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Research Article

Serum Uric Acid Level and Its Effect on Short Term Functional Outcome of Acute Stroke and TIA: Prospective Single Center Study

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Abstract

Background: The association between high serum uric acid (SUA) level and cardiovascular diseases (CVD) such as stroke is not well established. Additionally, the effect of high SUA and stroke functional out- come and prognosis remains controversial. Further large-scale studies are needed.

Objective: This study aims to assess the short-term functional outcome of patients admitted with acute stroke or Transient Ischemic attack (TIA) and elevated SUA. Additionally, it aims to deduce whether there is a trend or a relationship between the elevated SUA level, and stroke subtypes and TIA.

Method: This is a prospective observational single center hospital-based study performed at the Central Stroke Unit over 13 months period. Starting January 2014 and ending January 2015. After obtaining the ethical approval by the hospital's research committee; patient's data was collected in an excel sheet. The diagnosis of acute stroke or TIA for all included patients was confirmed by detailed history, examination, and brain imaging (CT or MRI). Both ischemic and intracranial hemorrhage subtypes were included as well as TIA. Only confirmed acute stroke or TIA cases with SUA done withing 48 hours of admission date that match all the inclusion and exclusion criteria were included.

Results: The final sample size was 187, they were 129, (69%) patients diagnosed with ischemic stroke (IS), 23 (12.3%) with intracranial hemorrhage (ICH) and 35(18.7%) with TIA. The mean age was 59.1 years of age. There were 111 men and 76 women. Elevated SUA was only found in 41 patients (36%) versus 73 (64%) patients with normal SUA level. There were 16 women with elevated SUA versus 25 men. Out of the 41 patients with elevated SUA and acute stroke or TIA; 26 had IS, and 10 had ICH and 5 with TIA. The length of admission ranged between 4-11 days, with a median of 6 days. 70.3% of the patients had moderate to severe disability upon admission, versus 47.6% upon discharge. Nine patients (4.9%) were died.

Conclusions: In this study, although elevated SUA level was not associted with worsening short term functinal out come for patients admitted with acute stroke or TIA. It is hard to draw a pricese conclusion due to the small smaple size. Therefore further large scale and multicenter studies are needed.

Keywords: *Serum Uric Acid; Acute Stroke; Ischemic Stroke; Intracranial Hemorrhage; Transient Ischemic Attack; Modified Rankin Scale*

Introduction

The association between high serum uric acid (SUA) level and cardiovascular diseases (CVD) such as stroke is not very well established [1-4]. The role of SUA as independent cardiovascular risk factor has been controversial for decades [5-10]. Some studies showed

that increase in SUA was independent predictor factor for recurrence of ischemic stroke (IS). In 2004; Niskanen., *et al.* [11] and his group concluded that SUA level is a strong predictor of cardiovascular disease mortality in healthy middle-aged individuals. Meta-analysis of 16 prospective cohort studies including 230,000 patients found that high SUA in adults is associated with a modest but statistically significant increased risk of stroke incidence and mortality[12]. Koppula., *et al.* [13] studied 550 patients with IS. He found that elevated SUA level was associated with increase poor outcome at 3 months with all IS subtypes except lacunar stroke. In 2015, Bandyopadhyay., *et al.* [14] reported high SUA found to be associated with good neurological outcome upon discharge in IS and insignificant poor neurological outcome in patients with intracranial hemorrhage (ICH). This unresolved ambiguity in the role and value of SUA level as prognostic factor in stroke obligate us to contact further studies. Our central stroke unit ran a one-year prospective cohort study to measure the SUA level in all patients admitted with acute stroke and TIA.

Objective

This study is meant to address the following:

- Aims to assess the short-term functional outcome of patients admitted with acute stroke or Transient Ischemic attack (TIA) and elevated SUA. Additionally, it aims to deduce whether there is a trend or a relationship between the elevated SUA level, and stroke subtypes and TIA.

Methods

Data

This is a prospective observational single center hospital-based study performed at the Central Stroke Unit over 13 months period. Starting January 2014 and ending January 2015. After obtaining the ethical approval by the hospital's research committee; patient's data was collected in data excel sheets. Confidential code was assigned to each patient. No personal data was divulged in the data collection sheets except age and sex. All the data was treated with confidentiality. Acute stroke was defined as an acute neurologic (5 days) insult due to a vascular etiology. Transit Ischemic attack (TIA) defined as acute neurological deficit lasting less than 60 minutes with normal neurological exam and negative MRI brain. The diagnosis of acute stroke for all included patients was confirmed by detailed history, examination, and brain imaging (CT or MRI). Both ischemic and intracranial hemorrhage subtypes were included as well as TIA. Ischemic stroke (IS) was further classified according to TOAST criteria. Serum uric acid (SUA) range was defined as normal if it falls within 220-547 umol/L as per our hospital reference range. Only (SUA) level above 547 umol/L and done within 48 hours of admission was included in the study. The inclusion criteria is: Age = > 18, Both gender, Both stroke subtypes, TIA (Positive history, negative TIA), only Hyperacute and Acute stroke.(5 days), confirmed diagnosis of acute stroke by either CT head or MRI brain and Serum uric acid done within 48 hrs of admission. The exclusion criteria include the following; age below 18, old Stroke(> 5 days), Acute stroke secondary to trauma, neoplasms, infections, or Iatrogenic stroke, Patients on iron or antioxidant, vitamins supplements, diuretics, and allopurinol or chemotherapy and Previous or current diagnosis of gout or cancer.

Patient description

All Patients aged 18 years of age and above admitted with acute stroke diagnosis or TIA were included. Original sample size was 350 patients. Only 300 patients were initially included. Large number of the patients were excluded either due to other diagnosis; stroke mimics, such as migraine, malingering, epilepsy, or others. Additional patients were excluded due to the presence of any other diseases or use of any medications listed on the exclusion criteria. Some patients were found to be on medications that alter the results of SUA, however they did not declare that at the beginning. All patients were admitted at the central stroke unit and were managed and followed up by a multidisciplinary stroke team. All patients had routine blood tests, chest x-ray, ECG, and brain imaging on admission. All patients

had confirmed acute Stroke by neuroimaging (Head CT or MRI brain). All patients had SUA test done within the first 48 hours of admission. Patient's disability was assessed by modified Rankin scale mRS upon admission and discharge.

Statistical analysis

Data were described using mean and SD for continuous variables and frequency and percentage for categorical variables. Association between two categorical variables were tested using either a Fisher's exact test or Likelihood ratio test. An Independent samples t-test was used to compare the mean score between two groups. Median scores were compared using the Mann-Whitney U-test. A McNemar test was applied for the pre-post comparison of mRS score. A value of $P< 0.05$ (2-sided) was considered statistically significant. All the analysis was carried out in IBM SPSS version 22.0.

Results

The total patient admitted with acute stroke or TIA to the stroke unit from January 2014 -January 2015 was 350. 163 patients were excluded due to other diagnosis or mimics. Additional more patients were excluded either because they were found to be on one of the medications or vitamin supplements that can alter or affect the result of SUA that was not declared initially by patients.

The final sample size was 187. Out of the 187 patients, they were 129, (69%) patients diagnosed with IS, 23 (12.3%) with ICH and 35(18.7%) with TIA. The mean age was 59.1 years of age. There were 111 men and 76 women in the sample. The length of admission ranged between 4 - 11 days, with a median of 6 days. 70.3% of the patients had moderate to severe disability upon admission, versus 47.6% upon discharge. Nine patients (4.9%) were died. Elevated SUA was only found in 41 patients (36%) versus 73 (64%) patients with normal SUA level (Table 1: Demographic and Clinical Profile of the Patients).

Variable	N (%)
Gender	
Male	111 (59.4)
Female	76 (40.6)
Age, mean±SD	59.09±14.20
Stroke	
ICH	23 (12.3)
IS	129 (69.0)
TIA	35 (18.7)
Serum Uric Acid	
Normal	73 (64.0)
Abnormal	41 (36.0)
mRS on admission	
0	1 (0.5)
1	30 (16.2)
2	24 (13.0)
3	40 (21.6)
4	44 (23.8)
5	46 (24.9)
mRS on discharge	
0	13 (7.0)
1	33 (17.8)
2	42 (22.7)
3	34 (18.4)
4	19 (10.3)
5	35 (18.9)
6	9 (4.9)
Length of hospital stay (days), median (IQR)	6 (4-11)

Table 1: *Demographic and clinical profile of the patients.*

There were 16 women with elevated SUA versus 25 men. Out of the 41 patients with elevated SUA and acute stroke or TIA; 26 had IS, and 10 had ICH and 5 with TIA. The Serum Uric Acid (SUA) level was not statistically significantly associated with type of strokes (p= 0.292) (Table 2: Association between Type of Strokes and Patient Characteristics).

Variable	Stroke			
	Haemorrhagic	Ischemic	TIA	
	N (%)	N (%)	N (%)	p-value
Gender				
Male	16 (69.6)	79 (61.2)	16 (45.7)	0.145
Female	7 (30.4)	50 (38.8)	19 (54.3)	
Age, mean±SD	57.04 ± 19.63	59.17 ± 12.54	60.11 ± 16.05	0.720
Serum Uric Acid				
Normal	10 (50.0)	56 (68.3)	7 (58.3)	0.292
Abnormal	10 (50.0)	26 (31.7)	5 (41.7)	
mRS on admission				
Good (mRS 0-1)	2 (8.7)	16 (12.6)	13 (37.1)	0.004*
Poor (mRS 2-5)	21 (91.3)	111 (87.4)	22 (62.9)	
Length of hospital stay (days), median (IQR)	8 (5-14)	6 (4-12)	4 (3-5)	0.0001*

Table 2: *Association between type of strokes and patient characteristics.*
**Statistically significant.*

The analysis of the data also revealed that SUA level was not significantly associated with poor stroke functional outcome (P = 0.194). All patients who had elevated SUA either improved or their disability remains stable upon discharge. (Table 3: Association between Functional Outcome and Patient Characteristics)

Variable	Outcome		p-value
	Good (mRS 0-1)	Poor (mRS 2-6)	
	N (%)	N (%)	
Gender			
Male	25 (22.9)	84 (77.1)	
Female	21 (27.6)	55 (72.4)	0.493
Age, mean±SD	57.04±14.72	60.08±13.83	0.206
Stroke			
Haemorrhagic	2 (8.7)	21 (91.3)	
Ischemic	25 (19.7)	102 (80.3)	
TIA	19 (54.3)	16 (45.7)	0.0001*
Serum Uric Acid			
Normal	17 (23.3)	56 (76.7)	
Abnormal	14 (35.0)	26 (65.0)	0.194
mRS on admission			
Good (mRS 0-1)	31 (100)	0 (0)	0.0001*
Poor (mRS 2-5)	15 (9.7)	139 (90.3)	

Table 3: *Association between functional outcome and patient characteristics.*
**Statistically significant.*

Discussion

Although the independent relation of SUA and stroke has been indicated in several meta-analysis studies, the causality of this association needs to be confirmed by further accumulated evidence[12, 15]. There is no obvious data to suggest that an elevated SUA is a risk factor for stroke. A high SUA with or without gout is associated with cardiovascular diseases such as hypertension, coronary heart disease, peripheral vascular disease, and stroke. However, the role of high SUA in stroke is controversial[16]. This is due to the fact that very few studies have evaluated the prevalence of hyperuricemia in stroke patients, and most importantly its impact on prognosis[17]. In our studies we did not show a significant relationship of raised SUA level and stroke subtypes (i.e. ICH or IS) or TIA. As indicated in table 3, the results do not show any significant increase in any of the stroke subtypes with an elevated SUA level. We would like to highlight, however, that due to the limitation of a small sample size, a significant relationship could not be determined.

SUA levels are influenced by age and gender. Furthermore, elevated SUA is associated with established cardiovascular risk factors such elevated triglyceride levels, cholesterol, hypertension obesity, insulin resistance and the metabolic syndrome [18,19]. This confounds the association of elevated SUA and stroke due to its association with multiple cardiovascular risk factors ultimately causing stroke.

On the other hand, other studies have shown that it is neuroprotective by acting as a free radical scavenger [19]. Some experimental animal studies demonstrated that, when administered early, uric acid has extended the benefits of recombinant tissue plasminogen activator (r-tPA) and, hence supporting its neuroprotective effect.

Therefore, the role of uric acid is still controversial in leading to stroke[19]. Additionally, other risk factors that are associated with elevated SUA confound the association between SUA and stroke. These include alcohol and medications (e.g. diuretics, cyclosporine) that predispose to hyperuricemia [20].

There is an established relationship between SUA and stroke, but causality is not yet reliably established. As evidenced by figure 1: (Relationship between SUA and mRS of stroke patients on admission) the mRS on admission is almost similar for both the elevated SUA and normal SUA groups. For example, at an mRS of 3, the percentage of both patients with normal and abnormal SUA are 22% and 20% respectively. A similar relationship is seen with the other results. The exception being at an mRS of 4, there is a significant difference between the two groups (23% in the uric acid group as opposed to 29% in the normal group). At an mRS of 2, there is a higher percentage of patients in the normal group (16%) in comparison to the uric acid group (8%). However, a similar percentage of improvement in the mRS was observed in both normal (13.8%) and uric acid (13.3%) groups of SUA.

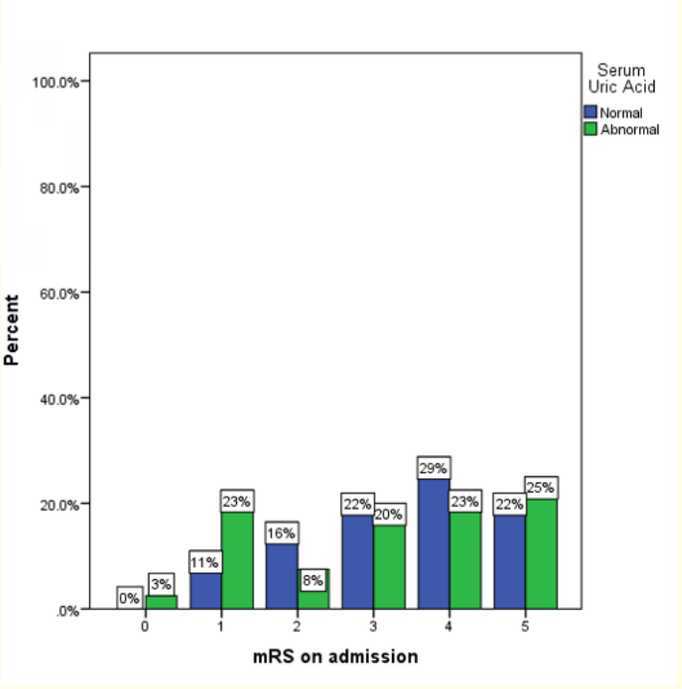

Figure 1: *Relationship between SUA and mRS of stroke patients on admission.*

It is important to note that many of these patients had other risk factors including insulin resistance, obesity, hypertension and the metabolic syndrome. Hence, it is difficult to determine a relationship between isolated elevations in SUA with stroke. It would be more informative to control other risk factors and be able to standardize them to derive a significant relationship.

This inconsistent relationship is also seen globally as seen by some studies conducted in Japan with some studies evidencing that it is independent risk factors while others are controversial [21,22].

The majority of stoke cases noted in different studies were IS. A study conducted by Saadat., *et al*. showed that most stroke cases (85.3%) were ischemic with the majority being thrombotic (57.9%). In their study, the presence of an elevated SUA was 18% [23]. In our study, we demonstrate a relationship of IS with elevated SUA, where 63.4% of patients with elevated SUA had stroke while 76.7% of patients with normal SUA level had stroke. In our study, Ischemic stroke was the most prevalent stroke subtype among the patients with an elevated serum uric acid level.

It has been demonstrated in several studies that elevated SUA is associated with an increased risk of for acute ischemic stroke, especially the thrombotic subtype. Proposed mechanisms include increased platelet adhesion, macrophage infiltration leading to smooth muscle proliferation and atherosclerosis[23]. It is worthwhile to consider the usage of SUA lowering medications and investigate the effect of pharmacologically lower SUA on cardiovascular outcome in patients with stroke [24,25].

This is a limitation in our study as we do not study the outcome associated with SUA lowering medications. It would be interesting to follow up the outcome for risk reduction of cardiovascular events such as stroke. Other limitation is the sample size. This makes it difficult to draw any conclusion in relation to TIA and SUA Therefore, a follow up study with a lager sample size might allow a better analysis of the results.

Conclusion

There are several studies that have demonstrated a relationship with elevated SUA and IS, but causation will require more evidence. This is due to the fact that we do not have controls (i.e. healthy patients with elevated SUA level) to establish a direct relationship. Therefore, the association is riddled with many confounding variables that are both related to an elevated uric acid (e.g. HTN) and can independently lead to stroke.

This article helps shed the light on this relationship. Furthermore, it introduces the reader to a diverse ethnic background in the gulf and specifically the Omani population which in itself displays heterogeneity in clinical presentation and manifestations of IS and levels of SUA. It also shown here that there is a preponderance of patients with the IS subtype and elevated SUA level. We hope in the future to study the relationship between uric acid lowering drug and the risk reduction in IS.

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