ORIGINAL ARTICLE

Serum Uric Acid Levels and its Association With Age-Related Macular Degeneration (ARMD)

S Subramani, MBChB*, S E Khor, MS, B I Livingstone, MS***, U V Kulkarni MD***

*Department of Medicine, Aberdeen Royal Infirmary, Aberdeen, UK, **Consultant Ophthalmologist, Eye Department, Hospital Tuanku Ja'afar, Seremban, Negeri Sembilan, ***Consultant Ophthalmologist and Head of Department, Hospital Tuanku Ja'afar, Seremban, Negeri Sembilan, Malaysia

SUMMARY

To investigate the possible association between serum uric acid levels, serum C-Reactive Protein (CRP), and age-related macular degeneration (ARMD). A total 232 patients of the eye department at Hospital Tuanku Ja'afar, Negeri Sembilan, Malaysia were recruited over 9 weeks. Participants were divided into ARMD (Non-Neovascular ARMD, and Neovascular ARMD) and control groups. 107 participants with non-neovascular ARMD, 6 with neovascular ARMD, and 119 controls participated in the study. The control patients had a similar average Serum Uric Acid level to the average of all patients with ARMD (P = 0.617). Control group: mean 299.19µmol/l ± std dev.89.847µmol/l. ARMD group: mean 302.53µmol/l ± std dev. 80.794µmol/l. The average serum uric acid levels were higher in patients with neovascular ARMD (median = 397 mean ± std dev = 389.67 ± 38 µmol/l) than in the non-neovascular ARMD group (288.5 µmol/l, 297.86 ± 80.26 µmol/l), and control group (295.5 µmol/l, 299.19 ± 89.95 µmol/l). Comparing the standardised serum uric acid levels in the control group (Median = 0.5) against the two ARMD groups separately, there was no significant difference to the non-neovascular group (P = 0.448) but there was a difference significant to the neovascular ARMD group (P = 0.044). The neovascular and non-neovascular ARMD groups had median CRP value of 0.25mg/l and were not significantly different. There is no association between serum uric acid levels and ARMD as a whole. There is potentially an association between serum uric acid and neovascular ARMD, an association needs to be established further. There is no association between serum CRP and ARMD.

KEY WORDS:
Age related macular degeneration, Uric acid, ARMD, Risk factors, Asian

INTRODUCTION

Age Related Macular Degeneration (ARMD) is a degenerative disease of the eye that is becoming increasingly prevalent. In the United States, up to 0.3% of whites aged 50-59 years old had ARMD, and above the age of 80, this figure rises to 16%. As the world's population ages, its socioeconomic impact is expected to increase[1]. Bonastre *et al* have estimated in 2002 that the yearly budget impact of ARMD was between €51.3 million and €101.1 million in the United Kingdom, France, Germany, and Italy, which were the four countries studied[2]. The presence of drusen in at least one eye is necessary for the diagnosis of ARMD (Bird *et al,* 1995)[3]. There are two subgroups of ARMD – non-neovascular (dry) ARMD, and neovascular (wet) ARMD. Non-neovascular ARMD is characterized by the presence of drusen in the macula, with or without geographical atrophy. Neovascular ARMD is characterized by choroidal neovascularisation and/or retinal pigment epithelium detachment in the macular region. Although neovascular ARMD is only responsible for 10% of cases, it is responsible for almost 90% of the severe vision loss due to ARMD[4]. Known risk factors include age, [1,5] race, genetics, [6-9] cigarette smoking, [10] and many more. The association of ARMD and biochemical factors such as C-reactive protein, [11] have also been demonstrated. This study's primary aim is to determine if there is an association between serum uric acid levels and Age-Related Macular Degeneration. An association between serum uric acid levels and various other conditions such as cataract[12] and myocardial infarction[13] have been previously demonstrated. Altered uric acid metabolism could thus possibly play a role in the pathogenesis and damage related to ARMD, and there is a need to determine if there is an association between serum uric acid levels and the incidence of ARMD (Mehryar *et al,* 2006)[14].

MATERIALS AND METHODS

Study Population

The Age-Related Macular Degeneration-Uric Acid Study was a case-control study. Participants were recruited from the ophthalmology out-patient clinic and in-patient ward at Hospital Tuanku Ja'afar, Negeri Sembilan, Malaysia. Malaysia has a multi-racial population of approximately 27 million people[15], comprising mainly of three main groups which are the Malays, those of Chinese ancestorial origin, and those of Indian ancestorial origin.

All participants must be a citizen or permanent resident of Malaysia aged over 40 years. The selected participants were grouped into the ARMD group (which included non-neovascular ARMD and neovascular ARMD) and control group. Control group participants must have maculae that are visible through clear media in both eyes. Those in the neovascular ARMD group must demonstrate evidence of choroidal neoovascular (CNV) membranes or pigment epithelial detachments, and have had a fluorescien angiogram to confirm the diagnosis either at time of recruitment or at the time of initial diagnosis. Those with

This article was accepted: 2 February 2010
Corresponding Author: Siddharth Subramani, 37C, Westburn Road, Arberdeen AB25 2SH, UK
Email: siddarth.subramani@nhs.net

non-neovascular ARMD must demonstrate evidence of drusen in the macula, with or without signs of geographical atrophy in at least one eye, and must have a confirmatory fluorescien angiogram to rule out choroidal neovascularisation if the diagnosis is uncertain. Patients with all other maculopathies were excluded from the study.

Participant Recruitment and Data Collection
Participants were recruited for a period of 9 weeks. Recruitment of patients was done by a one-stage ophthalmologic evaluation process by the ophthalmologists in the department. The diagnosis was made using slit lamp biomicroscopy with + 90D lens. The principal investigator obtained written consent, relevant demographic information, blood tests, and fundus photographs.

Biochemical Analysis
All biochemical analysis were performed at the Hospital Tuanku Ja'afar Pathology Lab, on a Dade Behring Dimension® RxL MAX analyser. For internal quality assessment purposes, the analyser analyzes dual level quality control material with known uric acid concentrations on a daily basis. It was also subjected to inter-laboratory comparison assessment,

Uric acid levels were measured by the URCA method. C-Reactive Protein levels were measured using the RCRP method. The reproducibility of the uric acid and CRP analysis was evaluated by drawing duplicate samples from 25% of patients, with approximately equal numbers being used to test for interbatch and intrabatch variation of results. For the analysis of serum uric acid, there was a mean intrabatch variation of 2.7% and interbatch variation of 4.6%. For the analysis of serum C-Reactive Protein, there was a mean intrabatch variation of 5.3% and interbatch variation of 0.6%.

RESULTS

Data was processed using Excel and Minitab 14 for statistical analyses. A P value of less than 0.05 was considered to be statistically significant. Data were first tested for normality using the Anderson Darling and Kolmogorov Smirnov tests to assess whether parametric (ANOVA, test statistic F) or non-parametric (Kruskal-Wallace, test statistic H) statistical tests were appropriate. If the variances in groups was not similar, even if data were distributed normally, non-parametric statistics were used.

A total of 113 cases and 119 controls were recruited during the 9 weeks of recruitment. Of the 113 cases, 107 had non-neovascular ARMD and 6 had neovascular ARMD. The primary hypothesis is that ARMD is associated with serum uric acid levels.

Demographic Data Analysis
The mean age of patients with ARMD (68.75 years, s.d=9.232) was significantly higher than that of the control patients (64.61 years, s.d=9.241, ANOVA F1, 230= 11.64, p= 0.001). However age did not correlate with levels of serum uric acid (r=0.1) or CRP (r=0.09).

A much higher proportion of the Chinese and Malay patients had ARMD (57% and 53% respectively) compared to Indian patients (39%) and these differences were significant in a chi square test (Table I).

Serum Uric Acid Analysis
The reference range for serum uric acid levels provided by the lab where samples were processed was between 208-428µmol/l for adult males and 155-357µmol/l for adult females.

Males had significantly higher serum uric acid levels than females (Median: 327 µmol/l vs 258 µmol/l, Kruskal-Wallace, H=30.0, df=1, p<0.001). The mean and standard variation in the samples were Males: 328.13 ± 85.58; Females 267.70 ± 72.71. These gender differences resulted in a bimodal distribution for serum uric acid levels within the two groups of participants, ARMD and Controls (Figure 1).

Race also affected serum uric acid (SUA) levels: Indians (n=96 Median=282) had lower values than the Chinese (n=87 Median=318) and Malay (n=45 Median=315; Kruskal-Wallace, 11.39 DF = 2 P = 0.003). The Chinese and Malay have very similar medians and ranks in the test, so are unlikely to be significantly different to each other.

These highly significant effects of gender and race have the potential to bias differences in serum uric acid levels among the control and ARMD groups of patients. As the serum uric acid levels were not normally distributed (Figure 1), GLM analysis with gender and race as covariates was not feasible. Therefore, the data were standardised for gender and race by assigning each patient into six groups: Chinese F, M; Indian F,M; and Malay F, M (Table II). For each patient, the group median serum uric acid level was subtracted from the patient's actual value to create a standardised value. This is negative if the patient's SUA value is less than the group median, positive if it is greater than the group median and is normally distributed. Note that this is a standardised value specific to this experiment and is not standardised to the population as a whole. (Similar results were obtained when the mean was used, but the median was preferred as the raw data were not normally distributed.)

The control patients had a similar average Serum Uric Acid level to the average of all patients with ARMD (Kruskal-Wallace test H = 0.25 DF = 1 P = 0.617). Control group: mean 299.19µmol/l ± std dev.89.847µmol/l, median 295.5µmol/l. N= 116, 3 samples did not return results. ARMD group: mean 302.53µmol/l ± std dev. 80.794µmol/l, median 300.0µmol/l. N= 112, 1 sample did not return results. This test was repeated for the standardised Serum Uric Acid Values with similar results (Control median = 0.50, ARMD median = -2.5, Kruskal-Wallace test H = 0.16 DF = 1 P = 0.685).

The average serum uric acid levels were higher in patients with neovascular ARMD (median = 397 mean ± std dev = 389.67 ± 38 µmol/l, N= 6) than in the non-neovascular ARMD group (288.5 µmol/l, 297.86 ± 80.26 µmol/l, N= 104), and control group (295.5 µmol/l, 299.19 ± 89.95 µmol/l, N=116). This difference among the groups appears to be significant for the "raw" serum uric acid levels (Kruskal-Wallace test H =7.74

Table I: The numbers of patients in the control and ARMD groups differs among races (Likelihood Ratio Chi-Square = 6.932, DF = 2, P = 0.03).

	Numbers of patients			Frequencies (percentages)		
	Control	ARMD	Total	Control	ARMD	Total
Chinese	38	51	89	42.7	57.3	100
Indian	60	38	98	61.2	38.8	100
Malay	21	24	45	46.7	53.3	100
Total	119	113	232	51.3	48.7	100

Table II: Average Serum Uric Acid levels for patients grouped by Race and Gender, irrespective of whether they presented with ARMD.

Group	Race	Gender	N	Mean	SE Mean	StDev	Median
1	Chinese	F	39	281.9	11.5	71.7	275
2	Indian	F	44	252.3	11.2	74.3	236
3	Malay	F	20	273.8	15.2	67.8	277
4	Chinese	M	48	340.0	11.1	76.9	342.5
5	Indian	M	52	298.7	11.0	79.4	299
6	Malay	M	25	366.6	19.2	95.8	355

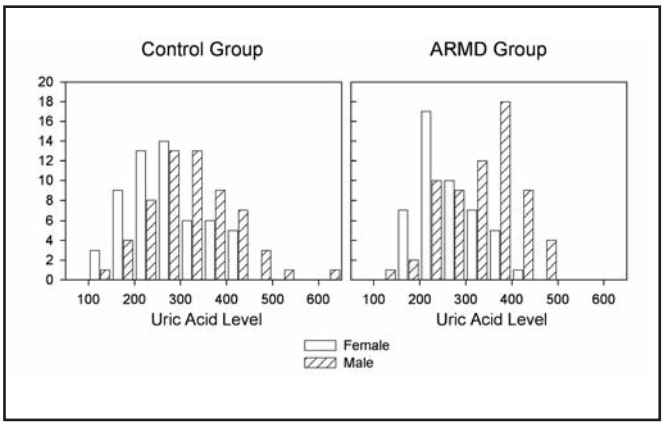

Fig. 1: Distribution of the serum uric acid levels of the control and ARMD groups in the ARMD-Uric Acid Study, 2007, by male and female patients. Note the bimodal distribution in the ARMD group. In both groups of patients, the males more frequently have higher levels than females, and this gender separation is greater among patients with ARMD.

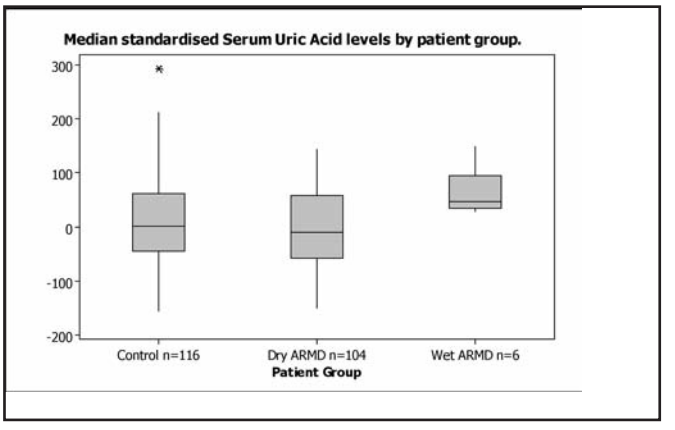

Fig. 2: Median standardised Serum Uric Acid levels by patient group. The standardised values are the difference between the patient's SUA level and the median of their demographic group (race/gender). Dry ARMD is the non-neovascular form and Wet ARMD is the neovascular form. Serum uric acid levels in patients with Wet ARMD were significantly higher than those in controls.

DF = 2 P = 0.021). However, four of the six patients with neovascular ARMD were male and all were Chinese or Malay, which could lead to a bias for higher levels of serum uric acid levels due only to gender and race. The standardised uric acid levels indicated a trend for higher levels in the neovascular ARMD group (Kruskal-Wallace test H = 4.85 DF = 2 P = 0.089). Comparing the standardised serum uric acid levels in the control group (Median = 0.5) against the two ARMD groups separately, there was no significant difference in the non-neovascular group (Median = -10.25; H = 0.58 DF = 2 P = 0.448) but there was a significant difference in the neovascular ARMD group (Median = 46.0; H = 4.05 DF = 2 P = 0.044).

Serum C-Reactive Protein (CRP) Analysis

The reference range for CRP values provided by the lab were categorized as low (<1.0mg/l), average (1.0-3.0mg/l) and high (>3.0mg/l). CRP values under 0.5mg/l were reported in the blood results as <0.5mg/l. Thus, an average value of 0.25mg/l is assumed for all CRP values reported as <0.5mg/l. The majority of records were 0.25mg/l, with frequencies of higher levels rapidly tailing off.

Gender and race did not influence levels of CRP to the same extent as for serum uric acid levels, and did not lead to a bimodal distribution, so standardisation for race and gender was not required. CRP values in males (Mean ± St.dev. 3.39 ± 0.99; median 0.25; average rank in Kruskal-Wallace 99.8) were significantly different to levels in females (Mean 4.12 ± 0.69; Median 0.25; rank 117.1; H = 4.10 DF = 1 P = 0.043). While the medians were the same, males had a lower average rank indicating that CRP values were lower in males. Race had no significant effect on CRP values (Chinese: Mean 3.53 ± 0.86; Median 0.25; Indian: Mean 3.12 ± 0.54; Median 0.25; Malay: Mean 5.39 ± 2.5; Median 0.25).

Similarly, the patient groups showed similar CRP values that were not significantly different: Control Mean = 3.36 ± 0.99;

Median 0.25; ARMD Mean = 4.12 ± 0.75; Median 0.25. The neovascular and non-neovascular ARMD groups also had median value of 0.25mg/l and were not significantly different.

DISCUSSION

Studies in the west showed that ARMD is more prevalent in fair-skinned people compared to those who have darker skin. Our study supports these findings. Among the ethnic groups in Malaysia, those of Chinese origin are generally the fairest, followed by the Malays, then those of Indian origin. Nearly two thirds of Chinese patients recruited into our study had ARMD compared to about a half of Malay patients and just over one third of Indian patients. These differences in ARMD prevalence depending on race were significant in chi-square analysis (Table I). All the cases of neovascular ARMD that were recruited involved those of Chinese origin (2 cases) and Malays (4 cases) who generally have fairer skin colour than those of Indian origin. Further studies should be carried out to confirm whether ARMD is race dependent in an Asian population.

There was a statistically significant difference in the mean age between those with ARMD and the control population. This indicates that amongst the sample population from which cases and controls were recruited, it is more common for an older person to have some age related degenerative changes of the macula. However, although the population in the study was subject to bias as the sample included only those who have come to the clinic for an eye-related problem, many cases of ARMD in this study were incidental findings amongst the population who visited the eye clinic for various other ophthalmologic problems. It therefore cannot be discounted that ARMD may be more common in Asian populations compared to what has been commonly perceived and reported.

The mean uric acid levels in those with non-neovascular ARMD and the control group was almost identical, making any association between serum uric acid and non-neovascular ARMD very unlikely. However the significantly higher mean serum uric acid level in the neovascular ARMD group compared to the control group when this case group was studied individually indicates a possible association between raised serum uric acid levels and neovascular ARMD. Whether raised uric acid levels is a cause, effect, or merely an indicator in neovascular age-related macular degeneration and other degenerative diseases such as cataracts and coronary heart disease should be determined by means of further studies.

C-Reactive Protein is a non-specific marker of inflammation, and previous studies have shown an association between serum C-Reactive Protein (CRP) levels and neovascular (wet) ARMD[16]. This study shows no significant association between serum CRP and ARMD as a whole, or with neovascular ARMD.

CONCLUSION

This study concludes that there is no association between serum uric acid levels and the presence of ARMD overall. However, it has discovered that there is potentially an association between the neovascular (wet) subtype of ARMD and serum uric acid levels. Due to the small population size of patients with neovascular ARMD in this study, a firm conclusion on this association cannot be made at present. Such an association needs to be established, as it will pave the way towards determining if uric acid lowering agents can be used in the prevention of neovascular ARMD, as it may add a significantly cheaper treatment to the options that are currently available.

ARMD is likely to become more prevalent in Asian populations as the population ages. Presently it is believed that many cases of ARMD in this population are not being detected. Higher number of cases of ARMD may be picked up with an effective national eye screening programme. As the treatment options increase and the cost of treatment decreases, it may be of greater social and economic benefit to detect and treat as many ARMD cases as possible.

ACKNOWLEDGEMENT

a. Funding / Support: University of Aberdeen Alumni Annual Fund (monetary funding of £250), Ministry of Health of Malaysia (support), Hospital Tuanku Ja'afar Directorate, Eye Department and Pathology Department (support).
b. Financial Disclosure: £250 in funding received from the University of Aberdeen Alumni Annual Fund.
c. Contributions of Authors: Design and conduct of the study (SS, SEK, BIL, UVK); Collection (SS); Management (SS, SEK, BIL); Analysis (SS, SEK, BIL); Interpretation of the data (SS, SEK, BIL); Preparation (SS); Review (SS, SEK, BIL)
d. Statement about Conformity: This study received prior approval from the director of Hospital Tuanku Ja'afar. Written consent was obtained from all participants.
e. Competing interests : Nil.

REFERENCES

1. Friedman DS, O'Colmain BJ, Munoz B *et al*. Prevalence of age-related macular degeneration in the United States. Arch Ophthalmol. 2004; 122: 564-72.
2. Bonastre J, LePen C, Anderson P *et al*. The epidemiology, economics and quality of life burden of age-related macular degeneration in France, Germany, Italy and the United Kingdom. Eur J Health Econ. 2002; 3(2): 94-102.
3. Bird AC, Bressler NM, Bressler SB *et al*: An international classification and grading system for age-related maculopathy and age-related macular degeneration. The International ARM Epidemiological Study Group. Surv Ophthalmol 1995; 39(5): 367-74.
4. Ferris FL 3rd, Fine SL, Hyman L. Age-related macular degeneration and blindness due to neovascular maculopathy.Arch Ophthalmol. 1984; 102(11): 1640-2.
5. Korner-Stiefbold U. Age related macular degeneration (ARMD) - Pathophysiological and clinical features and therapeutic concepts. Therapeutische Umschau. 2001; 58(1): 28-35.
6. Hageman GS, Anderson DH, Johnson LV *et al*. A common haplotype in the complement regulatory gene factor H (HF1/CFH) predisposes individuals to age-related macular degeneration. Proc Natl Acad Sci. 2005; 102: 7227-232.

7. Klein RJ, Zeiss C, Chew EY *et al*. Complement factor H polymorphism in age-related macular degeneration. Science. 2005; 308: 385-89.
8. Haines JL, Hauser MA, Schmidt S *et al*. Complement factor H variant increases the risk of age-related macular degeneration. Science. 2005; 308: 419-21.
9. Sepp T, Khan JC, Thurlby DA *et al*. Complement factor H variant Y402 H is a major risk determinant for geographic atrophy and choroidal neovascularization in smokers and non smokers. Invest Ophthalmol Vis Sci. 2006; 47: 536-40.
10. Tan JS, Mitchell P, Kifley A *et al*. Smoking and the long-term incidence of age-related macular degeneration: the Blue Mountains Eye Study. Arch Ophthalmol. 2007; 125(8): 1089-95.
11. Boekhoorn SS, Vingerling JR, Witteman JC *et al*. C-reactive Protein Level and Risk of Aging Macula Disorder: The Rotterdam Study. Arch Ophthalmol. 2007; 125(10): 1396-401.
12. Leske MC, Wu SY, Hyman L *et al*. Biochemical factors in the lens opacities. Case-control study. The Lens Opacities Case-Control Study Group. Archives of Ophthalmology. 1995; 113(9): 1113-9.
13. Bos MJ, Koudstaal PJ, Hofman A *et al*. Uric acid is a risk factor for myocardial infarction and stroke: the Rotterdam study. Stroke. 2006; 37(6): 1503-7.
14. Mehryar M, Farvardin M, Hosseini H *et al*. Potential role of uric acid in the molecular pathogenesis of age-related macular degeneration. Medical Hypotheses. 2006; 66(4): 793-5.
15. Malaysia Statistics Agency (http://www.statistics.gov.my) http://www.statistics.gov.my/eng/index.php?option=com_content&view=article&id=50:population&catid=38:kaystats&Itemid=11 (accessed 1 September 2008)
16. Seddon JM, Gensler G, Milton RC *et al*. Association between C-reactive protein and age-related macular degeneration. JAMA. 2004; 291(6): 704-10.