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Evaluation of serum semaphorin-3A and interleukin 6 levels in patients with neovascular age-related macular degeneration

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Abstract

Purpose To determine whether serum semaphorin 3 A (Sema3A) and interleukin 6 (IL-6) play a role in the common etiopathogenesis of nAMD and nAMD-associated systemic diseases by evaluating these mediators levels.

Methods This prospective case–control study included 74 patients divided into nAMD ($n=33$) and a control group ($n=41$). Serum Sema3A and IL-6 levels were analyzed using the enzyme-linked immunosorbent assay.

Results The nAMD group had a statistically higher IL-6 level [5,9 (1–16,9) pg/mL], compared to the control group [1,5 (0,38 – 2,96) pg/mL] ($p<0.001$). On the other hand, the Sema3A level of the nAMD group was lower at [26,3 (11,5-100) ng/mL] compared to the control group at [44,7 (16,8-100) ng/mL] ($p<0.001$). The IL-6 level in the hypertension (+) group [2,5 (0,5–16,9) pg/ml] was significantly higher than that in the hypertension (-) group [1,7 (0,4–15,3) pg/ml] ($p<0.001$). No significant difference was found between the hypertension (+) and hypertension (–) groups in terms of SEMA3A level. There was a negative correlation between serum SEMA3A and serum IL-6 levels of the whole participants ($p<0.001$, r=-0.471).

Conclusions Decreased levels of the anti-inflammatory and anti-angiogenic mediator Sema3A and increased levels of inflammatory mediator IL-6 detected in nAMD suggest that these molecules may play a role in systemic manifestations of this syndrome, such as inflammation, cardiovascular diseases, atrial fibrillation, and Alzheimer's disease.

Clinical trial number Not applicable.

Keywords Neovascular age related macular degeneration, Semaphorin-3A, Interleukin 6, Inflammation, Cardiovascular disease, Atrial fibrillation, Alzheimer's disease

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Introduction

Age-related macular degeneration (AMD) is the leading cause of visual impairment in developed countries [1]. AMD is characterized by distinct stages and potential neovascular or atrophic complications. Dry AMD accounts for approximately 85–90% of cases, whereas neovascular AMD (nAMD) comprises 10–15% of cases [2]. The term dry AMD includes all stages of the disease, from the early form to more advanced geographic atrophy (GA), and is characterized by the absence of neovascular complications [2]. In contrast, nAMD is characterized by the onset of macular neovascularization and exudation [2]. Fibrosis develops around retinal pigment epithelium (RPE) detachments or neovascular complexes in patients with wet nAMD, which is characterized by choroidal neovascularization (CNV) and leads to severe and rapid visual impairment accompanied by hard exudates, fluid leakage, or retinal hemorrhage. When considering the overall pathogenesis of AMD, inflammation plays a primary role in the onset and progression of both wet and dry forms [3, 4].

RPE has multiple functions, including the formation of the blood-retina barrier, maintenance of ocular immune privilege, and the secretion of soluble immunomodulatory factors that regulate immunogenic inflammation [5, 6]. RPE cells play a regulatory role by secreting soluble inhibitory molecules (transforming growth factor (TGF)-β and thrombospondin (TSP)-1) and converting T cells into regulatory T cells (Tregs) [7, 8]. In addition to RPE cells, microglia, dendritic cells, and perivascular macrophages also contribute to immunomodulation [9]. On the other hand, upon stimulation by inflammatory mediators such as tumor necrosis factor (TNF)-α, interferon (IFN)-γ, and interleukin (IL)-1β, RPE cells produce cytokines and chemokines, including IL-4, -5, -6, -8, -10, -13, -17, IFN-β, IFN-γ, TGF-β, MCP-1, and VEGF [10, 11]. The interaction between pro-inflammatory and anti-inflammatory cytokines ultimately leads to chronic inflammatory responses [10, 11]. Inflammatory cytokines may also enhance VEGF secretion, which triggers pathological CNV and retinal neovascularization in nAMD, with macrophages and lymphocytes observed during the active CNV stage [12]. Furthermore, RPE cells express a range of essential cytokine receptors, such as IL-1R, -4R, -6R, -8RA, -10RB, and IFN-AR1, and demonstrate sensitivity to systemic and retinal inflammatory signals [11].

Semaphorins (Semas), axon guidance molecules, are active in directing axonal growth cones and in vascular network formation [13]. Among Sema family proteins, semaphorin-3 A (SEMA3A) has been shown to play an important role in angiogenesis [14]. SEMA3A binds to Nrp1 and PlexA1-4, forming the Nrp1/PlexA1-4 complex [15]. In this receptor complex, Nrp1 functions as a binding element, whereas PlexA1-4 functions as a signal-transducing element [15]. Nrp1 is not only a receptor for SEMA3A but also acts as a co-receptor that enhances responses to various growth factors, including VEGF, TGF-β1, hepatocyte growth factor, and platelet-derived growth factor [16]. SEMA3A has been shown to inhibit the effects of VEGF on retinal angiogenesis and RPE proliferation, and to suppress the response to VEGF by competitively blocking Nrp1 [17, 18]. Moreover, SEMA3A blocks the formation of pathologic choroidal neovascularization induced by transforming growth factor beta [19].

IL-6 is a proinflammatory mediator associated with AMD [20]. In the retina, microglial cells protect the retina by secreting and interacting with various cytokines and chemokines; however, when exposed to pro-inflammatory cytokines such as IL-6 for prolonged periods, microglial activity becomes degenerative and promotes the recruitment of circulating immune cells [21]. In the endothelium, IL-6 activates the signal transducer and activator of transcription 3 (STAT3) signaling pathway, and also facilitates the release of chemokines such as interleukin-8 and monocyte chemotactic protein-1, as well as the surface expression of adhesion proteins [22]. These activities promote endothelial migration and tube formation [23]. thereby influencing on the amplitude of angiogenic response towards local VEGF [24]. IL-6 itself also induces VEGF expression [24]. STAT3 activation in the recruited immune cells also promotes the formation of choroidal neovascularization (CNV) [25]. Catalano reported that SEMA3A reduced the levels of inflammatory cytokines such as IL-6, TNF-α, and IL-23 in an experimental autoimmune arthritis model [26].

AMD shares common risk factors and processes, including vascular and inflammatory pathways, with many systemic disorders. Associations have been reported between AMD and hypertension, cardiovascular disease, cerebrovascular disease, dyslipidaemia, chronic kidney disease and neurodegenerative disorders [27].

To the best of our knowledge, no study has been conducted so far to analyze serum SEMA3A and IL-6 levels together in nAMD. Therefore, this study aimed to investigate the relationship between nAMD and systemic diseases and inflammation by evaluating the serum levels of these two interrelated mediators.

Materials and methods

Study participants

This observational case–control study was conducted at Recep Tayyip Erdoğan Training and Research Hospital Ophthalmology Clinic of Recep Tayyip Erdoğan University between June 2023 and October 2025. The study protocol was approved by the Recep Tayyip Erdogan University Ethics Committee (Approval ID: 2021/97)

and was conducted by the Declaration of Helsinki. Written informed consent was obtained from all subjects before participation. The study included two groups of 74 patients, 33 of whom were nAMD and 41 were controls. Participants with cardiovascular and cerebrovascular disease, chronic inflammatory disease (rheumatoid arthritis, diabetes mellitus, neurodegenerative disease, Behçet's, Crohn's, and ulcerative colitis, etc.), and collagen disease (systemic sclerosis, polymyositis/dermatomyositis, systemic lupus erythematosus, etc.) that may affect serum SEMA3A and IL-6 levels were not included in the study. Participants with a history of heart, liver, kidney failure, vasculitis (Takayasu's arteritis and giant cell arteritis, etc.), malignancy, schizophrenia, and depression were also excluded. Diseases such as retinal vein occlusion, pseudoexfoliation syndrome, glaucoma, and uveitis were not included in the study as they may affect the serum SEMA3A and IL-6 levels. Patients using corticosteroids, hydroxymethylglutaryl-coenzyme A reductase inhibitors, HIV antiretrovirals, carbamazepine, valproic acid and phenytoin, immunosuppressor drugs, nitrofurantoin, antimalarials, lithium, anti-psychotic drugs, those with chronic alcohol abuse, and smokers were also excluded. In addition, patients who had received intravitreal anti-VEGF treatment for at least 6 months were excluded from the study. Only participants receiving antihypertensive therapy with blood pressure below 140/90 mm-Hg were included in the study. All patients underwent a detailed ophthalmic examination including best-corrected visual acuity, slit-lamp examination, intraocular pressure measurement, dilated fundus examination, optical coherence tomography evaluation and retinal nerve fiber layer (RNFL) thickness analysis. Patients with dense cataracts that might affect their dilated fundus examination, optical coherence tomography evaluation and RNFL thickness analysis results underwent the same tests again after cataract surgery when the optical medium became transparent. Patients with OCT biomarkers of subretinal and intraretinal fluid (SRF, IRF), hyperreflective spots (HS), drusenoid pigment epithelial detachment (dPED), subretinal hyperreflective material (SHRM), outer retinal tubulations (ORT), onion sign, retinal pigment epithelium (RPE) tears, and subretinal fibrosis diagnosed as nAMD [28]. The vast majority of nAMD participants included in present study had SRF, IRF, HS, and SHRM, while a small number of patients had dPED, subretinal fibrosis, and onion signs. The control group consisted of age-sex-matched cataract patients without any nAMD signs and symptoms.

Table 1 Demographic and clinical data of the study group

	Control	nAMD	*p* value
	Mean ± SD; Median (min-max)	Mean ± SD; Median (min-max)	
Female n (%)	17 (41,5)	16 (48,5)	0,546
Male n (%)	24 (58,5)	17 (51,5)	
Normotensive n (%)	25 (61)	19 (57,6)	0,767
Hypertensive n (%)	16 (39)	14 (42,4)	
Age	75,2 ± 7,2	76,7 ± 7,6	0,364
Serum IL-6 level (pg/ml)	1,5 (0,38 – 2,96)	5,9 (1–16,9)	< 0,001
Serum SEMA3A level (ng/ml)	44,7 (16,8-100)	26,3 (11,5-100)	< 0,001

nAMD neovascular age related macular degeneration *IL-6* interleukin 6 *SEMA3A* semaphorin-3 A

Collection of blood samples

Venous blood samples (5 mL) were collected from the participants in the experimental groups immediately before intravitreal anti-VEGF injection, and the samples were stored in serum-separating tubes. Venous blood samples were collected from the control group before cataract surgery. The study included only participants diagnosed with senile cataracts.Venous blood samples (5 mL) were collected from all participants after 8-h of overnight fasting between 9:00 and 12:00 to avoid diurnal changes. The coagulated blood samples were centrifuged at 3000×g for 10 min to obtain sera, which were stored at – 20 °C until quantification of SEMA3A and IL-6 concentrations was performed.

Quantification of serum Sema3A and IL-6 levels

Serum SEMA3A (Cat. No: E-EL-H1274) and IL-6 (Cat. No: E-EL-H6156) levels were determined by enzyme-linked immunosorbent assay (ELISA) kits (Elabscience Biotechnology Inc, Texas, USA) following the manufacturer's instructions.

Statistical analysis

Statistical analyses were conducted using SPSS Statistics for Windows, Version 29.0 (IBM Corp., Armonk, NY, USA). The distribution characteristics of continuous variables were assessed using normality tests. For group comparisons, the independent samples t-test was used for normally distributed variables, whereas the Mann-Whitney U test was applied to non-normally distributed variables. The distribution of categorical variables between the groups was analyzed using the chi-square test. Spearman correlation analysis was performed to evaluate the relationships between the parameters. In all analyses, $p < 0.005$ was considered statistically significant.

Results

Baseline demographic and clinical characteristics of the participants are presented in Table 1. There was no significant difference among the two groups in terms of age, sex, or the presence of hypertension (HT) (all $p > 0.05$). The serum SEMA3A level of the nAMD group was significantly lower and IL-6 level was higer than that control

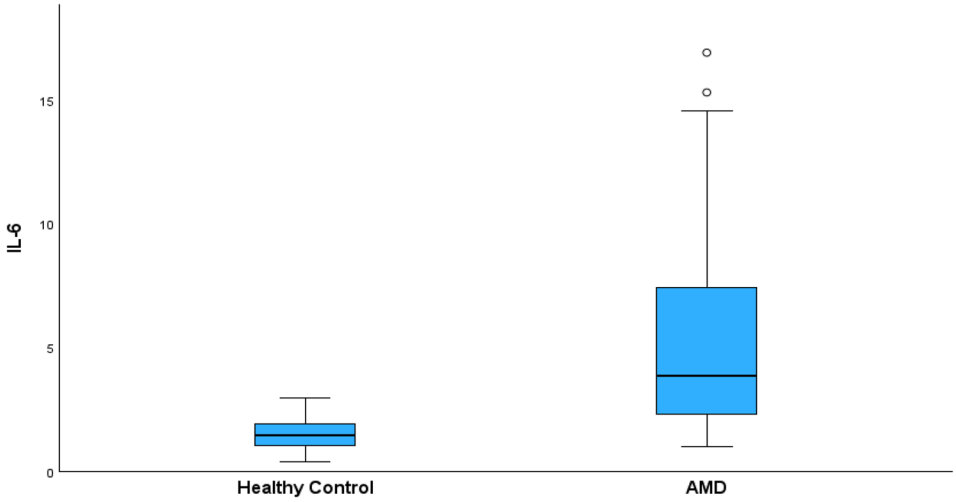


Fig. 1 Comparison of serum IL-6 levels of the control group and the study group. The IL-6 level of the neovascular age related macular degeneration group [5,9 (1–16,9) pg/mL] was statistically significantly higher than the control group [1,5 (0,38 – 2,96) pg/mL]

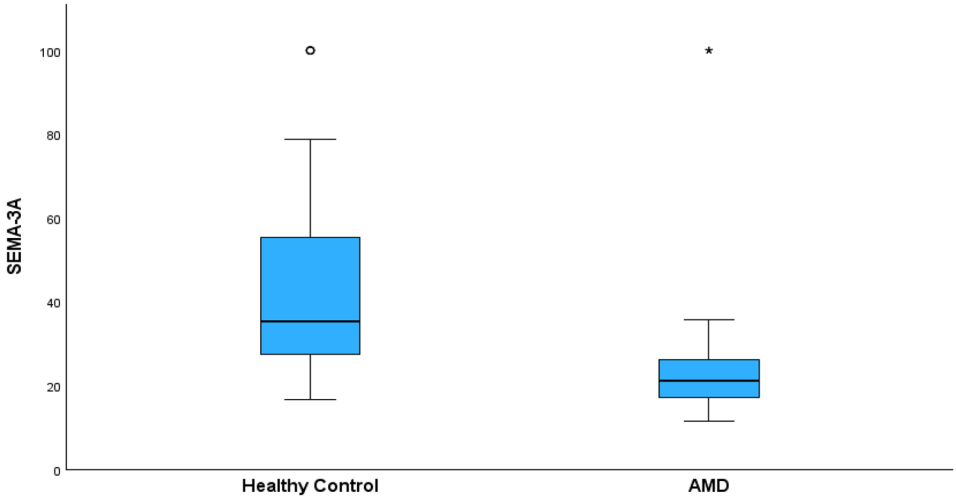


Fig. 2 Comparison of serum SEMA3A levels of the control group and the study group. The SEMA3A level of the neovascular age related macular degeneration group [26,3 (11,5-100) ng/mL] was statistically significantly lower than the control group [44,7 (16,8-100) ng/mL]

Table 2 Serum Sema3A and IL-6 level of normotensive and hypertensive group

	Normotensive	Hypertensive	*p* value
	Mean ± SD; Median (min-max)	Mean ± SD; Median (min-max)	
Female n (%)	16 (36,4)	17 (56,7)	0,085
Male n (%)	28 (63,6)	13 (43,3)	
Age (years)	75 (53–89)	78 (63,92)	0,106
Serum IL-6 level (pg/ml)	1,7 (0,4–15,3)	2,5 (0,5–16,9)	0,013
Serum SEMA3A level (ng/ml)	29,3 (12,2-100)	25,2 (11,5-100)	0,159

IL-6 interleukin 6 *SEMA3A* semaphorin-3 A

groups (all $p < 0.001$) (Table 1; Figs. 1 and 2). No significant difference was found between the hypertension (+) and hypertension (–) groups in terms of age and sex (all $p > 0.05$) (Table 2). The IL-6 level in the hypertension (+) group [2,5 (0,5–16,9) pg/ml] was significantly higher than that in the hypertension (–) group [1,7 (0,4–15,3) pg/ml] ($p < 0.001$) (Table 2). No significant difference was found between the hypertension (+) and hypertension (–) groups in terms of SEMA3A level ($p = 0.159$) (Table 2). Within the nAMD group, the IL-6 level in the HT (+) group [7.8 (2.4–16.9) pg/ml] was significantly higher than in the HT (–) [2.7 (1–15.3) pg/ml] ($P = 0.002$). However, no significant difference in SEMA3A levels was observed between the HT (+) [18.1 (11.5–32.7) ng/ml] and HT (–) [25.1 (12.1–100) ng/ml] groups ($P = 0.1$). There was a negative correlation between serum SEMA3A and serum

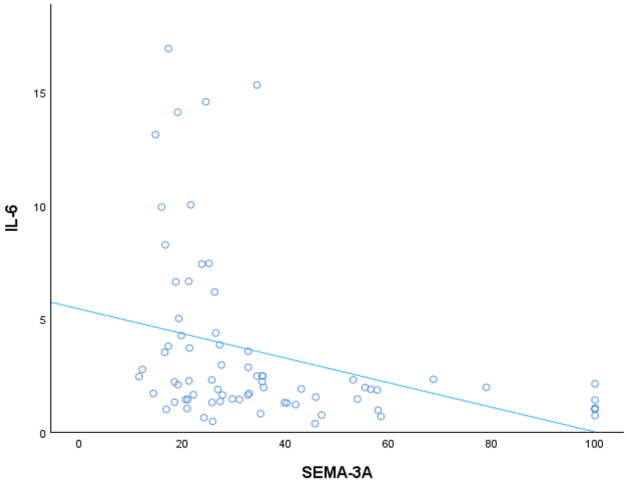


Fig. 3 Correlation between serum SEMA3A and serum IL-6 levels of whole participants. There was a negative correlation between serum Sema3A and serum IL-6 levels of the whole participants ($p < 0.001$, r=-0.471)

IL-6 levels of the whole participants ($p < 0.001$, r=-0.471) (Fig. 3).

Discussion

The present study demonstrated that, compared with the control group, patients with neovascular nAMD had lower systemic SEMA3A levels and higher IL-6 levels. In their meta-analysis, Nahavandipour et al. reported that systemic IL-6 levels were elevated in patients with AMD and that this increase was more closely associated with the late-stage subtypes of AMD [20]. In their study using a laser-induced CNV mouse model, Bai et al. reported that TGF-β and VEGF play roles in the development of CNV, whereas Sema3A inhibits CNV formation by suppressing TGF-β and VEGF [19]. The findings of the present study are consistent with those reported by Nahavandipour et al. and Bai et al.

Numerous studies have reported an association between AMD and cardiovascular diseases [29–31]. Mehta et al. reported that elevated IL-6 levels were associated with an increased risk of cardiovascular death, major adverse cardiovascular events, myocardial infarction, stroke, peripheral artery disease, and heart failure [32]. Studies reporting an association between AMD and cardiovascular diseases, together with the findings of Mehta et al. and the results of the present study, suggest that increased systemic IL-6 levels may play a role in the shared etiopathogenesis of AMD and cardiovascular disease. Tsai et al. reported a bidirectional association between atrial fibrillation (AF) and AMD [33]. Marcus et al. reported that IL-6 is a uniquely important mediator in the pathophysiology of atrial fibrillation [34]. The combined findings of Tsai et al., Marcus et al., and the present study suggest that elevated systemic IL-6 levels may contribute to the common etiopathogenesis of AF and AMD.

Lai et al. reported that loss of SEMA3A, which is associated with endothelial-mesenchymal transition in atrial fibrosis, plays a role in the pathogenesis of atrial fibrillation (AF) [35]. The findings of Tsai et al., Lai et al., and the present study suggest that decreased SEMA3A levels may be involved in the shared etiopathogenesis of atrial fibrillation (AF) and AMD.

Another disease associated with AMD is Alzheimer's disease [36]. Mody et al. reported that Alzheimer's disease and AMD are likely to share a common pathogenic pathway [36]. Amyloid-β is an abnormal protein that accumulates in the brains of patients with Alzheimer's disease and appears as plaques on magnetic resonance imaging (MRI) [36]. These plaques are a pathognomonic sign of Alzheimer's disease [36]. Similarly, amyloid-β deposits have been reported to accumulate beneath the retina in patients with AMD [36]. Furthermore, individuals with AMD have been found to be more likely to develop Alzheimer's disease than those without AMD [36]. Lyra et al. reported colocalization of IL-6 with astrocytes surrounding Aβ deposits in the hypothalamus of individuals with Alzheimer's disease [37]. Based on their findings, the researchers suggested that increased IL-6 production and signaling may be associated with cognitive decline and peripheral metabolic dysfunction in Alzheimer's disease [37]. Based on studies reporting elevated IL-6 levels in AMD, together with the findings of Mody et al., Lyra et al., and the present study, increased IL-6 levels are involved in the shared etiopathogenesis of AMD and Alzheimer's disease.

Numerous studies have reported that systemic IL-6 levels are higher in individuals with hypertension than in the control group [38, 39]. According to the results of the present study, IL-6 levels of participants with hypertension were significantly higher than those without hypertension.

Previous studies have identified hypertension as a risk factor for the development of nAMD [40–42]. The significantly higher IL-6 levels observed in HT (+) nAMD patients compared to HT (–) nAMD patients may elucidate one of the etiopathogenetic mechanisms underlying the association between nAMD and hypertension.

Substantial progress has been made in identifying genetic markers and pathogenic pathways of AMD [43]. Recent genetic evidence further supports the theory that AMD is a systemic disorder. Linkage and genetic association studies have identified genetic variants in the complement pathway, such as the Y402H polymorphism of the complement factor H (CFH) gene [44], and in the ARMS2/HTRA1 gene region [45, 46], both of which are strongly associated with prevalent and incident AMD. These genetic associations reinforce the hypothesis that inflammation is a key factor in the pathogenesis of AMD [47–49].

The reason for evaluating SEMA3A and IL-6 levels together in the present study was based on Catalano's study conducted in mice with experimentally induced autoimmune arthritis [26]. Catalano reported that SEMA3A reduced the production of inflammatory cytokines such as IL-6, TNF-α, IL-23, IFN-γ, and IL-17 and increased the level of the anti-inflammatory cytokine IL-10 [26]. Catalano's study found SEMA3A to be an anti-inflammatory mediator that acts on many inflammatory and anti-inflammatory cytokines [26]. The present study revealed a significant negative correlation between SEMA3A and IL-6 level. The findings of the present study are consistent with the results of Catalano's experimental study.

In conclusion, this study identified systemic SEMA3A deficiency and increased IL-6 as one of the etiopathogenesis of systemic inflammation detected in nAMD. The change in the range of these mediators also explains the cause of cardiovascular diseases, atrial fibrillation and, Alzheimer's disease compared to the healthy control group.

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None.

Author contributions
MO designed the study and collected blood samples and data, MA analyzed the serum Sema3A and IL-6 levels with ELISA kits and performed the statistical analysis, MO and MA interpreted the data and wrote the original draft; all authors reviewed, edited, and approved the final manuscript.

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Data availability
The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Ethical approval was obtained from the Ethics Committee of Recep Tayyip Erdogan University (Approval ID: 2021/97). The tenets of the Declaration of Helsinki were followed throughout this study. Written informed consent was obtained from all the participants before participation.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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