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Original Article

Pentraxin 3 serum levels in wet-type age-related macular degeneration

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Abstract

Introduction: Age-related macular degeneration (AMD) has become a catastrophic health problem throughout the world because of the aging population. Destruction of the macular architecture in the wet type form is a major problem that results from AMD and is irreversible. Working on preventive measures is, therefore, of critical importance. Because pentraxins (PTX) become elevated in the body in stressful, oxidized conditions, this study examines the role they play in AMD. The similarity between the pathophysiology of atherosclerosis and AMD and the role of PTX3 in atheromas were also factors that support conducting this study.

Methods: This case-control study used 40 eyes that were at different stages of wet type AMD. The eyes were from patients who were over the age of 50 and had not had intraocular surgery or choroidal neovascularization (CNV) due to non-AMD causes. The control group included 49 eyes with normal macula. These study groups were matched according to age and gender, and the serum levels of PTX3 were analyzed.

Results: The mean ages of the patients were 70.7 ± 9.0 and 69.6 ± 7.4 years among the case group and the control group, respectively (P = 0.540) while the male to female ratios were 2.64 and 1.19, respectively (P = 0.091). The PTX3 (P = 0.002), high-sensitivity C-reactive protein (hs-CRP) (P = 0.008) and triglyceride (TGs) (P = 0.032) were significantly higher among the wet type AMD cases.

Conclusion: PTX3 appears to be a component in the pathogenesis of AMD and, therefore, could be a target for possible pharmaceutical interventions to stop or reduce the progression of this ominous disease.

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Introduction

Age-related macular degeneration (AMD) is a neurodegenerative multifactorial macular disease that is a leading cause of central blindness among elderly patients, and its prevalence is increasing because of the world's aging population.[1] AMD is clearly divided into two large subtypes: dry-type and wet type (exudative) AMD. In dry-type AMD, which constitutes the majority of cases, the vision is usually near normal. But wet type AMD is a disabling disease that is characterized by the accumulation of lipid material (especially the oxidized form) in the Bruch's membrane and culminates in damage to the retinal pigment epithelium (RPE) and in choroidal neovascularization (CNV) spreading into the sub-retinal space. The visual loss is extremely prominent and when the lesion eventually heals it leaves an effete scar formation.[2]

In addition to aging, oxidative insults,

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abnormal lipid metabolism, peripheral and cardiovascular diseases and mutations in some genetic loci are considered to be important in the pathogenesis of this disease.[3-6] Several therapeutic modalities have been tested, such as photocoagulation, photodynamic therapy, surgical excision and intravitreal corticosteroids versus anti-vascular endothelial growth factor medications, but a definite therapy has not been found.[4]

Pentraxin 3 (PTX3), which is also known as tumor necrosis factor-stimulated gene 14, belongs to the acute phase reactant proteins. The gene responsible for manufacturing this biomolecule was located on the long arm of chromosome 3 (3q24-3q28).[7,8] PTXs have formed a highly conserved superfamily of proteins throughout their evolution. Structurally, they are divided into two branches: the short-chained subdivision, including high-sensitivity C-reactive protein (hs-CRP) and serum amyloid P component, and the long-chained subdivision, of which PTX3 is the most important member.[9]

Under normal conditions, we do not expect to encounter high serum levels of PTX3; they are generally around 2 ng/ml or less. However, during acute insults to the body, such as endotoxic shock and sepsis, dramatically high serum levels of PTX3 can be observed (200-800 ng/ml).[9-13]

PTX3 originates from a wide variety of tissues, especially endothelial cells, macrophages, and adipocytes.[14] The exact function of this biomolecule is not absolutely clear, but there is some evidence in favor of its protective role against infectious pathogens and its monitoring of immune system activity.[14-18] According to a laboratory study on animals, PTX3 knockout mice who were given additional PTX3 were far more likely to diffuse systemic fungal infections.[14]

In addition to these findings, PTX3 has been discovered to be invaluable in predicting degenerative and vascular disorders.[19] This has prompted several studies aimed at showing a possible correlation between human systemic diseases and PTX3.

Elevated serum levels of PTX3 were found in proteinuria that resulted from chronic renal disease, congestive heart failure (CHF),[20] ST elevation myocardial infarction (STEMI) central obesity and aortic stenosis. A positive correlation was even seen between PTX3 serum levels and mortality from STEMI and CHF.[21]

A study conducted on patients with wet type AMD showed fewer antioxidants and equally higher numbers of oxidant agents, such as oxidized low-density lipoprotein cholesterol (LDL-C). Therefore, the authors have found some clues in favor of the role of the oxidative environment in exudative AMD.[22]

Atherosclerosis is a suspected risk factor for AMD. Indeed, pathologically evaluated slides have revealed many similarities between atherosclerotic damage to arteries and deposits in the Bruch's membranes of patients with wet-type AMD.[23]

In a randomized controlled trial study on LDL-C receptor knockout mice with and without high-fat diets, degeneration of the Bruch's membrane and accumulation of lipid material similar to an atheroma formation was detected among the mice with high-fat diets. In addition, a strong expression of PTX3 was detected in response to oxidized LDL-C of the vascular wall in macrophages inside the arterial plaques. A study on cultured human endothelial cells has also shown that the antioxidants down-regulate the PTX3 gene.[24-26]

The association between PTX3 and cardiovascular diseases on the one hand and wet-type AMD and cardiovascular diseases on the other hand, and also the role of antioxidants, persuaded us to design a novel study in order to uncover the possible role of PTX3 in patients with wet-type AMD. The outcomes would help us to be able to develop measures that are likely to be preventive against this ominous disease.

Methods

All of the cases in this study were randomly selected from among the patients referred to the Nikookari Eye Hospital's Retina and Posterior Clinic, at the Department of

Ophthalmology, Tabriz University of Medical Sciences, Iran, between June 2008 and January 2009. We discarded the data from dry-type AMD cases. Ethical approval was obtained from the Medical Ethics Committee of Tabriz University of Medical Sciences and written informed consent was received from all patients according to the tenets of the Declaration of Helsinki.

Inclusion criteria were patients who were over the age of 50 and had angiographically classic wet-type AMD with no identified systemic disease. Exclusion criteria were smoking, a history of any intraocular operation, especially vitreoretinal surgery, significant cataracts that made the fundus examination difficult and any other diseases with CNV, except for wet-type AMD. All participants underwent macular optical coherence tomography and fluorescein angiography in order to reveal the cases that had background wet-type AMD.

Subsequently, 40 eyes at different stages of wet-type AMD were gathered according to the criteria outlined above. For the control group, 49 eyes of individuals who had no symptoms or signs of macular degeneration but had visited the general eye clinic were selected. We calculated the number of cases with a power of 90 and $\alpha = 5\%$ and patients in the case and control groups was matched according to their ages and their genders.

This was a case-control study with no intervention exerted on the patients; however, informed consent was signed by all participants. Following overnight fasting for 8 hours, 5 ml of venous blood was obtained through the antecubital vein by a single laboratory technician.

Plasma PTX3 concentrations were measured by using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Uscn, Life Science Inc.), with a detection range between 0.312 and 20 ng/ml. The standard curve concentrations used for the ELISAs were 20, 10, 5, 2.5, 1.25, 0.625 and 0.312 ng/ml. The minimum detectable dose of human PTX3 is < 0.114 ng/ml. Other laboratory parameters that were checked included total cholesterol (TC) of serum, high-density lipoprotein-cholesterol (HDL-C), triglyceride (TG) and fasting blood sugar (FBS). Each of these was checked with specific kits from Pars Azmoon Company. The LDL-C was calculated using the Friedewald formula and the hs-CRP were measured by the nephelometry method (Pars Azmoon Co.).

All data were gathered and analyzed by SPSS software (version 18, SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test showed the distribution style of the data. Independent t-test and Mann-Whitney U-test were applied for quantitative data; these had a normal and a skewed distribution, respectively. The correlation was evaluated by the Spearman's Rho method. $P < 0.050$ were considered to be statistically significant.

Results

The main purpose of our study was to test the serum levels of PTX3 among patients affected by wet-type AMD and to compare these to the serum levels of individuals with normal macular architecture. The total number was 89, of which 40 had wet type AMD while 49 had a normal macular appearance. The mean age of the patients was 70.9 ± 9.1 and 69.6 ± 7.4 years for the case and control groups, respectively ($P = 0.441$). The male to female ratios of these two groups were 2.64 and 1.19, respectively (chi-square; $P = 0.091$).

The laboratory parameters that were checked included the PTX-3, FBS, TC, LDL-C, HDL-C, TG, and hs-CRP. Only the PTX-3, HDL-C, TG, and hs-CRP had skewed distribution.

Our main parameter was the serum level of the PTX3, which was not normally distributed. Therefore, the Mann-Whitney U-test was applied to uncover any differences between the case and control groups. The PTX3 was significantly higher among the wet type AMD cases ($P = 0.002$). Other parameters, which were analyzed using the method mentioned above, were the hs-CRP and TG ($P = 0.008$ and 0.032, respectively). The hs-CRP

and TG were confirmed to be statistically higher in the wet-type AMD group.

Other laboratory parameters were normally distributed and analyzed by independent t-test. None of these had significant differences between them (Tables 1 and 2).

The correlation between PTX3 and other quantitative laboratory parameters was tested as an accessory finding. PTX3 had a fairly positive and significant correlation with the age of patients and the HDL-C serum level (Spearman's rho correlation; r = 0.386, P = 0.014 and r = 0.478, P = 0.002, respectively) (Figures 1 and 2).

Table 1. Demographic data for the case and control groups

Variable	Wet-type AMD (n = 40)	Control group (n = 49)	P
Height (cm) (mean ± SD)	163.35 ± 9.44	165.35 ± 7.47	0.268*
Weight (kg) (mean ± SD)	69.15 ± 13.03	72.43 ± 7.79	0.167*
BMI (kg/m^2) (mean ± SD)	25.80 ± 3.87	26.65 ± 3.90	0.308*
Age (years) (mean ± SD)	70.92 ± 9.10	69.57 ± 7.40	0.441*
Male/Female ratio	2.64	1.19	0.091**

*Performed by independent-sample t-test, **Performed by chi-square test
AMD: Age-related macular degeneration; BMI: Body mass index; SD: Standard deviation

Table 2. Laboratory results of the case and control groups in the study

Laboratory results	Wet-type AMD (n = 40)	Control (n = 49)	P
PTX3* (ng/ml)	1.2 (0.7-3.75)	0.8 (0.4-1.1)	0.004**
hs-CRP*	0.29 (0.15-0.5)	0.18 (0.07-0.34)	0.018**
TG (mg/dl)*	125 (100-167.75)	106 (90-130)	0.011**
TC (mg/dl) (mean ± SD)	184.00 ± 35.42	181.63 ± 36.77	0.759***
LDL-C (mg/dl) (mean ± SD)	113.25 ± 36.77	108.57 ± 34.37	0.535***
HDL-C (mg/dl) (mean ± SD)	44.30 ± 2.70	44.90 ± 3.00	0.31***
FBS (mg/dl) (mean ± SD)	91.80 ± 9.97	93.20 ± 11.47	0.544***

*Median and interquartile range due to skewed distribution, **Analyzed by Mann–Whitney U-test, ***Performed by independent-sample t-test
PTX3: Pentraxin 3; hs-CRP: High-sensitivity C-reactive protein; TG: Triglyceride; TC: Total cholesterol; LDL-C: Low-density lipoprotein-cholesterol; HDL-C: High-density lipoprotein-cholesterol; FBS: Fasting blood sugar; AMD: Age-related macular degeneration; SD: Standard deviation

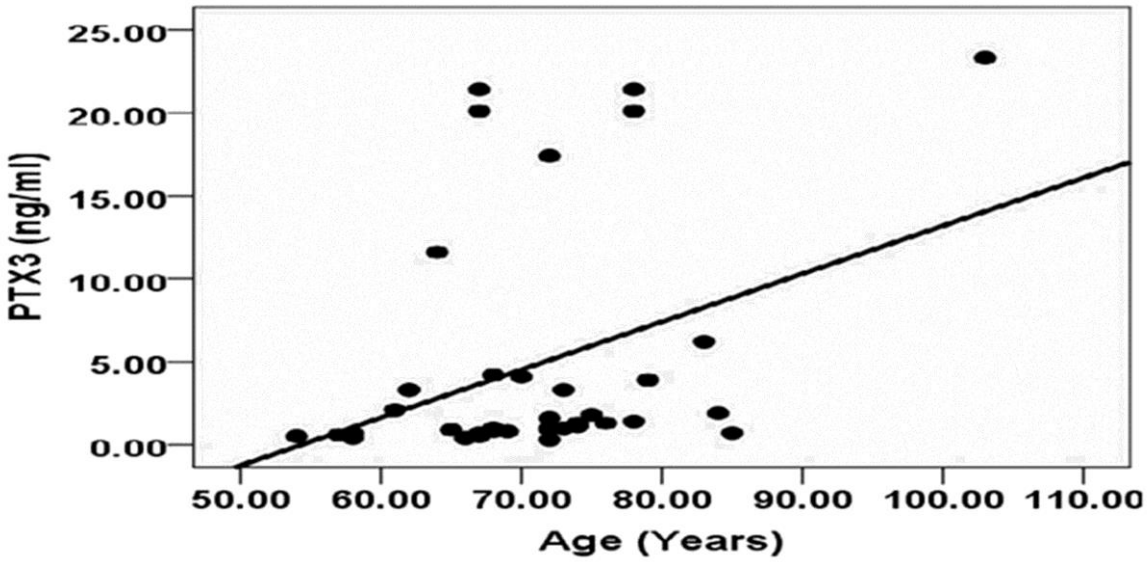

Figure 1. Correlation between pentraxin 3 and age in wet type age-related macular degeneration (AMD) patients (Spearman's rho correlation; r = 0.386, P = 0.014)
PTX3: Pentraxin 3

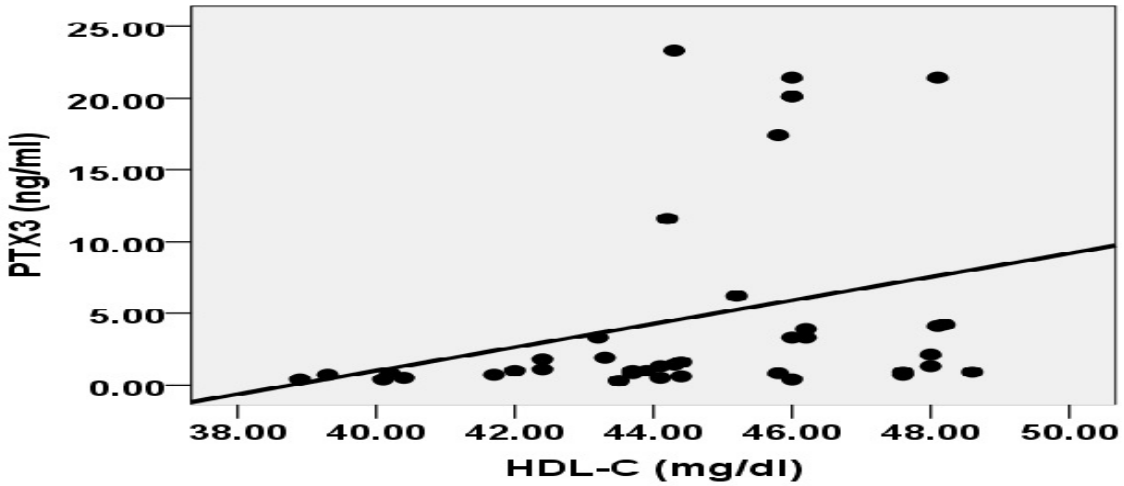

Figure 2. Correlation between pentraxin 3 and high-density lipoprotein-cholesterol in wet type age-related macular degeneration (AMD) patients (Spearman's rho correlation; r = 0.478, P = 0.002)
PTX3: Pentraxin 3; HDL-C: High-density lipoprotein-cholesterol

Discussion

Wet type AMD is a growing health problem throughout the world because of the aging population. In this disease, the Bruch's membrane loses its integrity, and eventually a fibrovascular tissue gains access to the sub-retinal space and disrupts the architecture of the photoreceptors and the RPE, with replacing it with a disciform scar. Clearly, the central vision will be lost permanently, and the lack of a definite treatment should urge us to work further to find preventive measures.[27]

PTX3 is an endogenous biomolecule that is an acute-phase reactant protein. In the study by Naito et al., increased levels of PTX3 were found in the serum and tissue of patients with aortic stenosis. It is not clear whether this increase is related to the background disease or represents a kind of stress on the body, particularly on the cardiovascular system.[28]

It has been shown on patients with STEMI and was able to illustrate a positive correlation between central obesity-visceral fat and PTX3 serum levels. The adipocytes are a major source of PTX3 throughout the body and, therefore, can justify this finding. The cellular damage and necrosis that follow a myocardial infarction are another crucial reason for increased levels of PTX3.[21]

A similar study was conducted by Dong et al.[29] on patients with unstable angina and STEMI. Increases in PTX3 were seen in both conditions, but much more dramatically in the STEMI cases. These studies emphasize the role that damaged cells play in the increased PTX3 and, consequently, in relation to the severity of the insult.

In the study by Yilmaz et al.,[18] chronic renal failure (CRF) with proteinuria was associated with higher serum levels of PTX3, but the administration of enalapril could alleviate this increase. Glomerular and tubular cellular damage, which are commonly observed in proteinuria that is due to CRF, can identify the condition clearly, but it should be stated that CRF patients suffer from a complex network of problems, and some degree of background inflammation is inevitable. Also, the cause of the CRF should be taken into account.

In our study, we encountered significantly higher levels of PTX3 among the patients who had wet-type AMD than among the normal population who had no definite and clinically proven disease. This finding can be evaluated in two different ways. First, it is likely that wet-type AMD would be a small part of a generalized disease that is accompanied by diffuse cellular damage including photoreceptors and RPE cells. Finding the cause of the abnormality would produce precious clues.

In the second hypothesis, the increase in PTX3 would be a primary condition that represents a low grade of inflammation throughout the body. The focal or diffuse

distortion and malfunction of the cells is, and then, gradually manifested and could eventually culminate in cellular damage.

PTX3 serum levels in CHF have been the subject of interest in other studies. Increased PTX3 was detected in patients with CHF and was, surprisingly, associated with higher mortality rates in accordance with its level. The authors attributed this event to the activation of tissue plasminogen and to injured arterial plaques.[30]

Other studies have shown the association of wet-type AMD and vascular diseases. Vingerling et al.[31] conducted an investigation on a large number of patients with wet type AMD. The odds ratios (ODs) for the existence of carotid artery plaque and peripheral artery disease were 4.7 and 2.5, respectively. In a similar study, the risk of mortality due to cardiovascular and cerebrovascular diseases was 5 and 10 times higher among those with wet type AMD than in the general population. These outcomes were achieved after adjustment for age and gender. Curcio et al.[25] demonstrated the presence in the Bruch's membrane of wet type AMD patients of cholesterol esters identical to those that are routinely expected to be in the atherosclerotic arterial intima. Killingsworth et al.[26] detected the same accumulation of phospholipid-containing macrophages in the Bruch's membrane of AMD cases as in atheroma.

On the other hand, strong expressions of PTX3 were observed in response to atherogenic inflammatory signals, including the existence of oxidized LDL-C material in the plaques. This overproduction of PTX3 might originate from the injured vascular endothelium and migratory macrophages that are engorged with oxidized lipid materials and may occur in a similar way in wet-type AMD. This provides reasonable justification for the dramatically high levels of PTX3 that we detected among our wet-type AMD cases.[24,32,33]

In other similar studies conducted on the excised CNV of wet-type AMD patients, overexpression of scavenger receptors was prominent on macrophages and RPE cells similar to atherosclerosis. This condition is probably due to the presence of oxidized LDL-C in the deposits of the Bruch's membrane, and the serum levels of oxidized LDL-C have been confirmed to be significantly higher among cases of wet type AMD. These recent investigations would suggest an identical mechanism for both wet type AMD and vascular abnormalities. In spite of the evidence noted above, some of the studies found no significant association.[34,35]

Evidence of increased PTX3 in recent vascular diseases necessitates an evaluation of the status of this biomolecule in wet type AMD, which we did it. The PTX3 was higher in these patients but not in individuals with normal macular architecture. Our finding supports a pathway that would be important in the pathogenesis of wet-type AMD and be influenced or modulated by PTX3.

In a review article, Wong et al.[36] hypothesize that oxidative agents, such as excess iron, could damage the retina and provoke AMD. In a laboratory study on cultured human endothelial cells, antioxidant agents in the media down-regulated the PTX3 gene expression.[37] These outcomes put a finger on the crucial role of oxidative insults in cellular damage, including photoreceptors and RPE death. Therefore, PTX3 might be just an indicator of antioxidant capacity in the body.

In a study by Norata et al.,[38] HDL-C induced the vascular expression of PTX3 that was considered to be a local trend and no concomitant increase in short PTXs, such as hs-CRP, was detected. It is thought that the S_1P component of HDL-C is involved in the overproduction of PTX3, and this is consistent with our accessory finding that the PTX3 and HDL-C had a fairly positive correlation. In contrast, Gustin et al.[39] did not find any PTX3 over-expression in exposed immortalized endothelial cells to the S_1Pcomponent of HDL-C.

The purpose of this study is to reveal undiscovered pathways that eventually lead to wet-type AMD. Showing these

mechanisms can help us to be able to adopt desirable interventions (such as pharmaceutical ones) that could stop or, at least, slow the progression of the disease.

Conclusion

Although this study discovered some positive findings, further studies using larger numbers of cases and detailed classifications would demonstrate more definite outcomes.

It would also be important in future studies to check the antioxidant capacity of serum, to show its influence on the evolution of AMD.

Conflict of Interests

Authors have no conflict of interest.

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