Original Article

Risk factors in patients with macular telangiectasia 2A in an Asian population: A case–control study

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Purpose: The aim of this study was to evaluate risk factors in patients with macular telangiectasia (MacTel) 2A in an Asian population. This was a hospital-based case–control study. **Methods:** We reviewed the case records of patients in our hospital, diagnosed as MacTel 2A over a 3-year period from April 2011 to March 2014. Controls were selected from patients seen in the hospital at the same time for visual defects after matching for age and sex. A multivariate logistic regression model was constructed using the variables that showed a statistically significant association ($P < 0.05$) with MacTel 2A in the univariate analysis. **Results:** The mean age of the patients with MacTel 2A was 58.63 years. A majority (76; 73.8%) of the patients were female. Of the patients with MacTel 2A, 61 (59.2%) patients had diabetes mellitus, and 50 (48.5%) revealed hypertension. Multivariate logistic regression analysis revealed the presence of diabetes mellitus to be the risk factor with the highest odds ratio (OR) of 5.7 followed by hypertension with an OR of 2.6. Binary logistic regression showed hypermetropia to have a greater risk factor compared to emmetropia, OR 2.64. **Conclusion:** Our case–control study revealed that MacTel 2A is significantly associated with systemic diseases. Diabetes mellitus was found to have the strongest association with MacTel 2A, showing a high OR of 5.7. Systemic hypertension followed by an OR of 2.6. Compared to emmetropia, hypermetropia was significantly associated with MacTel 2A. There could be a genetic link between the two. Determining risk factors draws us close to the goal of identifying the etiopathogenesis of MacTel 2A.

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Macular telangiectasia (MacTel) type 2A, an acquired bilateral neurodegenerative macular disorder, occurs in the fourth to sixth decades of life and results in vision loss in one or both the eyes; it is also known as idiopathic juxtafoveal telangiectasia type 2A.[1,2] The etiology and pathogenesis of MacTel 2A continue to be an enigma. It appears to be a primary neuroretinal degeneration associated with a secondary vascular involvement. It has become evident that photoreceptor loss is integral to the disease and it may be considered a disease of neural origin.[3-7] Müller cell dysfunction is a major contributor to the pathological features of MacTel 2A.[5] Müller cells are important for the proper functioning of the retinal capillary endothelium and the health of the surrounding neurons.[8-11] The retinal neuronal cells and the Müller cells interrelate very closely. They exhibit neuroprotective properties by secreting antioxidants and neurotrophic factors.[12] Hence, Müller cell degeneration is associated with loss of neurons.[13] This leads to central macular thinning and cavities in the retina.[14,15] Loss of macular pigment in MacTel 2A could be triggered by the impairment of Müller cells.[16]

The aim of the study was to evaluate risk factors in patients with MacTel 2A in an Asian population. There has been a paucity of information on MacTel 2A in the Asian population.

Methods

The institutional ethics committee approval for this study was exempted by the Technical Committee of the Institutional Review Board as the study was a retrospective one, and the data were taken from medical records of patients, with confidentiality maintained. The study was designed as a hospital-based case–control study. We reviewed the case records of all the patients in our hospital who had been newly diagnosed as MacTel 2A over a 3-year period, April 2011 to March 2014. Controls were selected from outpatients seen in the hospital at the same time for visual defects, without MacTel 2A, after matching for age and sex. The diagnosis of MacTel 2A was made by a senior retinal consultant, based on typical features on biomicroscopic examination, fluorescein angiographic features, spectral-domain optical coherence tomography (SDOCT), and fundus autofluorescence (FAF). Patients with features of concomitant retinal disease such as diabetic maculopathy, branch retinal vein occlusion, or radiation retinopathy were excluded. Patients with lens or media opacities significant enough to prevent clinical, angiographic, or optical coherence tomography (OCT) imaging were excluded. Every patient

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underwent a comprehensive, standardized evaluation, which was documented in his/her medical record. Data from medical records were entered in a standardized proforma and analyzed. The following data were included: age, sex, associated systemic diseases based on the history and medical records of the patients, refractive error, best-corrected visual acuity (BCVA), stage of the disease at presentation, detailed slit lamp examination of the anterior segment, intraocular pressure using the Goldmann applanation tonometer, dilated fundus examination using the binocular indirect ophthalmoscope and 20-D lens, and stereoscopic examination of the disc and macula using the 78-D lens. Color fundus photography, SDOCT, and FAF using Spectralis–HRA OCT (Heidelberg Engineering, GmBH) were performed in all the patients who were clinically diagnosed with MacTel 2A. Spherical equivalent (SEq) was calculated using the spherical dioptric power plus half the cylindrical dioptric power. Emmetropia was defined as SEq of zero diopter. Myopia was defined as SEq >–0.10 D, and hypermetropia was defined as SEq >+0.10 D.

Statistical analysis

Demographic characteristics of participants were summarized using descriptive statistics, which were expressed in terms of means and standard deviation (SD) or proportions. Risk factor analysis was carried out using multivariate logistic regression model. Categorical data were analyzed using the Chi-square test and continuous variables using *t*-tests. Initially, univariate analysis was performed on individual variables. A multivariate logistic regression model was constructed to further explore the association of risk factors that showed a statistically significant association ($P < 0.05$) with MacTel 2A in the univariate analysis. Statistical analysis was done using SPSS software, version 20.0 (IBM Corp, Armonk, NY 10540, USA), and statistical package R 1386, version 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria). $P < 0.05$ was considered statistically significant.

Results

In this study, 206 patients were enrolled, of which 103 patients were newly diagnosed with MacTel 2A and 103 patients served as controls who were age- and sex-matched participants taken from the outpatient population. The diagnoses among the control subjects were mainly refractive error, presbyopia, pseudophakia, and dry eyes. Of the 103 patients with MacTel 2A, 89 had bilateral disease (178 eyes), and 14 had unilateral disease (total: 192 eyes with MacTel 2A; controls 220 eyes).

The demographic features of the patients are given in Table 1. The mean age of patients with MacTel 2A was 58.63 years (range, 38–76 years; SD, 8.18 years). The highest proportion of patients with MacTel 2A was above 60 years of age. Majority (76; 73.8%) of the patients were female. Of the patients with MacTel 2A, 61 (59.2%) had diabetes mellitus and 50 (48.5%) revealed systemic hypertension.

Table 2 shows the results of univariate analysis carried out to determine the association between potential risk factors and MacTel 2A. The analysis was done for individuals as a whole. The Chi-square test was used for the univariate analysis. The risk factors evaluated included the presence of diabetes mellitus and other systemic diseases such as systemic hypertension, bronchial asthma, ischemic heart disease (IHD), and hypercholesterolemia. Associated systemic diseases, namely, diabetes mellitus, systemic hypertension, and hypercholesterolemia showed a statistically significant association with MacTel 2A in the univariate analysis ($P < 0.05$). No statistically significant association was found between bronchial asthma, IHD, and MacTel 2A.

Table 3 shows the multivariate logistic regression analysis. Risk factors that showed a statistically significant association with MacTel 2A in the univariate analysis were considered for multivariate logistic regression analysis. The following variables showed a statistically significant association with MacTel 2A in the multivariate logistic regression analysis:

Table 1: Demographic features of patients with macular telangiectasia 2A and controls

	Cases	Controls
Total number of patients	103	103
Male	27 (26.2)	27 (26.2)
Female	76 (73.8)	76 (73.8)
Mean age in years (range, SD)	58.63 (38-76, 8.18)	58.74 (38-77, 8.13)

SD: Standard deviation

Table 2: Macular telangiectasia 2A risk factors - univariate analysis

Characteristics	MacTel 2A present, number of patients (%)	MacTel 2A absent, number of patients (%)	*P*
Diabetes mellitus			
Present	61 (59.2)	28 (27.2)	<0.001**
Absent	42 (40.8)	75 (72.8)	
Systemic hypertension			
Present	50 (48.5)	25 (24.3)	<0.001**
Absent	53 (51.5)	78 (75.7)	
Bronchial asthma			
Present	5 (4.9)	5 (4.9)	1.000
Absent	98 (95.1)	98 (95.1)	
Ischemic heart disease			
Present	11 (10.7)	6 (5.8)	0.200
Absent	92 (89.3)	97 (94.2)	
Hypercholesterolemia			
Present	30 (29.1)	13 (12.6)	0.004**
Absent	73 (70.9)	90 (87.4)	

Chi-square test. MacTel: Macular telangiectasia. **: Statistically significant

Table 3: Macular telangiectasia 2A-multivariate logistic regression analysis

Characteristics	OR	95% CI		*P*
		Lower	Upper	
Diabetes mellitus	5.7	3.02	11.08	0.001**
Hypertension	2.6	1.3	5.1	0.004**
Hypercholesterolemia	1.4	0.6	3.08	0.350

CI: Confidence interval, OR: Odds ratio, **: Statistically significant

diabetes mellitus (odds ratio [OR], 5.7; $P = 0.001$) and systemic hypertension (OR, 2.6; $P = 0.004$). The presence of diabetes mellitus was the highest risk factor (OR, 5.7) among all the potential risk factors studied. Hypercholesterolemia, which was significant in the univariate analysis, was not significant in the multivariate logistic regression analysis.

The BCVA was measured in terms of logarithm of the minimum angle of resolution (logMAR). In patients with MacTel 2A, the mean BCVA was logMAR 0.38 (Snellen visual acuity [VA] 6/12) (range, 0–1.80 logMAR; SD, 0.35 logMAR). Among controls, the mean BCVA was logMAR 0.06 (Snellen VA 6/6) (range, 0–1.8 logMAR; SD, 0.23 logMAR). Refractive error was expressed in terms of SEq. When considering patients with MacTel 2A, the mean SEq was +0.90 D (range, −1.50 to +6.75 D; SD, 1.37 D). The mean SEq among controls was +1.08 D (range, −8.70 to +4.75 D; SD, 1.64 D).

To explore the role of refractive error as a risk factor for MacTel 2A, binary logistic regression was performed with emmetropia taken as the reference category [Table 4]. Individual eyes were taken into account for the analysis. Hypermetropia had an OR of 2.64 ($P = 0.001$). Myopia had an OR of 1.91 ($P = 0.09$). It was inferred that compared to emmetropic patients, hypermertopic patients had 2.64 times greater risk of developing MacTel 2A, which was statistically significant. Myopic patients showed 1.91 times higher risk of developing MacTel 2A, compared to emmetropic patients. However, it did not attain statistical significance. OR was calculated to determine which of the refractive errors carried the highest risk of developing MacTel 2A [Table 5]. Hypermetropia was determined to have the highest risk of developing MacTel 2A, (OR, 1.96; $P = 0.002$), compared to myopia (OR, 0.85; $P = 0.59$) and emmetropia (OR, 0.39; $P = 0.001$).

Discussion

One hundred and three patients with newly diagnosed MacTel 2A were included in the study. Of these, 76 (73.8%) were women and 27 (26.2%) men. We noticed that there was a preponderance of females among the cases. An equal number of males and females were chosen as controls in order for them to be gender matched. Our results compared well with the MacTel Project[17] Report 2, which reported 64% of participants to be female patients. However, in their study, Gass and Oyakawa[18] observed a preponderance of men (9/12 patients). The results of studies done by Yannuzzi *et al*.[19] and Gass and Blodi[1] showed no sex difference in the cases.

The mean age of patients with MacTel 2A in our study was 58.63 years. Our study compared well with that of Yannuzi *et al*.,[19] who reported a mean age of 59 years. The disease is typically diagnosed in the fifth or sixth decade of life.[20] Results from studies by Gass and Blodi,[1] Gass and Oyakawa,[18] and Shukla *et al*.[21] showed a mean age of 55, 56, and 57 years, respectively. Clemons *et al*.[22] documented a slightly higher mean age of 61.1 years. This concurred with the study conducted by Charbel Issa *et al*.[23] who reported a mean age of 61.9 years.

Diabetes mellitus was observed in 61 (59.2%) patients with MacTel 2A. The association between the diseases was statistically significant ($P = 0.001$). Multivariate logistic regression analysis showed people with diabetes mellitus to be at 5.7 times higher risk of developing MacTel 2A than those without diabetes mellitus. Considering all the risk factors analyzed, the presence of diabetes mellitus was found to be the highest risk factor with an OR of 5.7. Clemons *et al*.[22] studied medical characteristics of patients with MacTel 2A and reported in the MacTel Project Report 3 that they showed a significantly enhanced prevalence of diabetes mellitus, hypertension, obesity, and cardiovascular disease compared with same-aged patients in generally older communities. The prevalence of systemic conditions in participants of the MacTel Project Natural History Observation (NHO) study was compared with those of the National Health and Nutrition Examination Study (NHANES).[22] Cohorts from the United States, Australia, and Europe were compared. The OR for diabetes mellitus in the US MacTel cohort was 3.8 and in the European cohort 4.7. The Australian cohort showed an OR of 5.5 which compared well with our study (OR 5.7). All the results attained statistical significance ($P < 0.0001$). Many studies[17,20,21,24,25] have suggested an association between MacTel 2A and diabetes mellitus based on histological similarities and high incidence of abnormal glucose tolerance. Clemons *et al*.[17] in the MacTel Project Report 2 suggested that there was an association between MacTel 2A and abnormal glucose metabolism. Of the 28 patients who underwent glucose tolerance testing (GTT), 35% showed abnormal GTT results. The fasting blood sugars were within normal limits. Green *et al*.[24] noted the similarity of electron microscopic changes in the retinal capillaries to those of diabetes mellitus.

Millay *et al*.[25] observed that bilateral telangiectasia was frequently associated with abnormal glucose metabolism

Table 4: Binary logistic regression analysis-refractive error and macular telangiectasia 2A

Refractive error	OR	95% CI		*P*
		Lower	Upper	
Hypermetropia	2.64	1.505	4.660	0.001**
Myopia	1.90	0.902	4.039	0.091
Emmetropia (reference category)	-	-	-	-

CI: Confidence interval, OR: Odds ratio, **: Statistically significant

Table 5: Refractive error as a risk factor for macular telangiectasia 2A - Chi-square test

Characteristics	MacTel (number of eyes)		χ^2	OR	95% CI		*P*
	Yes (%)	No (%)			Lower	Upper	
Hypermetropia	124 (64.6)	172 (78.2)	9.372	1.96	1.271	3.038	0.002**
Myopia	26 (13.5)	26 (11.8)	0.276	0.85	0.478	1.531	0.599
Emmetropia	42 (21.9)	22 (10.0)	11.01	0.39	0.227	0.693	0.001**

CI: Confidence interval, OR: Odds ratio, MacTel: Macular telangiectasia, **: Statistically significant

than unilateral disease. In five of their patients, the results of GTT were consistent with diabetes mellitus although fasting blood glucose levels were at normal limits. Clemons *et al*.[22] observed that there was a substantial increase in the prevalence of diabetes mellitus in the population with MacTel 2A, despite exclusion criteria based on the presence of clinical diabetic retinopathy of more than just a few microaneurysms. In fact, very few participants were excluded on this basis suggesting that while diabetes mellitus may be associated with MacTel 2A, the genetic basis of MacTel 2A, if there is one, may protect against diabetic retinopathy. This was similar to the findings of a review of the case records of 104 patients with MacTel 2A at a tertiary eye care center in India by Shukla *et al*.[21] They found that 59% of patients with MacTel 2A showed diabetes; however, diabetic retinopathy was absent or mild in 99% of participants. This compared well with our study, in which 59% exhibited diabetes mellitus but none diabetic retinopathy.

Gass and Blodi[1] and Gass and Oyakawa[18] excluded diabetic patients from their initial studies because of the confounding effect of diabetes on the diagnosis of MacTel 2A. However, some studies have postulated that there is no association between diabetes mellitus and MacTel 2A. Gass and Blodi[1] studied 92 patients with MacTel 2A, of which two patients revealed diabetes mellitus and were excluded from the study. They postulated that although diabetes mellitus may be a predisposing cause for MacTel 2A, most of them do not exhibit diabetes, nor will it develop in them. Approximately 15% of patients with MacTel 2A may exhibit evidence of systemic diseases including systemic hypertension, borderline diabetes, coronary artery disease, and renal failure. Yannuzzi *et al*.,[19] in their study of 26 patients with MacTel 2A, reported only five (19.2%) patients with diabetes mellitus, which was not a significant association.

Systemic hypertension was observed in almost half the patients with MacTel 2A in our study (50, 48.5%). A statistically significant association was noted between systemic hypertension and MacTel 2A (P = 0.004). Multivariate logistic regression analysis revealed that patients with hypertension showed 2.6 times greater risk of developing MacTel 2A than those without it. Considering all the risk factors, systemic hypertension was found to be the second highest risk factor for developing MacTel 2A. Clemons *et al*.[17] observed in the MacTel Project Report 2 that 45% of patients in their cohort showed high blood pressure (systolic ≥140 mm Hg or diastolic ≥90 mm Hg). This was similar to the results from our study. In the comparison of participants in the MacTel Project NHO study and age- and sex-matched participants of the NHANES,[22] it was observed by Clemons *et al*.[22] in the MacTel Project Report 3 that there was a higher prevalence of hypertension, history of cardiovascular disease, and obesity among patients with MacTel 2A. The OR for hypertension in the European MacTel Cohort was 2.6 (95% confidence interval, 1.8–3.6; $P < 0.001$). This compared very well with our study, which also reported an OR of 2.6. There was a higher proportion of patients in the MacTel 2A cohort showing hypertension: US MacTel, 62.3%; Australian MacTel, 44.0%; and European MacTel, 52.0%, compared with participants in the NHANES[22] (48.6%, 40.6%, and 31.6%, respectively). One of the most prominent features of MacTel 2A is retinal vascular telangiectasis,so it is of interest that significant risk factors such as systemic hypertension and diabetes mellitus are also vascular diseases.

Multivariate logistic regression analysis showed two risk factors that exhibited a statistically significant association with MacTel 2A, namely, diabetes mellitus and hypertension. The presence of diabetes mellitus was the risk factor with the highest OR of 5.7, followed by hypertension: 2.6. There appears to be a pathogenic relationship between MacTel 2A and the associated systemic diseases although the nature of the same remains unclear. This relationship may give a clue to the pathogenesis of MacTel 2A.

The association between refractive error and MacTel 2A was statistically significant. Binary logistic regression revealed hypermetropic patients to have 2.6 times higher risk of developing MacTel 2A compared to emmetropic patients, which was statistically significant. Patients with myopia had 1.90 times greater risk of developing MacTel 2A compared to emmetropes. Among the refractive errors, patients with hypermetropia were found to have the highest risk of developing MacTel 2A. To the best of our knowledge, there has not been any study evaluating the role of refractive error on MacTel 2A.

Being a rare disease, obtaining 103 new cases of MacTel 2A in 3 years are significant, considering the ongoing process of transition in chronic disease frequency. This finding may be an early sign of increase of incidence of MacTel 2A. A literature search did not reveal any study correlating refractive error and Mactel 2A. To the best of our knowledge, our study is the first of its kind to do so.

Conclusion

Our case–control study revealed that MacTel 2A is significantly associated with systemic diseases. Diabetes mellitus was found to have the strongest association with MacTel 2A, showing a high OR of 5.4. Systemic hypertension followed with an OR of 2.6. Compared to emmetropia, hypermetropia was significantly associated with MacTel 2A. There could be a genetic link between the two. A statistically significant association does not necessarily imply a causal relationship. Determining risk factors draws us closer to the goal of identifying the etiopathogenesis of the disease.

Further research is required to establish whether tight glycemic control or optimal treatment of hypertension could reduce the risk of progression of the disease. The causative factors of MacTel 2A remain elusive. The knowledge of potential risk factors may contribute to a deeper understanding of the disease as research progresses.

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Conflicts of interest

There are no conflicts of interest.

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