AL-QADISIYAH MEDICAL JOURNAL , QAD.MED.J. 21 (2): JUNE-DECEMBER 2025
WWW.qmj.qu.edu.iq

REVIEW ARTICLE

The role of IL-13 serum levels with its genetic polymorphism in the risk of developing chronic rhinosinusitis

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Abstract:

Background:The chronic optic neuropathy known as slowly developing primary open-angle glaucoma (POAG) is typified by unique patterns of optic nerve degeneration and vision field loss. is the most prevalent kind, a complicated, multidimensional illness with a pathophysiology influenced by both genetic and environmental variables.

Objective: This study's objective is to find a relation between polymorphism of the MCP-1 gene and open-angle glaucoma disease susceptibility along with their proposed role in disease pathogenesis.

Materials and Methods: Two groups were the subjects of a case-control study: The first group included 40 patients who had previously been diagnosed with glaucoma, all cases that were observed in AL-Diwaniyah Teaching Hospital/Eye Department and ophthalmology private Al-Hayat clinics/AL-Qadisiyah/Iraq. In the period from October 2023 to December 2023. under the supervision of an experienced ophthalmologist and medicine specialists, and information was collected about each case. From the patient, in addition to the tests that were performed in the center's departments, such as eye pressure and optical coherence tomography (OCT). The second group included 40 healthy volunteers (with no family history of glaucoma).

Results: The current investigation showed the mean serum MCP-1 level in the patients' group was noticeably higher than that of the control group, 3.63 ± 2.45 pg/ml versus 1.51 ± 0.66 pg/ml, respectively ($p < 0.001$). Additionally, the current investigation found the genotypes AA, AG, and GG showed no significant difference ($p > 0.05$) when comparisons were made between the patient group and control group. Thus, none of them can be regarded as a risk or a protective factor.

Conclusion: Even this study found no significant association between the MCP-1 (2518A/G) polymorphism and the occurrence of primary open-angle glaucoma in a sample of Iraqi individuals. However, its serum level reflects signs of involvement in pathogenesis and disease development.

Keywords: MCP-1, OCT, genetic polymorphism, open-angle glaucoma disease.

Introduction

Primary open angle glaucoma (POAG) is a chronic, progressive eye illness characterized by the loss of the optic nerve rim and retinal nerve fiber layer (RNFL), in addition to visual field abnormalities (1). POAG susceptibility is defined by a complex disease process that is influenced by a number of clinical factors, including age, race, myopia, central corneal thickness, intraocular pressure, and a family history of glaucoma (2). POAG generally begins slowly, progresses steadily, and causes minimal pain(3). Individuals in the later stages of glaucoma are often asymptomatic until central vision is lost, which may be asymmetrical. For more than 95 million individuals globally, the second most prevalent cause of blindness is glaucoma (4). POAG is confirmed through testing the optical field, layer of nerve fibers, and optical nerve (5). Bilateral blindness affects an estimated 8% of the population. Glaucoma affects 0.46 percent of Indonesia's population. This indicates that glaucoma affects 4-5 out of every 1,000 persons (6). Primary open-angle glaucoma (POAG), the second leading cause of blindness after cataracts, affected 57.5 million people globally in 2015. This is an incurable condition. By 2020, that number had risen to 65.5 million (7). Elevated intraocular pressure is the only changing risk factor(8). Although there are several improved treatment options, including pharmaceutical, laser, and surgical interventions, it is anticipated that glaucoma will affect 111.8 million people by 2040 (9).

Monocyte chemoattractant protein-1 (MCP-1), or chemokine C–C ligand 2 (CCL2), the recent name of this chemotactic cytokine, is a member of the C–C chemokine family and a potent chemotactic factor for monocytes (10). A variety of retinal neurodegenerative illnesses are characterized by progressive loss of retinal ganglion cells (RGCs), which can result in irreversible visual loss (11). However, overexpression of MCP-1 causes microglia and astrocyte dysfunction, which leads to neurological illnesses. (12).

The level of immune responses may have an unexpected relationship with the development of glaucomatous optic nerve degeneration. Under some situations, this association may result in an abnormal immunological signaling pathway, which eventually leads to the death of retinal ganglion cells (13).

2- Materials and Methods

Study participant

Two groups participated in case-control research: The first group included 40 patients who had previously been diagnosed with open-angle glaucoma, all cases that were observed in the Teaching Hospital / Diwaniyah / Eye Department and AL Hayat Ophthalmic Center. Between October 2023 and December 2023, information has been collected on each case under the supervision of an ophthalmologist. From the patient, in addition to the examinations carried out in the various sections of the center, like the ocular pressure examination, OCT, and others. The second group included forty volunteers who were healthy and had no family history of glaucoma. These two groups had venipunctures to collect five milliliters of venous blood, which was subsequently extracted using a disposable syringe while rigorous hygiene standards were followed. Blood samples are collected with two tubes.

Approximately 3 ml of blood was collected in an EDTA tube for complete DNA extraction in order to investigate the genetic polymorphism for MCP-1 SNP (2518 A/G).

In this study the primer design was carried out according to the complete sequence of MCP-1 (2518 A/G) obtained from the NCBI GenBank database and Primer 3 Plus online, which was provided by Humanizing Genomics Microgen, Korea, as the following table (1):

Primer	Sequence Sequence 5'-3		Product Size	Reference
MCP-1	MCP2518 CL	5-TGAGTGTTCACATAGGCTTC-3	175 bp	38
	MCP2518 GL	5-GTGGGAGGCAGACAGCTG-3		
	MCP2518AL	5-GTGGGAGGCAGACAGCTA-3		

2 ml of blood was extracted and allowed to coagulate in a standard gel tube. Following that, the serum was separated and centrifuged for five minutes at 13,000 rpm to separate it. Serum was collected in an Eppendorf tube and kept at -20°C for use in the human MCP-1 ELISA assay, as shown in the research design view.

In the current study, the ELISA kit (FAVORGEN / Korea), which uses a single-step, double-antibody sandwich enzyme-linked immunosorbent assay method to measure MCP-1 in human serum, has been used. After spectrophotometric measurement of the color change at 450 nm to determine the MCP-1 concentration in the samples, the O.D. of the chemokines is compared to a standard curve to calculate the chemokines' concentration.

Polymerase Chain Reaction (PCR) methodology was used to determine MCP-1 SNP (2518 A/G) in all patients and in healthy control blood samples as the following steps:

The GoTaq® Green Master Mix Kit (Promega/USA) was used to elaborate the PCR master mix, and the manufacturing company's instructions, as shown in table 2, were followed in the preparation of this master mix.

PCR Master Mix	Volume
GoTaq®G2 Green Master Mix	12.5 µl
DNA Template	5 µl
Upstream Primer	2 µl
Downstream Primer	2 µl
Nuclease-free Water	3.5 µl
Total Volume	25 µl

Table 2: PCR Master Mix

The above-mentioned components of the PCR master mix were then added to standard test tubes together with GoTaq® Green Master Mix, contained all of the elements needed for a PCR reaction, such as Tris-HCl, dNTPs, and Taq DNA polymerase.

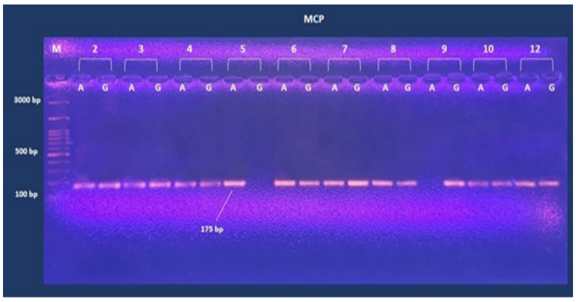
pH: 9.0, KCl, MgCl2, tracking dye, and stabilizer. Each PCR tube was then inserted in a PCR thermocycler (Promega/USA) after being spun for five minutes at 3000 rpm in an Exispin vortex

PCR Step	Temperature	Time	No. of Cycles
Initial Denaturation	94 °C	5 min	1
Denaturation	94 °C	30 sec.	35 Cycle
Annealing	53 °C	30 sec.	
Extension	72°C	30 sec.	
Final Extension	72°C	5 min.	1
Hold	4°C	-------	-

Table 3: PCR Thermocycler program

PCR product analysis

The hexon gene PCR amplification products were analyzed by migration on agarose gel electrophoresis. At first, 1X TBE was used to create a 1% agarose gel, which was subsequently dissolved in water. Allow the bath water to cool to 50°C after 15 minutes at 100°C. To the agarose gel solution, added 0.5 µl of previously produced ethidium bromide stain (1% W/V). And after positioning the comb, the agarose gel preparation was poured into the tray. The comb was carefully removed from the tray, with 10µl of the 100bp ladder in one well and 10µl of each PCR amplification product for each test sample serving as the standard reference. The gel was then let to grow.



Figure(1): MCP-1(2518 A/G) the agarose gel electrophoresis picture that revealed the PCR analysis of MCP-1 SNP gene polymorphisms.

3: Results

Comparison of serum MCP-1 between patients: Table 4 displays the group and the control group. The mean serum MCP-1 was significantly higher in the patients' group in comparison with the control group, 3.63 ± 2.45 pg/ml versus 1.51 ± 0.66 pg/ml, respectively (p < 0.001).

Table 4: Serum MCP-1 levels in the patient and control groups are compared.

Characteristic	Patients group n = 40	Control group n = 40	p
Serum MCP-1			
Mean ±SD	3.63 ±2.45 pg/ml	1.51 ±0.66 pg/ml	< 0.001 I ***
Range	1.26 -13.33	0.32 -3.46	

SD: standard deviation; I: independent samples t-test; ***: significant at p 0.001

The frequency distribution of patients and control subjects according to MCP-1 A/G genotypes is shown in Table 5. Overall, the genotypes AA, AG, and GG showed no significant difference (p > 0.05) when comparisons were made between the patient group and control group. Thus, none of them can be regarded as a risk or a protective factor.

Table 5: The frequency distribution of MCP-1 A/G genotypes in patients and control subjects.

MCP-1 A/G Genotypes	Patients group n = 40	Control group n = 40	p	OR	95 % CI
AA, n (%)	12 (30.0 %)	15 (37.5 %)	0.478 C NS	0.71	0 . 2 8 -1.81
AG, n (%)	27 (67.5 %)	25 (62.5 %)	0.639 C NS	1.25	0 . 5 0 -3.13
GG, n (%)	1 (2.5 %)	0 (0.0 %)	0.314 C NS	3.08 a	---

OR: odds ratio; CI: confidence interval; C: chi-square test; F: Fischer exact test; NS:not significant;*: significant at p ≤ 0.05; ***: significant at p ≤ 0.001; a: approximate odds ratio.

A comparison of the frequency distribution of MCP-1 A/G alleles between the patient group and control group is shown in table 6. Allele A and G frequencies were not significantly different when the patients' group was compared to the control group, 63.8% versus 68.8% and 36.3% versus 31.3%, respectively (p = 0.504).

Table 6: Comparison of the frequency distribution of MCP-1 A/G alleles between the patient group and control group.

MCP-1 A/G Alleles	Patients group n = 80	Control group n = 80	p	OR	95 % CI
A	51 (63.8 %)	55 (68.8 %)	0504C NS	0.80	0.41- 1.54
G	29 (36.3 %)	25 (31.3 %)		1.25	0.65- 2.41

OR: odds ratio; CI: confidence interval; C: chi-square test; F: Fischer exact test; NS: not significant.

4- Discussion:

The present study found a significant increase in the mean serum CCL2 level associated with glaucoma patients compared to healthy controls. This result agreed with the result achieved by Vidal-Villegas et al. (2022), who found that the levels of monocyte chemoattractant protein-1 (monocyte chemotactic and activating factor) were higher in the pseudoexfoliative glaucoma group (14). Additionally, Cueto et al. (2021) observed that the systemic levels of MCP-1 were significantly higher in the normal-tension glaucoma group than in the control group (15).

MCP-1 levels in the aqueous humor of glaucoma patients have already been bound. This cytokine may induce macrophage infiltration into local tissue as well as leukocytes, leading to excessive inflammatory and fibrotic responses (16). The release of MCP-1 is controlled by both cytokines with pro-inflammatory properties and those with anti-inflammatory properties. Inflammatory cytokines, including IL-1, TNF-α, and IL-6, have the potential to augment MCP-1 secretion in early inflammation (17).

When chemokines are activated, they attach to adequately exposed receptors in immune cells via chemical interaction gradients (18). Suitable cells with such receptors may spread from chemokine-rich sites to perform immunological, homeostatic, or both activities (19).

Normal trabecular meshwork cells (TM) produce inflammatory chemokines, including monocyte chemo-attractant protein (MCP)-1, which is increased in the aqueous humor of primary open-angle glaucoma (20). Patients with primary open-angle glaucoma (POAG) have consistently higher levels of monocyte chemoattractant protein (MCP)-1 in their aqueous humor (AH). Furthermore, the levels of MCP-1 show a positive connection with the levels of IOP (21). These inflammatory cytokines may reduce proliferation of the TM cells by promoting cell migration away from the outflow tract, or they may exert a direct cytotoxic effect (22). TM cells produce MCP-1 receptors (CCR2), which enhance MCP-1 in an anti-crime way and have reciprocal regulatory effects on each other, while TGF-β inhibits MCP-1 production (23). TM cells release a wide range of chemicals, including cytokines, chemokines, and matrix metalloproteinase, to modulate cell and extracellular matrix activity. CCR2, the MCP-1 receptor, is significantly expressed in TM cells (24). Activation of the MCP-1/CCR2 axis stimulates chemotaxis and activation of inflammatory cells, as well as a variety of signaling cascades in ocular fibrosis (25).

Human TM cells produce MCP-1 and exhibit its receptors, indicating that it is essential to regulating aqueous outflow. MCP-1 induced actin stress fibers and focal adhesions in TM cells and also increased phosphorylation of myosin light chain (MLC) and paxillin, indicating that this chemokine regulates cellular contractility and adhesive interactions, potentially regulating AH outflow and IOP levels (26). Chemokines activate their actions by binding to G-protein coupled receptors on target cell surfaces. Chemokine receptors also activate Rho family proteins, which enhance cellular motion by actin polymerization (27). The sudden rise in MCP-1 in pathologic conditions may have a direct effect on the contractile activity of TM cells via their highly expressed receptors, thus leading to IOP elevation (28).

Moreover, concerning the MCP-1 SNP, the present study did not reveal an association between the MCP-1 −2518 A/G single nucleotide polymorphism and open-angle glaucoma. Therefore, our data do not confirm the findings and do not support the hypothesis that the MCP-1 −2518 A/G SNP is directly involved in the genetic susceptibility to POAG. The MCP-1-2518 G allele is known to stimulate MCP-1 gene expression (29), and the current study found that the G allele was significantly more prevalent in the patient's group compared to the control group. However, these SNPs did not show a significant association with glaucoma in this study on the Iraqi population.

Even with the lack of such statistical significance value, which might be related to sample size, it did not rule out the impact of such SNPs on disease development. Some of these SNPs may be of functional significance, and their frequencies may vary significantly between different ethnic groups; no single mutation was shared by all ethnic populations (30). It may also suggest that a single gene locus may not cause glaucoma but act interactively with other gene variants (31).

MCP-1 is induced by tumor necrosis factor-α (TNF-α), which further regulates leukocyte recruitment, thus playing a key role in the inflammation. Anti-MCP-1 medications effectively restrict phagocytic cell penetration into cells; hence, MCP-1 levels are greater in patients when the infection is detected and evaluated and lower following therapy. This explains the current results, as well as the tiny difference in levels between patients and controls and the small sample size (32). The patient's age is another factor to consider. MCP-1 levels seem to be greater in younger patients; another reason is a patient's development. MCP-1 levels rise in adolescence and are suspected of the development of diseases (33). For another cause, it depends on the location of the damage in the patient's body, in addition to the patient's ethnic origin (34).

Conclusion:

The current study provides evidence that the MCP-1 (2518A/G) variant did not show statistical correlation with disease susceptibility not related to susceptibility ($p > 0.05$) when comparisons were made between the patient group and control group. However, its serum level reflects signs of involvement in pathogenesis and disease development.

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