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Cytokine Profiles in Myasthenia Gravis Subgroups and the Lack of Any Effect of Immunosuppression

Merve Cebi^{1,2} | Hacer Durmus³  | Arman Çakar³  | Mehmet Güven Günver⁴  | Yesim Parman³ | Feza Deymeer³ | Güher Saruhan-Direskeneli¹

¹Department of Physiology, Istanbul Medical Faculty, Istanbul University, Istanbul, Turkey | ²Department of Medical Biology, School of Medicine, Recep Tayyip Erdogan University, Rize, Turkey | ³Department of Neurology, Istanbul Medical Faculty, Istanbul University, Istanbul, Turkey | ⁴Department of Biostatistics, Istanbul Medical Faculty, Istanbul University, Istanbul, Turkey

Correspondence: Güher Saruhan-Direskeneli (gsaruhan@istanbul.edu.tr)

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ABSTRACT

Introduction/Aims: Myasthenia gravis (MG) is a clinically and immunologically heterogeneous autoimmune disease and there is little known about the differential effects of cytokines in disease subgroups. This study aimed to compare serum cytokine profiles across distinct MG subgroups, including early-onset MG (EOMG), late-onset MG (LOMG), muscle-specific kinase antibody-positive MG (MuSK-MG), thymoma-associated MG (TAMG), and healthy controls (HC) in order to distinguish and determine relatively specific targets for the disease subgroups.

Methods: Serum samples from 22 EOMG, 23 LOMG, 17 MuSK-MG, 25 TAMG patients, and 25 HC were analyzed for a panel of cytokines involved in T and B cell interactions using multiplex bead-based immunoassays and ELISA. Additionally, paired serum samples of the same patients before and after immunosuppressive therapy were evaluated in a subset of patients.

Results: IL-17A, IL-4, IFN- γ , IL-21, and IL-9 were significantly elevated in EOMG and MuSK-MG groups, whereas IL-17F, IL-37, IL-2, TNF- α , and IL-13 were higher in EOMG only compared with HC. Increased levels of IL-6 in MuSK-MG and IL-37 in EOMG were found in these subtypes. In contrast, LOMG and TAMG patients showed limited cytokine alterations, with significant increases only in IL-21 in LOMG and IL-17A in TAMG. Immunosuppressive therapy did not significantly alter serum cytokine concentrations.

Discussion: The findings reveal heterogeneous cytokine signatures among diverse MG subgroups, separating EOMG and MuSK-MG from TAMG and LOMG with some similarities and highlighting the impact of age and thymoma presence on immune responses. This assessment of disease subgroups has provided a broader understanding of the cytokines in MG.

1 | Introduction

Myasthenia gravis (MG) predominantly presents with detectable autoantibodies against the acetylcholine receptor (AChR), while a smaller subset of patients exhibits autoantibodies targeting muscle-specific kinase (MuSK). Antibodies against low-density lipoprotein receptor-related protein 4 (LRP-4) may also be found associated with the MuSK or AChR antibodies or in isolation. Cases lacking detectable autoantibodies against MuSK or AChR are generally classified as seronegative MG [1, 2].

Patients positive for AChR autoantibodies are further stratified based on age at disease onset into early-onset MG (EOMG) for those younger than 50 years, and late-onset MG (LOMG) for those aged 50 years and above [3]; moreover, approximately 15% of cases are associated with thymoma, referred to as thymoma-associated MG (TAMG) [4].

The production of autoantibodies in MG is driven by T helper and B cell interactions orchestrated mainly by cytokines. The studies evaluating cytokines in MG have yielded inconsistent

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results. Evidence indicates that Th1, Th17, T follicular helper (Tfh), and regulatory T (Treg) subsets and the cytokines such as IL-17 and IL-6 play central roles in MG pathogenesis [5–10], although some studies have shown inconsistent results in MG [11, 12]. The effects of IFN- γ [13–16] and TNF- α have been linked to the disease in some studies with inconsistent results [17, 18]. Tfh cells are also elevated in MG [14–16, 19–21], with increased IL-21 levels probably contributing to autoantibody production. Findings for IL-4 in helper T cells remain inconsistent as well [10, 11, 15, 16, 18, 22, 23].

Most of the studies have focused generally on the AChR-MG subgroup and have also not accounted for the effects of immunosuppressive (IS) therapy. Considering the heterogeneity of MG, including AChR-MG, MuSK-MG, and TAMG, a comprehensive and systematic assessment is warranted. Moreover, clinical differences between early- and late-onset AChR-MG may be reflected in cytokine responses, and paired serum samples obtained from newly diagnosed patients before and after IS therapy may allow a more accurate evaluation of therapy-related changes in immune responses. In this context, the present study aims to systematically analyze cytokine profiles across well-defined MG subgroups and to investigate the impact of IS therapy, with the goal of providing insights that may inform future therapeutic strategies.

Given the clinical and immunological heterogeneity of MG, the study aimed to evaluate the serum levels of cytokines that are critically involved in T cell–B cell crosstalk and the orchestration of autoantibody production. By comparing distinct MG subgroups, defined by autoantibody status and clinical characteristics, with HC, we sought to identify potential immunological signatures that may underlie MG pathogenesis in different subgroups.

2 | Method

2.1 | Study Group

MG patients were identified from the Neuromuscular Unit of the Department of Neurology, Istanbul Medical Faculty. The diagnosis of MG was based on clinical presentation, supported by electrophysiological examination and antibody determinations. The serum samples were tested for both autoantibodies by radioimmunoassay (DLD Diagnostika GmbH, Hamburg, Germany) or ELISA (AChR-IgG, EUROIMMUN, IBL-Tecan GmbH, Germany) with commercial kits.

Inclusion criteria required AChR antibodies in patients with AChR-MG and TAMG, while all MuSK-MG patients were positive for MuSK and negative for AChR antibodies. None of the MG patients had received IS therapy at the time of the initial blood sampling. Only patients with generalized MG were included.

Samples of healthy controls (HC) were selected from among the stored sera of healthy donors with similar age and sex distribution and tested at the same time.

This study was approved by the Clinical Research Ethics Committee of Istanbul University Istanbul Medical Faculty. All study participants provided informed consent.

2.2 | Measurement of Cytokines

Cytokines were measured in the sera samples stored at the Neuroimmunology Unit of Istanbul Medical Faculty, where the patients were referred to for antibody measurements. The samples were aliquoted and stored in a freezer at -80°C . Follow-up serum samples of the same patients who were under IS treatment were included as well, and both the treatment naïve and treated serum samples were tested in parallel. Cytokine levels in donors' serum samples were analyzed using a Th cytokine panel kit (LEGENDplex BioLegend, USA) according to the manufacturer's instructions. Included cytokines and the assay sensitivities (pg/mL) were as follows: IL-5 (2.4), IL-13 (2.9), IL-2 (1.2), IL-6 (1.2), IL-9 (1.7), IL-10 (1.4), IFN- γ (2.8), TNF- α (2.4), IL-17A (1.2), IL-17F (1.7), IL-4 (2.4), and IL-22 (1.3). In addition, IL-21 and IL-37 levels were evaluated in the same sera using ELISA kits (Invitrogen, USA) according to the manufacturer's protocols, with a sensitivity of 8 pg/mL for IL-21 and 31.3 pg/mL for IL-37. The levels of cytokines were interpolated with a curve covering the range of the kit used. The cytokine analysis was performed once per sample. Values below the detection limit were recorded as 0 pg/mL.

2.3 | Statistical Analysis

Statistical analyses were performed using the Mann–Whitney U test to compare cytokine levels between different patient groups and HC. This non-parametric test was chosen due to the non-normal distribution of cytokine data, as assessed by the Shapiro–Wilk test. Paired *t*-test was used to compare cytokine levels before and after IS treatment. Variables are presented as median and interquartile ranges (IQR). A *p* value <0.05 was considered statistically significant. All analyses were conducted using SPSS version 29 (IBM, Armonk, NY, USA) or GraphPad Prism version 10 (GraphPad Software, Boston, MA, USA).

Cytokine levels across the study groups were explored using a heatmap-based visualization approach. For this purpose, median serum concentrations of each cytokine were calculated for all study groups. To enable comparisons across cytokines with different concentration ranges, data were standardized using z-score transformations. Heatmap visualization and hierarchical clustering were performed in R using the pheatmap package. Values were standardized by z-score normalization to allow comparison across cytokines with differing concentration ranges, thereby reflecting relative differences between groups rather than absolute serum levels.

3 | Results

3.1 | Baseline Serum Cytokine Levels in MG Subgroups

The clinical profiles of the patients are presented in Table 1. Eighty-seven patients were clinically diagnosed as having MG and classified by the presence of AChR and MuSK antibodies. The AChR antibody positive patients were also divided EOMG,

LOMG, and TAMG when they had thymoma. Overall, 64% of the MG cohort were women.

Baseline serum cytokine profiling revealed distinct immunological patterns among MG subgroups when compared with healthy controls. In the EOMG group, significantly elevated serum levels of IL-2 ($p=0.01$), TNF- α ($p=0.02$), IL-13 ($p=0.03$), IL-17A ($p=0.03$), IL-17F ($p=0.05$), IL-37 ($p=0.01$), IL-4 ($p=0.0004$), IFN- γ ($p=0.04$), IL-21 ($p=0.02$), and IL-9 ($p=0.02$) were observed relative to healthy controls (Figure 1). Collectively, these findings indicate a broadly enhanced cytokine profile in EOMG patients.

In the MuSK-MG group, significant increases were observed in the levels of IL-17A ($p=0.03$), IL-4 ($p=0.002$), IFN- γ ($p=0.03$), IL-21 ($p=0.01$), and IL-9 ($p=0.05$). Additionally, as a distinguishing/distinct biomarker, IL-6 was increased in this disease subgroup ($p=0.04$), pointing at a differential mechanism in the immunopathogenesis of MuSK-MG (Figure 1).

In contrast, the LOMG subgroup showed no significant differences in most cytokines compared with healthy controls. Only IL-21 levels were significantly increased in LOMG patients ($p=0.04$), while all other cytokines remained comparable to controls (Figure 1).

Similarly, only IL-17A levels were found to be elevated in the TAMG subgroup compared to HC ($p=0.047$, Figure 1a) indicating a predominance of Th17-driven immune mechanisms in TAMG.

Cytokine profiling across MG subgroups demonstrated distinct immunological differences between EOMG and MuSK-MG patients compared to LOMG and TAMG groups (Figure 2). EOMG patients exhibited significantly higher levels of IL-5 ($p=0.01$), IL-6 ($p=0.05$), IL-17F ($p=0.05$), IL-9 ($p=0.05$), IFN- γ ($p=0.02$) and IL-4 ($p=0.002$) relative to LOMG, indicating a heightened proinflammatory response.

Additionally, IL-13 ($p=0.04$), IL-2 ($p=0.02$), IL-9 ($p=0.03$), and IL-4 ($p=0.003$) were elevated in EOMG compared to TAMG. No significant differences were observed between EOMG and MuSK-MG patients.

In parallel, MuSK-MG patients also exhibited significantly higher IL-5 ($p=0.01$), IL-6 ($p=0.01$), IL-17F ($p=0.05$), IFN- γ ($p=0.02$), and IL-4 ($p=0.006$) levels compared to LOMG. IFN- γ ($p=0.04$) and IL-4 ($p=0.018$) levels were also significantly

elevated in MuSK-MG patients compared with TAMG patients (Figure 2).

Importantly, no significant differences in cytokine levels were observed between LOMG and TAMG groups, suggesting a comparable immunological profile of these subgroups displaying a similar, lower inflammatory profile.

These findings reveal a significantly elevated and distinct cytokine signature in EOMG and MuSK-MG subgroups relative to LOMG and TAMG, indicating differential T cell-driven immune responses.

To further characterize the distribution of serum cytokine levels across MG subgroups, median cytokine concentrations were visualized using a heatmap (Figure 3). Hierarchical clustering analysis showed that EOMG and MuSK-MG patients clustered separately from LOMG, TAMG, and healthy controls. This pattern indicates that EOMG and MuSK-MG share similar alterations in several serum cytokines. In contrast, LOMG and TAMG patients displayed clustering patterns closer to healthy controls, suggesting relatively limited changes in their cytokine profiles.

3.2 | Serum Cytokine Levels Following Immunosuppressive Treatment

To evaluate the effects of conventional treatments on serum cytokine levels in disease subgroups, sera of the selected patients under treatment were used for the same measurements in parallel. The treatment of the patients during the follow-up sampling is included in Table 2. At the time of sampling, 18 out of 22 EOMG patients, all LOMG patients ($n=23$), all 16 MuSK-MG patients, and 8 TAMG patients were being treated with IS drugs. Treatment of the patients included thymectomy (at least 1 year before) in all patients with EOMG and TAMG, in half of the patients with MuSK-MG and in none with LOMG; corticosteroids (at least 3 months) in the majority of the patients in all groups; azathioprine (at least 6 months) in almost all patients with LOMG and TAMG, and in some patients with MuSK-MG. When all MG patients were considered together, the interval between diagnosis and initiation of IS therapy ranged from 37 days to 6491 days, with a median of 52 months.

Comparisons of serum cytokine levels before (immunosuppressive negative, ISN) and during IS treatment (immunosuppressive

TABLE 1 | Demographic features of MG subgroups and healthy controls.

	AChR-MG		MuSK-MG	TAMG	HC
	EOMG	LOMG			
<i>n</i>	22	23	17	25	25
Women (%)	18 (82)	10 (43)	16 (94)	12 (48)	13 (52)
Median age	25	63	27	40	38

Abbreviations: AChR-MG, acetylcholine receptor antibody positive MG; EOMG, early-onset MG; HC, healthy controls; LOMG, late-onset MG; MuSK-MG, muscle-specific kinase antibody positive MG; TAMG, thymoma-associated MG.

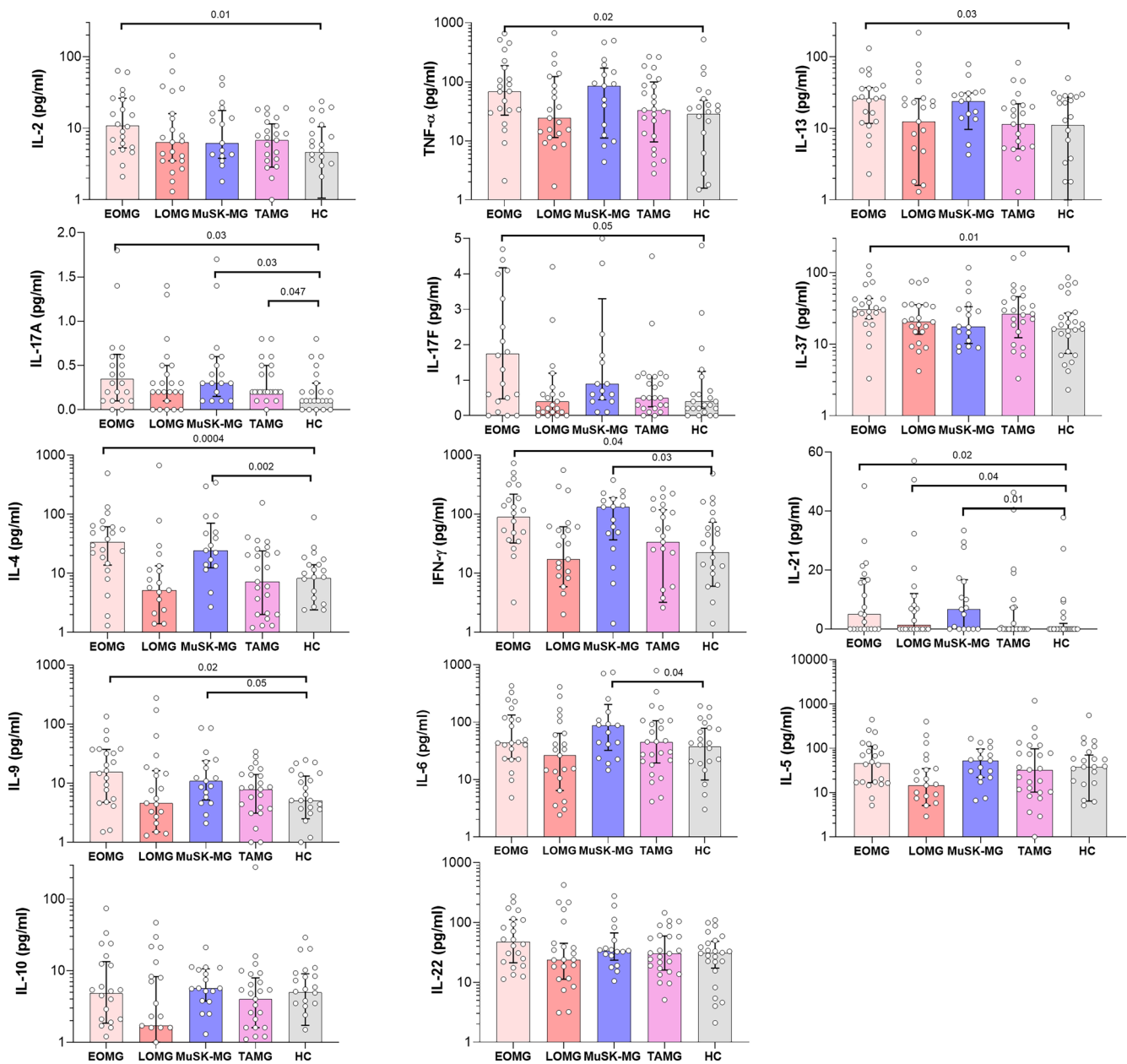


FIGURE 1 | Serum cytokine profiles between treatment-naïve MG subgroups and healthy controls. Serum cytokine concentrations were compared among treatment-naïve early-onset MG (EOMG, $n = 22$), late-onset MG (LOMG, $n = 23$), MuSK-MG ($n = 17$), thymoma-associated MG (TAMG, $n = 25$) patients with healthy controls (HC, $n = 25$). Data are shown as median with interquartile ranges. Significant p values are shown on horizontal lines.

positive, ISP) in the same patients revealed no statistically significant changes in all disease groups in any cytokine, suggesting a limited effect of treatment on serum cytokine profiles in MG patients (Figure S1). The effect of thymectomy in these groups could not be evaluated separately, as 4 of the patients in the EOMG group had TX only.

4 | Discussion

In the present study, distinct cytokine profiles were identified across MG subgroups, with EOMG and MuSK-MG patients exhibiting a markedly more active systemic cytokine response

compared to LOMG and TAMG. These findings underscore the immunological heterogeneity of MG and suggest that subgroup-specific immune mechanisms may contribute to disease pathogenesis.

Evidence indicates that the pathogenesis of MG is driven by complex cytokine-mediated interactions between T helper cells and B cells. Notably, EOMG and MuSK-MG subgroups exhibit a significantly more active cytokine profile. Increased levels of cytokines associated with Tfh and Th17 cells such as IL-4, IFN- γ , IL-17A, and IL-21 suggest their potential roles in sustaining autoantibody production and inflammation in these subgroups. Interestingly, elevated IL-9 levels were also observed in the EOMG and

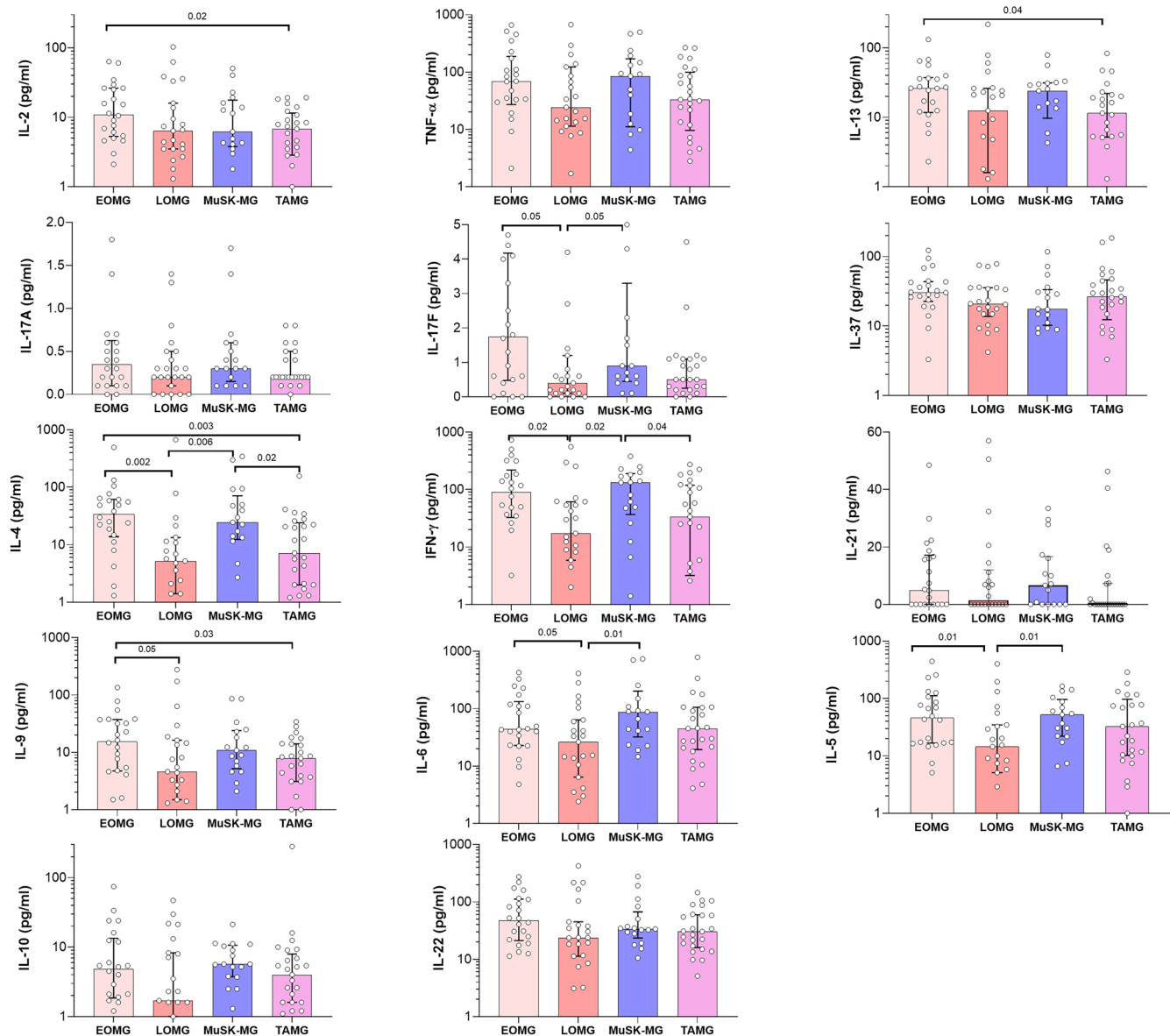


FIGURE 2 | Comparative serum cytokine profiles between treatment-naïve MG subgroups only. Serum cytokine concentrations were compared among treatment-naïve early-onset MG (EOMG, $n = 22$), late-onset MG (LOMG, $n = 23$), MuSK-MG ($n = 17$), and thymoma-associated MG (TAMG, $n = 25$). Data are shown as median with interquartile ranges. Significant p values are shown on horizontal lines.

MuSK-MG patient groups. Although data on IL-9 in the context of MG remain limited, studies using the EAMG model support a role for this cytokine in disease progression. Specifically, neutralization of IL-9 was shown to reduce disease severity, suppress effector T cell responses, and modulate the humoral immune profile in EAMG [24]. Similarly, administration of recombinant IL-9 (rIL-9) ameliorated disease symptoms and decreased serum anti-AChR IgG levels in the EAMG model [25]. Notably, the rIL-9 used did not act as a classical agonist but exhibited antagonistic effects by binding to IL-9 receptors, competitively inhibiting endogenous IL-9 signaling. Thus, both direct IL-9 neutralization and receptor-level antagonism converge on the suppression of IL-9 signaling, which appears to confer therapeutic benefits in EAMG [25]. Moreover, recent evidence suggests that IL-9 plays a critical regulatory role in the differentiation and activation of Tfh cells, thereby influencing antibody production. Tfh cells deficient in IL-9 receptor expression demonstrated significantly reduced levels of signature molecules such as BCL6, CXCR5,

IL-4, and IL-21, accompanied by impaired germinal center formation and attenuated antibody responses [26]. Taken together, these findings indicate that the elevated IL-9 observed in EOMG and MuSK-MG subgroups may promote autoantibody production through Tfh cell-mediated mechanisms.

In contrast, TAMG and LOMG patients exhibited only limited cytokine alterations compared to HC, with a significant increase observed in IL-17A in the TAMG group and IL-21 in the LOMG group. This differential cytokine expression may reflect distinct immunopathological mechanisms or localized immune responses, as suggested by prior studies identifying thymic inflammation in TAMG and age-related immune modulation in LOMG. Th17 cell-mediated proinflammatory responses may contribute to disease development in TAMG. Previous studies have reported increased IL-17 production and expansion of Th17 cells in patients with thymoma, supporting the notion that thymoma may foster a Th17-skewed immune environment that contributes

to MG pathogenesis [27]. The observation of a significant increase only in IL-21 levels in the LOMG group suggests that the cytokine response in this subgroup primarily reflects activation of the Tfh cells related mechanisms in particular. Additionally, the more limited cytokine activity observed in LOMG patients compared to EOMG patients may be one of the factors contributing to the better clinical prognosis seen in the LOMG patients [3, 28–30]. The older age distribution of LOMG and TAMG patients raises the possibility that immunosenescence may contribute to the attenuated systemic cytokine responses observed [31, 32]. Immunosenescence is characterized by a decline in T cell function, reduced cytokine production capacity, and a general weakening of immune responses

[33]. In this context, it is plausible that age-associated alterations in immune function partially underlie the differences in cytokine profiles observed among MG subgroups.

The impact of IS therapy on the immune response in MG patients remains incompletely understood. Previous studies conducted by our group involving heterogeneous cohorts of treated and untreated MG patients have demonstrated limited alterations in cytokine levels in *in vitro* comparisons [16, 27]. To more accurately assess the impact of IS therapy on serum cytokine profiles, we compared cytokine levels before and after/during treatment in the same patients. Despite this within-subject design, no statistically significant changes in serum cytokine concentrations were observed following IS therapy. These findings suggest that standard IS regimens may have limited capacity to modulate systemic cytokine production. In line with this, a recent cross-sectional study reported lower levels of several pro-inflammatory cytokines in MG patients receiving glucocorticoid therapy compared with untreated patients; however, the lack of paired pre-post analyses may partly explain differences from the present longitudinal findings [34].

This study has certain limitations. The retrospective design and extended recruitment period limited the availability of standardized clinical data, preventing robust correlations with disease severity and antibody titers. While paired serum samples were available for a subset of patients, the intervals between samplings differed considerably, restricting formal longitudinal analyses. In addition, changes in antibody detection methodologies over time limited direct numerical comparisons of antibody levels. Although treatment-related analyses were explored, the number of patients within specific IS regimens was insufficient for detailed treatment stratification.

Analysis of serum-derived cytokine signatures in relation to MG subgroups reveals the heterogeneous nature of MG immunopathogenesis and demonstrates that age, autoantibody profile, and the presence of thymoma are key determinants

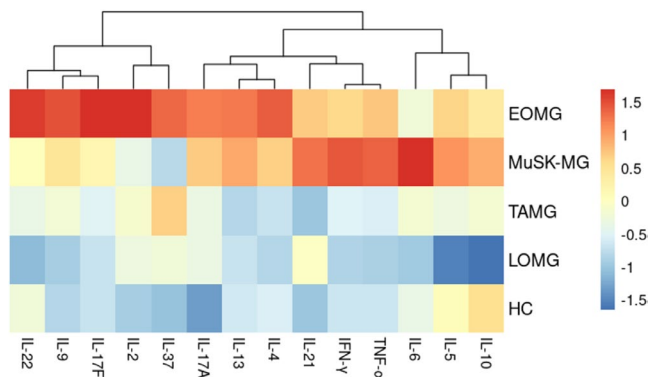


FIGURE 3 | Heat map of serum cytokine profiles across disease subgroups and healthy controls. Median serum concentrations of each cytokine were calculated for all study groups and visualized using a heat map. Values were standardized by z-score normalization to allow comparison across cytokines with differing concentration ranges, thereby reflecting relative differences between groups rather than absolute serum levels. Rows represent study groups (early-onset MG (EOMG), late-onset MG (LOMG), muscle-specific kinase MG (MuSK-MG), thymoma-associated MG (TAMG), and healthy controls (HC)), and columns represent individual cytokines. Hierarchical clustering was applied to cytokines to illustrate similarities in serum cytokine patterns across groups.

TABLE 2 | Details of treatments of the patients tested while receiving treatment.

	Total	AChR-MG			
		EOMG	LOMG	MuSK-MG	TAMG
Follow-up sera, <i>n</i>	69	22	23	16	8
women/men	49/20	18/4	10/13	15/1	6/2
Time between 1 and 2 samples (median/months)	52	67	55	26	78
TX only	4	4	0	0	0
TX + CS	20	11	0	8	1
TX + CS + AZA	14	6	0	1 ^a	7
CS only	7	1	3	3	0
CS + AZA	24	0	20	4 ^b	0

Abbreviations: AChR-MG, acetylcholine receptor antibody positive MG; AZA, azathioprine; CS, corticosteroid; CYC, cyclophosphamide; EOMG, early-onset MG; LOMG, late-onset MG; MuSK-MG, muscle-specific kinase antibody positive MG; TAMG, thymoma-associated MG; TX, thymectomy.

^aOne of the patients received mycophenolate mofetil instead of azathioprine.

^bOne of the patients received cyclophosphamide instead of azathioprine.

of the immune response. In conclusion, distinct cytokine patterns observed across MG subgroups support the involvement of subgroup specific T cell mediated pathways and age-related immune alterations in disease pathogenesis.

Author Contributions

Merve Cebi: conceptualization, writing – original draft, data curation, investigation. **Hacer Durmus:** conceptualization, validation, data curation, supervision, writing – review and editing. **Arman Çakar:** conceptualization, data curation, writing – review and editing. **Mehmet Güven Günver:** formal analysis, data curation. **Yesim Parman:** conceptualization, supervision, writing – review and editing. **Feza Deymeer:** conceptualization, investigation, writing – review and editing, supervision. **Güher Saruhan-Direskeneli:** conceptualization, investigation, funding acquisition, writing – original draft, writing – review and editing, formal analysis, project administration.

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Ethics Statement

All authors confirm that they have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Cytokine levels in the sera of EOMG ($n = 22$), LOMG ($n = 23$), MuSK-MG ($n = 16$), and TAMG ($n = 8$) patients and their corresponding samples when treated with immunosuppressive are presented as pairs. The paired t -test was performed for these comparisons.