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Screening of Uric Acid Levels in Sudanese Tuberculous Patients

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Tuberculosis is a major contributor to the global burden of disease and it has received considerable attention in the recent years, particularly in low- and middle-income countries where it is closely associated with HIV/AIDS. Poor adherence to treatment is common despite various interventions aimed at improving treatment completion. Treatment adherence is currently a major obstacle to finding effective solutions. The aim of this systematic review of qualitative studies was to understand the factors considered important by patients, caregivers and health care providers in contributing to Anti-Tuberculous medication adherence() (1). TB is a global health concern, with an estimated 8.9 million new cases worldwide in 2004 and two million deaths each year. It is a major contributor to the burden of disease, especially in low- and middle-income countries, where it is being fuelled by the HIV/AIDS epidemic() (2,3).

Directly Observed Treatment, short course (DOTS) is the internationally recommended control strategy for TB (4).This strategy includes the delivery of a standard short course of drugs, lasting 6 moth for new patients and 8 moth for retreatment patients, to individuals diagnosed with TB. The delivery includes DOT, either by a health worker or by someone nominated by the health worker and the patient for this purpose (sometimes called a DOT supporter). The strategy has been promoted widely and implemented globally.

Globally, more than 1 in 3 individuals are infected with TB (5). According to the WHO, there were 8.8 million incident cases of TB worldwide in 2010, with 1.1 million deaths from TB among HIV-negative persons and an additional 0.35 million deaths from HIV-associated TB. In 2009, almost 10 million children were orphaned as a result of parental deaths caused by TB. TB rates in women have declined with age, but in men, rates have increased with age. In addition, men are more likely than women to have a positive tuberculin skin test result. The reason for these differences may be social, rather than biologic, in nature.

The estimated sex prevalence for TB varies by source, from no sex prevalence to a male-to-female ratio in the United States of 2:1.

Higher rates of TB infection are seen in young, non-white adults (peak incidence, 25-40 y) than in white adults. In addition, white adults manifest the disease later (peak incidence, age 70 years) than do non-white persons.

In the United States, more than 60% of TB cases occur in the age range 25-64 years; however, the age-specific risk was highest in persons older than 65 years. TB is uncommon in children aged 5-15 years. (6).

The increase in uric acid levels is associated with many pathophysiological states as well as with some exposures to either chemicals or drugs, below is the main causes(7).

As a result, high serum uric acid (SUA) levels can exceed the solubility threshold and precipitate in the form of sodium urate crystals, ultimately leading to gout and urolithiasis (8). Uric acid elevation is known to cause serious health hazards including gout, urolithiasis, and urate nephropathy(9,10). Extremely high uric acid levels can overwhelm the kidneys and cause acute renal failure. Approximately 70% of uric acid is excreted from the kidneys; the remainder passes into the gastrointestinal tract, where it is oxidized to allantoin, allantoic acid, urea, and carbon dioxide. Uricase and other enzymes present in intestinal bacteria metabolize these compounds (11).

Many medications have been associated with elevated uric acid levels. Pyrazinamide and Ethambutol are two Anti-Tuberculous drugs that have been reported to induce hyperuricemia(12). Pyrazinamide is a strong urate retention agent, causing a greater than 80% reduction in renal clearance of uric acid at a 300-mg therapeutic daily dose(13). The metabolite pyrazinoic acid is oxidized by xanthine oxidase and is likely responsible for the hyperuricemic effect. Hyperuricemia has been reported in 43% to 100% of patients treated with pyrazinamide (alone or in combination)(14).

Furthermore, gouty attacks have been associated with patients taking pyrazinamide(15). Ethambutol can also cause hyperuricemia by decreasing renal uric acid clearance, but it does so less consistently and to a lesser degree than pyrazinamide. Calcineurin inhibitors have also been shown to raise uric acid levels(16).

This study was carried on to evaluate the prevalence of hyperuricemia as an ADR among Tuberculous patients without history of hyperuricemia in addition to assessment of the incidence of TB among Patients with different Gender. economic and Educational levels.

METHODS AND MATERIAL

Study Area and Design

This is a cross-sectional study involving patients attending to the TB center at Kostiteachinghospital.Kosti city is 300 Km south of the Khartoum (The capital of the Sudan). The study was conducted between November to December 2016. It was authorized via ethical clearance from the hospital research office. Eighty patients satisfied the inclusion criteria were admitted to the TB center .

Study population:

Tuberculouspatients living nearby Kosti city in the White Nile state in Sudan. The candidates enrolled in the study signed a consent and agreed on the collection of blood sample for uric acid level determination. They filled a questionnaire and allowed access to their medical history.

Sample size:

Blood samples were taken from the out-patient after the consent being signed by the participants. All the patients who attended the tuberculosis center during the study period were included in the study.

Inclusion criteria:

Out patients Males and females diagnosed as Tuberculous Patients with different age groups Under TB therapy were admitted to the study

Exclusion criteria:

Known cases of hyperuricemic and inpatients were excluded.

Methodology for the assessment of uric acid levels :

Uric Acid levels were been Determined using Colorimetric Enzymatic Method according to (Tholen DW et al., 2004) (17), 2

milliliters of blood sample were taken from each patient and placed in lithium heparin container. Plasma only was used after separation. One micrometer was taken from the plasma and mixed with one milliliter of uric acid reagent (from Spinreact company). The mixture was incubated for 10 minutes and then the amount of uric acid for each sample was read using an automatic colorimeter (from Biosystem company).

Statistical analysis:

The statistical analysis was conducted using the Statistical Package for Social Sciences SPSS. The statistical analysis features the descriptive statistics with frequency and percentage tables besides the counting of prevalence for hyperuricemia among the study participants. Chi-squared statistic was used to study associations.

Ethical clearance for the study:

The approval from the research committee of Omdurman Islamic University followed by the approval from the TB center in Kosti governmental hospital. The samples and data were collected from the patients after signing the consents.

THE RESULTS

During the 2 months' study, 80 Tuberculous patients receiving Anti-Tuberculous medications based on the national guideline in the TB control program were enrolled as per the inclusion criteria. Out of total Tuberculous patients 58.75 % were male and 41.25% were female patients. The age of patients enrolled in the study varies as follows: 3 patients (6.38%) belonged to the age group of 0-14 years, 14 patients (29.79%) belonged to the age group of15-29 years, 13 patients (27.66%) belonged to the age group of 30-44 years and 17 patients (36.17%) above 45 years.

Table 3.1: Age distribution among the participants' according to the genders:

	Male		Female	
Age (year)	**No.**	**%**	**No.**	**%**
0-14	3	6.38	3	9.1
15-29	14	29.79	14	42.42
30-44	13	27.66	9	27.27
Above 45	17	36.17	7	21.21
Total	**47**	**100**	**33**	**100**

Normal serum uric acid level was observed in 60 patients (75%) (see figure 2). Out of which 35 (43.75%) were male and 25 (31.25%) were female patients (see figure2). Above normal serum uric acid level was observed in 20 patients (25%) (see figure 2). Out of which 12 (15%) were male and 8 (10%) were female patients.

Table 3.5 : The educational level.

Educational Level							
Illiterate		**Primary School**		**Secondary School**		**University**	
No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
33	41.25	26	32.5	14	17.5	7	8.75

Patients within the first two month of treatment initiation were more likely to have elevation of the uric acid compared to patients passed this period. Normal uric acid levels were observed among 28 patients (70%) within the first two months of treatment initiation and 12 hyperuricemic patients (30%) were observed during this period . After 2 months of treatment initiation normal uric acid levels were observed among 32 patient (80%) and above normal levels were observed among 8 patients (20%) .

Table 3.6 : The Financial status of the study participants.

Financial Status							
Very low (less than500SDG)		**Low (500-1000SDG)**		**Medium (1000-2000SDG)**		**High more than 2000SDG**	
No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
32	40	24	30	1822.5		67.5	

Furthermore, the education level of Tuberculous patients indicated as follows: 33 patients (41.25%) were illiterates, 26 patients (32.5%) enrolled in the primary school level, 14 patients (17.5%) enrolled in the secondary school level and 7 patients (8.75%) enrolled in the university level.

Table 3.7: The level of uric acid .Reference value according to medscape : male : 2.5 – 8 mg/dL , female : 1.9 – 7.5 mg/dL

Uric Acid Levels			
Within normal limits		**Above normal limits**	
No.	**%**	**No.**	**%**
60	75	20	25

Table 3.8: The level of uric acid among participants' according to the gender:

Male uric acid levels				**Female uric acid levels**			
Within normal limits		**Above normal limits**		**Within normal limits**		**Above normal limits**	
No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
35	43.75	12	15	25	31.25	8	10

The gender implication to the development of hyperuricemia as an adverse effect of TB treatment was investigated via cross-tabulation and chi-square statistics. However, no significant association was found (p-value = >0.05).

Table 3.9: Chi-square cross-tabulation for the gender association to hyperuricemia.

	Normal	**Hyperuricemia**	***Row Totals***	**Chi-square**	***p-value***
Male	35 (35.25)	12 (11.75)	47	0.0172	0.895
Female	25 (24.75)	8 (8.25)	33		
Column Totals	**60**	**20**	**80 (GrandTotal)**		

Patients are also divided on the basis of economic status according to their income. Majority of the patients belonged to very low economic status 32 patients (40%), 24 patients (30%) belonged to low economic status, 18 patients (22.5) belonged to

medium economic status and 6 patients (7.5) % belonged to high economic status.

Table 3.10: The uric acid level according to time of treatment initiation :

During 2months of initiation				**After 2months of initiation**			
Normal level		**High level**		**Normal level**		**High level**	
No.	%	No.	%	No.	%	No.	%
28	70	12	30	32	80	8	20

DISCUSSION

This study found that TB infection increases as the level of education of patients decrease (Table 3.5).

This study revealed what was been previously stated, the TB incidence rates correlate with poor socio-economic conditions (Table 3.6). (18)

The issue of patient's tolerance of Anti-Tuberculous drugs is extremely important for the treatment outcomes and as a consequence for TB control in general(19).There is much debates, therefore concerning the frequency and severity of ADRsin patients with TB chemotherapy (20) . It has been suggested that only a minority of patients successfully complete their full course of anti-TB chemotherapy without significant ADRs(21) .

The development of hyperuricemia by Tuberculous patients might adversely affect their adherence patterns which might affect the overall performance of the TB control program more specially that auxiliary medications are not freely available for the patients who are almost incapable of affording the healthcare seeking cost due to iatrogenic (drug induced) consequences.

Recent studies revealed an increased prevalence of MDR-TB among Tuberculous patients population due to therapy withdrawal and increased prevalence of ADR including

hyperuricemia (22,23).The main adverse effects of Anti-Tuberculous drugs usually occur during the first two to three weeks of treatment. The timely strict monitoring for and management of notified adverse effects are therefore essential (24) . Proper monitoring has to be carried out during the whole treatment course, including patient education, clinical examination, laboratory tests, etc.(25)

In this study hyperuricemia was documented in 25 % of patients (Table 3.7), but it was asymptomatic for all participants therefore, patients weren't need any medical intervention to control up normal levels of uric acid , but according to the specialist who was responsible about the TB center some patients develop gout and need medical intervention. While Andersen M. and co-workers (2014) were reported that Anti-tuberculous medications such as pyrazinamide and Ethambutol have been associated with increasing uric acid levels. Locally in the Sudan and at the same area of this Study (Kosti TB center), Mutasim and coworkers 2009, found that about 40% of patients treated with the drugs, complained of Arthritis (26). Although often considered asymptomatic, severe hyperuricemia can ultimately lead to renal failure. Numerous treatments and prevention strategies exist for managing hyperuricemia. Some of these include NSAIDs, intra-articular glucocorticoids, colchicine, probenecid, allopurinol, urinary alkalinization, and hydration. Rasburicase treatment has been used in a small number of patients, in an off-label manner, to rapidly treat severe hyperuricemia. Quick treatment reduces uric acid levels to alleviate the burden on the kidneys and further decrease the chance of renal injury (27) .The trend was almost the same across gender groups (Table 3.9).

Patients in the initiation phase during the first two month show higher potential to hyperuricemia (Table 3.10). Previous study conducted by Khanna BK and Jitendra K. (1990) was revealed that the onset of hyperuricemia among

group of patient receiving regimens contain only Pyrazinamide and among other group received regimens containing Ethambutol plus pyrazinamide administered concomitantly was higher and more rapid compared to group of patient received only Ethambutol. A rise in serum uric acid level was observed in the three groups (28).

CONCLUSION AND RECOMMENDATIONS:

The current study suggest an existing need for more intense pharmacovigillence studies and evidence based evaluation of the current status of hyperuricemia in Tuberculous patients. In accordance to the recent approach of GLC in association to the Global Fund and WHO, the therapy withdrawals, lack of adherence, and adversely affected quality of life should be minimized via cautious prevention of Tuberculosis among Tuberculous patients. The revealed prevalence of hyperuricemia which was found to be 25% among the study participants seems to be within the global estimates.

Close coordination with the TB program would help reserving auxiliary medicines that can help alleviating the burden of ADRs including medicines for gout.

The study was only directed to point-in-time assessment of the prevalence of hyperuricemia among Tuberculous patients. Continuous monitoring of uric acid level for each patient throughout the duration of therapy can give more detailed and valuable results.

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