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Comparison of Concentrations of MMP2 and MMP9 in Aqueous Humor of Patients Suffering with Acute Primary Angle Closure Short Title: MMPs and acute primary angle closure

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Abstract:- Objective- Inflammation with neovascularization leads to elevated intraocular pressure(IOP) which is only modified risk factor for acute primary angle closure (APAC) caused by decreased aqueous humor outflow from the anterior chamber. The present study has been planned to compare the levels of MMPs in aqueous humor of patients with APAC and aimed to analyse the molar ratio of MMPs with respect to the other MMPs.

Methods- Aqueous humor samples were collected from 46 healthy control persons (non-glaucomatous) and 52 APAC patients undergoing cataract surgery. Molar concentrations of all the MMPs were measured using multiplexed immunoassays Kit Methods. Statistical significance was assessed with Mann–Whitney U tests, and Spearman's method was used to assess correlations with age and IOP.

Results: Concentrations of MMP1 (p = 0.003), MMP2 (p = 0.0001), MMP3 (p = 0.002), MMP7 (p = 0.002), MMP8 (p = 0.001), MMP9 (p = 0.0001), MMP12(p = 0.002) and MMP13 (p = 0.002) were significantly increased in aqueous humor samples from APAC versus healthy control group. For the majority of MMP- molar ratios calculated and after comparing the APAC group to healthy controls, the molar ratios of MMP2 and MMP-9 with respect to other MMPs showed a significant increase in APAC samples. Conversely, the MMP2/MMP9 (p = 0.045) and MMP9/TIMP2 (p = 0.033) molar ratios were not significantly increased.

Conclusions: An imbalance among concentrations of MMPs was found in glaucomatous aqueous humor samples, with a shift toward raised molar ratio of MMPs except MMP2/MMP9. This may result in the inhibition of MMP activity, leading to an altered ECM composition in the TM and thereby contributing to increased outflow resistance.

Keywords:- *MMP2, MMP9 , Acute primary angle closure.*

I. INTRODUCTION

The restriction of the eye's drainage angle results in acute angle closure[1]. The balance between aqueoushumorproduction (in the ciliary body) and drainage (mainly through the trabecular meshwork) determines intraocular pressure[2]. Reduced drainage creates increased intraocular pressure, which may harm the optic nerve and cause pupillary block (primary cause of angle closure)[3]. In addition, conditions including mature cataracts, lens displacement, intraocular tumours, and enlargement of the uvea is due to inflammation and neovascularization, such as diabetic retinopathy, retinal vascular occlusions, and ocular ischaemia[4]. Inflammation is directly related with the levels of MMPs and practically every physiological process in the various eye structures involves MMPs whereas age-related macular degeneration in humans has been associated with elevated levels of MMP-2 and MMP-9 in choroidal neovascularization (CNV)[4,5].

A Zn2+-dependent enzyme known as MMP-2 (gelatinase A), it is linked to inflammation and plays a significant part in the destruction of the extracellular matrix (ECM) that is involved in angiogenesis and tumour invasion[6]. It contributes to atherosclerotic plaque rupture, renal fibrosis, and thoracic aortic aneurysm, as well as its participation in neurological disorders such as Parkinson's and Alzheimer's diseases, glaucoma, osteoarthritis, and glaucoma[6]. Adenomas of the pituitary, breast, ovarian, endometrial, gastric, and non-small cell lung cancers have all been linked to MMP-2 expression, according to meta-analyses done in various studies. MMP-2 plays a significant role in inflammation, metabolic dysregulation, cardiovascular and skeletal diseases, and the majority of its harmful effects are linked to elevation of its expression or activity[7,8].O- and N-glycans are both present in MMP 9 (gelatinase B)[9]. Numerous autoimmune, inflammatory, degenerative, and neoplastic disorders have been linked to elevated MMP-9 levels, however this correlation does not necessarily imply a functional role for MMP-9 in these pathologies[10]. Cytokine, chemokine, and MMP induction are caused by receptor contact. These three vascular problems of diabetes have been linked to elevated MMP-9 levels, which could serve as a biomarker for disease progression[11]. The section on eye illnesses includes additional discussion on diabetic retinopathy and the

function of MMP-9. A diabetic wound's ability to heal depends heavily on the MMP-2 and MMP-9 levels.

As a result, imbalances between MMPs in the aqueoushumormay have a significant impact on the results and prognosis of **acute primary angle closure**[4]. MMP-2& 9 have reportedly changed in patients with primary open-angle glaucoma, according to several studies. The association between MMP2 and 9 levels in patients has not yet been explored in detail. In the current study, we analysed the **comparison of concentrations of MMP2 and MMP9 in aqueous homor of patients suffering with acute primary angle closure.**

II. MATERIAL AND METHODS

This study was performed according to the guidelines of the Declaration of Helsinki and approved by the local Ethics Committee of the Rajshree Medical Research Institute Bareilly UP. Participants were recruited prospectively and consecutively in the Ophthalmology Department between Feb. 2018 and Sept. 2019. Written informed consent was obtained from all participants.

All recruited APAC patients fulfilled the following inclusion criteria: age >55 years; APAC treatable with topical and systemic antiglaucomatous medications; and coexisting cataract in the affected eye. APAC was defined as (1) the presence of at least 2 of the following symptoms: ocular or periocular pain, headache, blurred vision, and nausea with/without vomiting; (2) the presence of the following signs: conjunctival injection, a mid-dilated unreactive pupil, corneal edema, and shallow anterior chamber; and (3) an IOP >40 mm Hg by Goldmann applanation tonometry[12,13].The inclusion criteria included the following: (1) previous APAC patients with an APAC attack within 1 month before admission to our hospital; (2) uncontrolled IOP under standardized medication for APAC patients following pupil block release; and (3) agreement to finish 18 months of follow-up[10].

Patients without glaucoma of similar age were enrolled as a control group. The exclusion criteria included a history of previous ocular surgery, evidence of inflammation, fundus pathology, optic nerve disease, or systemic diseases, such as hypertension and diabetes.

Sample Collection [14]
AH samples (60–220 µL) were aspirated via limbic paracentesis using a 27-gauge needle at the beginning of the phacoemulsification procedure. Specifically, samples from APAC patients were collected at the beginning of the trabeculectomy, and samples from control patients were collected at any time. During the procedure of collecting aqueous humor, all collections were carefully performed without touching any intraocular tissue. Aqueous humor samples were immediately frozen in liquid nitrogen and transferred into a -20 °C environment. The samples were stored at –20 °C for up to 1 month and at –80 °C thereafter until all specimens had been collected for in-parallel analysis[14].

Quantitation ofMMPs[15,16]:-
Concentrations in AH SamplesMMPsconcentrations of AH samples were analyzed using a multiplex system (Bio-Plex Magpix Multiplex Reader). With this system, multiple analytes can be detected and quantified in parallel in a single 25-µL sample. In the current study, the concentrations of the following analytes were measured with the commercial multiplex bead immunoassay kit; MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP9, MMP-12 and MMP-13 (Milliplex Map Human MMP Magnetic Bead Panel 2, Millipore; working range: 12–20,000; 68–50,000; 20–20,000; 548–400,000;49–50,000; 14– 10,000; 20–20,000 and 27–20,000 pg/mL, respectively). AH samples were diluted 1:1 for processing with the MMP kit. All analytic procedures were performed according to the manufacturer's instructions. Briefly, magnetic microspheres tagged with a fluorescent label were coupled to specific capture antibodies and mixed with samples containing unknown quantities of the proteins. Biotinylated detection antibodies and streptavidin Rphycoerythrin were then added. The mixture was analyzed using the Luminex Magpix system. The 2 lasers of the instrument identified the microsphere type and quantified the amount of bound antigen. A concentration standard was run in parallel on each test plate for the generation of a standard curve to which the sample values were compared.

III. RESULTS

The present study has been planned to evaluate the concentration of MMPs in aqueous humor of patients with APAC and in healthy control group. We aimed to analyse the molar ratio of MMPs with respect to the other MMPs. It has been observed in our finding that the levels of MMP-1,2,3,7,8,9,12 & 13 are significantly increased in aqueous humor samples of APAC group as compare to healthy control group.

In both APAC and healthy control groups, the aqueous samples have measurable MMP-1,8,9,12 & 13 concentrations ranges from 12- 200 pg/mL whereas the concentration of MMP 3 & 7 ranges from 210-680pg/mL. The concentration of MMP-2 ranges from 7.5- 4.1 ng/mL.

In the majority of analysis, the aqueous humor samples (AHS) from group B has significantly higher concentrations as compare to healthy control. However, significant differences in concentration were seen for MMP1 ($p = 0.003$), MMP2 ($p = 0.0001$), MMP3 ($p = 0.002$), MMP7 ($p = 0.002$), MMP8 ($p = 0.001$), MMP9 ($p = 0.0001$), MMP12($p = 0.002$) and MMP13 ($p = 0.002$), with all analytes presenting an increased median concentration in APAC.

The increases in MMP-7 and MMP12 remained significant after correction for multiple testing. In addition, the median concentration of MMP-2 and MMP-9 was three fold increased in APAC group ($p = 0.0001$). The molar concentrations of MMPs like 1,3,7,8,12& 13 are also increased by 1.2-2.0 folds but this increase was not much more pronounced as compare to MMP-2 &9 in APAC group as compare to healthy control group.

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We sought to determine the presence of an imbalance between specific MMPs. Thus, we calculated the stoichiometric molar ratios. When comparing the APAC group to healthy controls, the molar ratios of MMP2 and MMP-9 with respect to other MMPs showed not a significant increase in APAC samples. Conversely, the MMP2/MMP9 (p = 0.045) and MMP9/TIMP2 (p = 0.033) molar ratios are not significantly increased. On comparison of median molar ratios of both the groups, it was observed that ratio of MMP2 and MMP9 with respect to other MMPs was increased by 1.5-2.5 folds as shown in table 1. These significant changes to MMPs molar ratios were likely due to the increase in MMPs concentrations in APAC group. Several MMPs molar ratios correlate with IOP in glaucomatous aqueous humorsamples.Nevertheless, none of these analytes or molar ratios correlated with age for POAG samples.Molar ratios for MMP2 in combination with any of the four MMPs, as well as MMP2/MMP9, correlated positively with IOP (p = 0.004–0.024).

Profile		**Healthy control (N=46)**		**Diabetic group (N=52)**		**P value**
1	**Gender M/F**	32/24		29/23		0.248
2	**Age**	67.23±10.54		69.61±12.87		0.215
3	**Intra oracular pressure (Median)**	NA		21.2 (18.0-23.0)		NA
4	**Optical cup/ disc (Median)**	NA		0.87 (0.65-0.92)		NA
5	**Disease duration (Mean ± SD)**	NA		6.83 ± 2.44		NA
Concentrations		**Median**	**Range**	**Median**	**Range**	
6	**MMP-1**	18.1	15.6-22.1	35.6	27.1-47.8	0.003
7	**MMP-2**	8623.22	7921.31-9732.14	25743.54	21232.11-39654.22	0.0001
8	**MMP-3**	402.3	334.5-460.2	713.4	543.1-989.3	0.002
9	**MMP-7**	269.3	229.5-298.2	398.6	221.4-647.2	0.002
10	**MMP-8**	87.6	77.3-92.1	121.4	80.2-160.5	0.001
11	**MMP-9**	60.1	55.3-65.2	198.2	136.1-312.7	0.0001
12	**MMP-12**	34.1	29.3-38.3	42.1	32.1- 53.7	0.002
13	**MMP-13**	88.3	79.2-94.3	105.2	90.2-135.2	0.002
Ratio						
14	**MMP-2/MMP-1**	476.42	507.77-440.36	723.13	783.47-829.58	0.003
15	**MMP-2/MMP-3**	21.43	23.68-21.14	36.08	39.09-40.08	0.002
16	**MMP-2/MMP-7**	32.20	34.51-32.63	64.58	95.89-61.27	0.002
17	**MMP-2/MMP-8**	98.43	102.47-105.66	212.05	264.73-247.06	0.0001
18	**MMP-2/MMP-9**	**143.48**	**143.23-149.49**	**128.88**	**156.00-126.81**	0.045
19	**MMP-2/MMP-12**	252.88	270.35-254.10	611.48	661.43-738.43	0.0001
20	**MMP-2/MMP-13**	97.65	100.01-103.20	244.71	235.38-293.30	0.0001
21	**MMP-9/MMP-1**	3.32	3.54-2.95	5.56	5.02-6.54	0.003
22	**MMP-9/MMP-2**	**69.69×10^{-4}**	**$(69.81\text{-}66.99)\times10^{-4}$**	**76.99×10^{-4}**	**64.10-78.85 $\times10^{-4}$**	0.033
23	**MMP-9/MMP-3**	14.93×10^{-2}	$(16.53\text{-}14.16) \times 10^{-2}$	27.78×10^{-2}	$(25.05\text{-}31.60)\times10^{-2}$	0.0001
24	**MMP-9/MMP-7**	22.31×10^{-2}	$(24.09\text{-}21.86) \times 10^{-2}$	49.72×10^{-2}	$(61.58\text{-}48.31)\times10^{-2}$	0.0001
25	**MMP-9/MMP-8**	**68.60×10^{-2}**	**$(71.53\text{-}70.79) \times 10^{-2}$**	**1.63**	**1.69-1.94**	0.0001
26	**MMP-9/MMP-12**	1.76	1.88- 1.70	4.70	4.32-5.82	0.002
27	**MMP-9/MMP-13**	**68.06×10^{-2}**	**$(69.82\text{-}69.14) \times 10^{-2}$**	**1.88**	**1.50-2.32**	0.0001

Table 1: Demographic and Stoichiometric analysis of MMPs among the groups

Note: Median and range calculated for values in range reported as pg/ml. Significance was tested by means of Mann–Whitney U and a p value <0.001 was considered significant.

IV. DISCUSSION

The purpose of the present was to assess the levels of comparison of MMP2 and MMP9 concentrations in aqueous homor of patients suffering from acute primary angle closure. Comparing APAC samples to healthy control samples, a substantial rise in MMP concentrations was found. This finding is generally in agreement with other findings in the literature17. We have included clinical data in our analyses, unlike the majority of earlier studies of MMP levels in aqueoushumorsamples, and we discovered that several of the MMPs molar ratios obtained for APAC aqueoushumorsamples closely linked with IOP. MMP levels increase to participate in tissue healing after significant injury. Affected tissue remodelling and wound healing may be the result of MMP changes18.

As a result, the results and prognosis of trabeculectomy may be significantly impacted by imbalances between MMPs in the aqueous humour. According to various investigations, MMPs have altered in patients with primary open-angle glaucoma. Numerous

studies have demonstrated that a number of mechanisms, including expression, secretion, activation, extracellular localization, inhibition, endocytosis, and lysosomal destruction19, affect MMP-2 function.

Glaucoma development has been connected to an imbalance between MMPs in aqueoushumorsamples20. In this investigation, we measured changes in MMP2&9/MMPs molar ratios, quantified the levels of numerous MMPs in aqueoushumorin APAC and control samples, and linked these findings with clinical characteristics. According to our findings, MMP-2 and MMP-9 predominate across all aqueoushumorsamples. However, the elevated levels of MMP2 and MMP9 result in an imbalanced MMP2/MMP9 molar ratio in the aqueoushumorsamples of APAC patients compared to those of healthy controls, which suggests that the overall activity of MMP2 and MMP9 in terms of concentrations may be decreased or may not be increased in the APAC group. MMP inhibition is found to be elevated in POAG aqueoushumorsamples, which is associated with the decrease in active MMP levels reported for glaucomatous aqueoushumorsamples21, according to a study by. This finding is consistent with the reported rise in ECM deposition within the glaucomatous TM22 and may lead to decreased ECM component clearance.

TIMPs, MMPs, and MMP/TIMP molar ratios were found to have a number of significant correlations with age in cataract samples, which may help explain the known age-associated increase in ECM deposition within the TM of healthy individuals23. In contrast, In our study, no such associations with age were observed in APAC samples. However, a correlation was determined between the MMP2/MMP9 molar ratio and disease duration in APAC samples in our study.

In our study, MMP2 and MMP9 molar concentrations were elevated in APAC patients, demonstrating alterations in gene expression related to senescence, which include elevated MMP secretions. Previous research showed a favourable link between the MMP/TIMP ratio and IOP, and current research shows that TIMPs are powerful MMP inhibitors24. IOP may also alter the amounts of MMPs by stretching the TM mechanically, which changes how MMPs are secreted25. Therefore, it is conceivable that TM cells have a direct role in the MMP alteration in the aqueous humour. TIMPs also function as cell surface receptors, MMP inhibitors, and regulators of cell proliferation, differentiation, migration, and apoptosis24. In our investigation, we focused on the hitherto unreported MMP-independent effects, namely a direct suppression of other TM cell functions like contractibility and phagocytosis that may alter aqueous fluid outflow. MMP-2 and MMP-9 levels had greatly increased, which was the explanation for this; nevertheless, the molar ratios of MMP-2 and MMP-9 to other MMPs had not significantly increased in the APAC samples. 24,26,27 According to our study's findings, there is a positive correlation between MMP2/MMP9 ratios and IOP, which suggests that a higher IOP may be linked to a decrease in anti-apoptotic signaling28. This might result in less cellularity in the TM and insufficient aqueous humor outflow as a result. MMP levels may rise in reaction to changed MMP secretion or possibly in response to other processes taking place in the anterior chamber, but it is yet unclear whether these changes in aqueoushumor compositions are a result of or a cause of the disease.

In conclusion, According to this study, future research should solely concentrate on MMPs upregulation with regard to both changes in TM cellularity and ECM composition in APAC.

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