiopathic uveitis. Gas6 levels increased in all of them during periods of active uveitis.

In the study conducted by Bu-Kao Ni et al.,[23] serum Gas6 was identified as a biochemical parameter that assists in evaluating the severity of brain trauma and predicting the prognosis in patients with severe traumatic injury. Zhang et al.[24] demonstrated that serum Gas6 may serve as a potential prognostic biomarker for aneurysmal subarachnoid hemorrhage. Smirne et al.[26] stated in their review that, despite the absence of in vivo validation studies on large patient series, serum Gas6 appears very promising in the evaluation of liver patients.

In the study by Kuo et al.,[16] it was observed that the Gas6 protein level was higher in women, although this difference did not reach statistical significance. However, it has been reported that the level of Gas6 protein is proportionally linked to insulin sensitivity in women. This suggests that Gas6 could serve as a crucial biomarker for detecting early signs of inflammation and insulin resistance in women. The study conducted by Stepan et al. was pioneering in demonstrating that Gas6 serum concentration is elevated in pregnant women with preeclampsia. This finding adds valuable insights to our understanding of the role of Gas6 in the context of preeclampsia during pregnancy.[17] This study excluded pregnant women from participation.

The study conducted by Hayashi et al.,[18] focusing on the prediction of prognosis in hepatocellular carcinoma patients based on serum Gas6 levels, indicated an association between high Gas6 levels and an increased incidence of portal vein tumor thrombosis. In the study conducted by Hayashi et al.,[19] elevated levels of Gas6 and Axl were correlated with advanced histological stage in primary biliary cholangitis. In this study, which examined Gas6 levels during the active uveitis period caused by various diseases, determining its efficacy or impact on prognosis was challenging. This difficulty arises from the diverse treatment protocols specific to each pathology causing uveitis and the individualized response of patients to these treatments. The tyrosine kinase receptor Axl and its ligand Gas6 play a critical role in the pathogenesis of high-grade glioma.[20]

Gas6 may contribute to tissue repair processes while potentially causing organ damage and loss of function, depending on the prevailing balance between its anti-inflammatory and profibrotic properties. In this study, which included both infectious and noninfectious patients, a clear conclusion about whether Gas6 promotes tissue repair processes or causes organ damage might be challenging due to the diverse nature of the cases investigated. Laurance et al.,[21] in their study, highlighted the significance of Gas6 as a crucial regulatory switch for the vascular system. This underscores the multifaceted role of Gas6 in governing vascular functions and homeostasis. In this context, Gas6 is believed to be implicated in the etiology of numerous cardiovascular diseases, including atherosclerosis, owing to its association with both inflammation and thrombosis.

In the literature, it has been observed that the serum Gas6 level decreases in some diseases and remains unaffected in others. Huang et al.[22] demonstrated a decrease in serum Gas6 levels in patients with early onset preeclampsia. In the study conducted by Te-Yu Lin et al.,[23] a reduction in plasma Gas6 concentrations was observed in HIV patients. Crintea et al.[24] identified a moderate positive correlation between Gas6 values after the first dose of chemotherapy in lung cancer. In the study conducted by Liu et al.,[25] Gas6 was not found to be associated with coronary artery disease. In cases of active uveitis, there may exist biomarkers that exhibit elevated levels in the serum, as well as other values that are diminished. For instance, Chiu et al.[26] observed reduced levels of serum 25-hydroxy vitamin D in patients with active uveitis. This finding is rational, given that autoimmune diseases triggering uveitis tend to be activated in the presence of vitamin D deficiency.

The most significant argument that makes this study valuable is its demonstration that elevated Gas6 levels in the serum of active uveitis patients decrease with treatment, a finding that has not been previously addressed in the literature.

Our study has certain limitations. First, a larger sample size could have improved the generalizability of our findings. In addition, comparing Gas6 levels based on different types of uveitis

could have provided a more detailed analysis. Lastly, assessing Gas6 levels according to the grading of active uveitis could have helped better understand the relationship between disease severity and this biomarker. In this study, four patients had Behçet's disease, and eight patients had idiopathic uveitis. The anterior and posterior uveitis of the patients were treated and inactivated. We do not know whether the systemic complaints of these patients have been resolved or if they are in systemic remission. It can be stated that they are in remission and inactive in terms of the eye; however, the state of activation and involvement in other parts of the body is unknown. Addressing these limitations in future studies may contribute to a more comprehensive understanding of the subject.

Conclusion

This study indicates that serum Gas6 levels are inclined to be elevated in all instances of active uveitis, irrespective of the underlying cause (infectious or noninfectious). To successfully integrate serum Gas6 levels into the diagnostic and follow-up protocols for active uveitis, additional comprehensive investigations are imperative.

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of Istanbul Medeniyet University Goztepe Training and Research Hospital. Decision number: 2023/0642. The study protocol adhered to the principles of the Helsinki Declaration. Written informed consent was obtained from all patients. For participants under 16 years of age, written informed consent was obtained from their parents.

Consent for publication

Not applicable.

Author contributions

Ozgur Cakici: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft.

Omer Faruk Yilmaz: Conceptualization; Data curation; Formal analysis; Investigation; Supervision; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The data sets used and analyzed during the current study are available from the corresponding author on reasonable request.

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