

## **Approach to a Case of Hyperuricemia**

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### **Case Study**

**A 45 years old asymptomatic aircrew reported for periodic medical examination. Except for being overweight (BMI: 27kg/m<sup>2</sup>), the general and systemic examination was within normal limits. The routine laboratory investigations revealed a serum uric acid of 8.8 mg/dl. The individual denied consumption of alcohol/ medication and had no symptoms referable to joints. The various issues involved in the aeromedical decision making in this aircrew are as follows:-**

- (a) Does he require medication for his condition?
- (b) Is he fit to exercise flying privileges?
- (c) What are the underlying pathology and the prognosis?

### **What is uric acid and what role does it has in the body?**

Uric acid, a normal constituent of human body, is an end product of the degradation of purine compounds. Endogenous production accounts for two thirds of total body urate, while the remaining one third is accounted for by dietary purines. Unlike other biological laboratory variables where statistical definition is utilized for deriving the normal range, the definition for uric acid is based on the solubility limit of urate in body fluids. This is so because of the non-normal distribution of serum urate concentrations in most population. The solubility of the principal physiologic salt of uric acid, monosodium urate (MSU), in the connective tissue is normally close to 7.0 mg/dl, and the solubility declines progressively at cooler temperature such as those in the peripheral joints. These MSU crystals directly trigger, amplify and sustain an inflammatory response known as “acute gouty attack”. Hyperuricemia is thus defined as a serum uric acid concentration of more than 7.0 mg/dl by uricase method. These values are approximately 1 mg/dl lower than those obtained with colorimetric methods. Unlike many other mammals, humans lack the enzyme uric acid oxidase (uricase) which

oxidizes poorly soluble uric acid to more soluble compound allantoin. This deficiency of uricase along with lower fractional excretion of uric acid is responsible for the higher levels of uric acid observed in humans. In humans the ‘normal’ serum urate concentration thus provides only a narrow margin of safety for urate crystal deposition. The urate elimination depends on kidneys (70%), and the gastrointestinal tract (30%); in chronic kidney disease (CKD), the gastrointestinal contribution of urate excretion increases to compensate for the decreased elimination by the kidneys.

Uric acid is a negative phase reactant and is considered to be an antioxidant; many believe that elevated serum uric acid is a secondary phenomenon that is either innocuous or perhaps beneficial.

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### **What is the normal uric acid level in the body?**

The serum uric acid level in the body is a function of balance between the breakdown of purine and the rate of urate excretion. The normal serum uric acid as measured by automated enzymatic (uricase) method is less than 7.0 mg/dl for adult male and any value more than 7.0 mg/dl is considered to represent hyperuricemia. The values however differ for women and children who have lower normal serum uric acid. This is so because the estrogenic compound in premenopausal women enhances renal urate clearance by inhibition of renal urate reabsorption via organic ion transporter.

### **What is asymptomatic hyperuricemia? What is the underlying mechanism for hyperuricemia?**

Asymptomatic hyperuricemia is the term applied to settings in which the serum urate concentration is elevated, but neither symptoms nor signs of urate crystal deposition have occurred. It is a common laboratory finding and in itself does not represent a disease. Although gout may develop in a hyperuricemic individual at any point, it is likely that more than two-thirds of the hyperuricemic individuals will remain asymptomatic.

Hyperuricemia can be a consequence of either overproduction or underexcretion of uric acid. Overproduction accounts for only a minority of patients presenting with hyperuricemia and the cause for the overproduction can be either exogenous (purine rich diet) or endogenous (increase in purine nucleotide breakdown as in blast crisis of leukemias, cytotoxic therapy and rhabdomyolysis). Few overproducers have enzymatic deficiency which includes complete deficiency of hypoxanthine guanine phosphoribosyltransferase (HGPRT) in Lesch-Nyhan syndrome, partial deficiency of HGPRT (Kelley-Seegmiller syndrome), and increased

production of 5-phospho-alpha-d-ribosyl pyrophosphate (PRPP) activity.

Most case of hyperuricemia is a consequence of underexcretion of uric acid. In the kidneys the urate is filtered by the glomerulus and undergoes reabsorption, secretion, and postsecretory reabsorption. A decrease in glomerular filtration (CKD)/ tubular secretion (acidosis) or enhanced tubular reabsorption (diuretic therapy and diabetes insipidus) can thus lead to hyperuricemia. In acidosis (diabetic ketoacidosis, starvation ketosis, ethanol or salicylate intoxication), there is accumulation of organic acids and these organic acids compete with urate for tubular secretion thus causing hyperuricemia. At times both the mechanism occurs simultaneously the example being alcohol consumption.

### **How do we classify hyperuricemia?**

Hyperuricemia can be classified into two types:-

- (a) *Primary or idiopathic hyperuricemia:* The hyperuricemia is considered primary when it exists in the absence of coexisting diseases or drugs that alter uric acid production or excretion. It usually last lifelong.
- (b) *Secondary hyperuricemia:* This refers to excessive urate production (overproducer) or diminished renal clearance (underexcretor) occurring as a consequence of another disease, drug, dietary product, or toxin.

### **How common is this problem?**

Hyperuricemia is a commonly encountered medial entity. With the wide spread accessibility to medical care and laboratory facilities more and more cases are being identified at the community level. It is estimated that approximately 5% of the general population and up to 25% of the hospitalized patients have hyperuricemia. The vast majority of

these patients are at no clinical risk and do not require medications directed towards lowering the serum uric acid.

The prevalence of hyperuricemia varies with the race, sex and age. A higher incidence of hyperuricemia is observed in African Americans and certain indigenous races of the Pacific. The incidence of both asymptomatic hyperuricemia and gouty arthritis is more in men than in women and only 5% of patients with gout are females; the uric acid levels however increases in women after menopause. The highest incidence of gout occurs between the age of 30 and 45 years in men, and between 55 and 70 years in women. The normal level of uric is lower in children than in adult and the levels increases withincreasing age.

#### **Is hyperuricemia synonymous with gout?**

Hyperuricemia and gout are not synonymous. Though hyperuricemia predisposes to the development of gout, its presence does not always leads to gout and in fact only about one-tenth exhibit gout in long run. It appears that the individual differences in the formation of crystals or in inflammatory responses to those crystals (or both) may play a role in determining whether a person with hyperuricemia will develop gout. Conversely a small percentage of acute gouty arthritis patients may have a normal or low uric acid level. This is so because the stress induced ACTH and disease induced inflammatory cytokines are uricosuric. There is ample evidence of an association between the level of hyperuricemia and gout. Serial serum uric acid levels in 2046 healthy male were followed up for 15 years in one study and they found the annual incidence of gout to be 4.9, 0.5, and 0.1 percent for serum urate levels of greater than 9.0, 7.0 to 8.9, and less than 7.0 mg/dl (1). Gout is an inflammatory response to the MSU crystals formed secondary to hyperuricemia. It typically affects

middle aged to elderly male and presents with episodic acute and chronic arthritis and deposition of MSU crystals in connective tissue tophi and kidneys. The most common presentation of acute gout is acute onset monoarthritis commonly involving the first metatarsal-phalangeal (MTP) joint. This predilection for the first MTP joint is not fully understood. It is postulated the predilection may be due to relative coolness of the feet thus reducing the solubility of MSU, repeated microtrauma to which the MTP joint is subjected and the differential reabsorption into the joint of exuded solvent (joint fluid) and solute (urate) from the periarticular area when weight bearing is replaced by recumbency. It is however pertinent to note that post menopausal women and hypertensive male with alcohol abuse may present with acute polyarticular involvement.

#### **What are the aeromedical implications of asymptomatic hyperuricemia?**

Hyperuricemia has long being associated with development of increased propensity for cardiovascular diseases, hypertension, metabolic syndrome, dyslipidemia and atherosclerosis. It is increasingly now thought to play an important role in the pathogenesis of endothelial dysfunction and insulin resistance. There is thus a need to follow up all such aircrew with respect to the above mentioned diseases.

The relationship between hyperuricemia and cardiovascular disease is hotly debated. The National Health and Nutrition Examination Survey (NHANES) [1] studied 5421 patients for 17 years and concluded that there is no association between the two in men; in women however the rate of mortality and ischemic heart disease rose with the serum uric acid levels [2]. Retrospective analysis of NHANES data followed 5926 patients for an average of 16.4 years and observed that

hyperuricemia was significantly and independently associated with cardiovascular mortality in both sexes [3]. A multivariate analysis of the Framingham Heart Study data reviewed 6763 patients with mean age of 47 years after adjusting for age and other risk factors for ischemic heart disease. The investigators could not find any association between hyperuricemia and coronary artery disease [4]. It was also proposed that the MSU crystals augment platelet aggregation and thus enhances the risk of coronary thrombosis in patients of coronary artery disease [5]. It is thus clear from the above studies that there is a disagreement in the medical community about the association between hyperuricemia and cardiovascular disease. It is likely that the association between the two is not truly independent; rather is dependent on other variable risk factors for coronary artery disease. It is also known that pharmacological therapy for hyperuricemia does not necessarily protect against coronary artery disease [6].

Hyperuricemia is seen in 26-33% of patients with essential hypertension [7]. It is now considered an independent risk factor for hypertension and the relation is independent of obesity or renal function [8]. Mixed relationship exists between hyperuricemia and carotid atherosclerosis. No statistically significant relationship between the two was observed in a study involving 145 patients by Pan WH et al [9]. Other study however points towards an independent association between the two [10].

Hyperuricemia is strongly associated with endothelial dysfunction and lowering serum uric acid improves endothelial dysfunction markedly in different clinical situations [11, 12]. Recent studies suggest association of hyperuricemia and insulin resistance. It is suggested that hyperuricemia is a marker of insulin resistance which in turn is implicated in pathogenesis of metabolic syndrome.

There is a school of thought which proposes that the association between hyperuricemia and cardiovascular disease, if any may be secondary to this linkage with insulin resistance. Conversely the amelioration of insulin resistance by diet or insulin sensitizing medication decreases the serum uric acid [13]. It is hence suggested that even in absence of clinical gout, estimation of serum uric acid be considered in all hypertensive patients, because if elevated, it serves as an inexpensive tool to suggest the presence of insulin resistance. Hyperuricemia is present in more than 80% of patients with hypertriglyceridemia [14].

#### **How will you evaluate a case of hyperuricemia in an aircrew?**

The history and clinical examination, in patients with hyperuricemia is directed towards identifying causative etiology, presence of coexisting comorbidities and clinical manifestations if any. Acute gouty arthritis is an inflammatory arthritis and presents with warm, swollen, erythematous and tender joint. Chronic cases may have tophi over the helix or antihelix of the ear, olecranon bursa or along the ulnar surface of the forearm. The laboratory investigations can be divided in to the following heads:

1. Test directed towards establishing the diagnosis
  - (a) Serum uric acid
  - (b) Joint aspiration and demonstration of strongly birefringent needle shaped intra and extracellular crystals in cases of gout.
2. Test directed towards the pathophysiology
  - (a) 24 hours urinary uric acid estimation: Excretion of >800 mg of uric acid per 24 h on a regular diet suggests overproduction of purine as the etiology. It is also useful in assessing the risk of stone formation

and in deciding whether to start uricosuric therapy or not.

3. Tests directed towards establishing the etiology
  - (a) Complete blood counts: for hemolytic anemia or hematological malignancies
  - (b) Liver function test: base line liver function is required before initiation of allopurinol therapy. It also aids in the detection of metabolic disorders.
  - (c) Blood sugars: for underlying diabetes mellitus and glycogen storage disorders.
  - (d) Renal function test and serum electrolytes: for underlying renal disease and acidosis
  - (e) Serum calcium and phosphate: for hyperparathyroidism, sarcoidosis and myeloma.
  - (f) Thyroid stimulating hormone: to rule out hypothyroidism.
4. Radiological evaluation: radiological feature of advanced chronic gouty arthritis includes soft tissue masses, cystic changes and well-defined erosions with sclerotic margins and overhanging bony edges.

#### **What is the pathogenesis of urate crystal induced inflammation?**

Gout is known as the 'king of diseases' and 'disease of kings' and a malady that affect boozy, overweight hedonists. The total body urate store in healthy male is approximately 1.2 gm (range 800-1600 mg) and about half this value in healthy women. Microscopic tophaceous deposits of urate crystals are often present in the synovial membrane and the cartilage. When there is an abrupt rise or fall in the serum urate levels as with use of alcohol,

diuretics and antihyperuricemic drugs, urate crystals are released from the tophi in to the joints, bones and soft tissues. Free urate crystals have proinflammatory potential and acts by activation of leukocytes, synovial lining cells and compliment system thus triggering an inflammatory cascade.

The phagocytosis of MSU crystals by neutrophils and the subsequent cytokine release plays a central role in an acute attack of gout. These locally produced cytokines play an important role in activation and recruitment of further inflammatory cells. Colchicine inhibits tyrosine phosphorylation in response to the MSU crystals and also interferes with the microtubule function and thus inhibits the neutrophil migration. This is the basis for use of colchicine in the treatment and prophylaxis of gout. A typical attack of acute gout even without any treatment resolves within a few weeks. Many mechanisms play a role in limiting the duration of an acute attack and includes upregulation of anti-inflammatory mediators, death and deactivation of inflammatory cells and inactivation of various inflammatory mediators.

#### **When is treatment for hyperuricemia contemplated?**

Hyperuricemia may be symptomatic or asymptomatic. While the subsets of people with symptomatic hyperuricemia do require medications directed towards alleviation of the symptoms and normalization of serum uric acid level, a vast majority of those with asymptomatic hyperuricemia do not ordinarily require medication. Therapy may however be contemplated in few cases of asymptomatic hyperuricemia under specific circumstances. These include

- (a) Patient who are to receive chemotherapy or radiotherapy and where extensive tumor cytotoxicity is anticipated.



- (b) Patients with very high levels of uric acid (more than 12-13 mg/dl in men and more than 10 mg/dl in women).
- (c) Patients with history of renal stones, gouty tophi, or moderate renal function impairment
- (d) Very strong family history of gout, uric acid nephropathy or urolithiasis.
- (e) Urinary uric acid excretion in excess of 1100 mg/ day, as it is associated with a 50 percent risk of uric acid calculi.

**What life style and preventive therapy will you suggest to this aircrew?**

The preventive therapy for hyperuricemic patients towards lowering the urate levels and prevention of progression to gout includes medication and dietary changes. Obesity is a major risk factor for gout, and losing weight is an important goal towards achieving normal urate levels, this is especially so in Indian context. It needs to be emphasized to the aircrew that the weight loss is to be achieved by regular exercise and dietary discretion and not by starvation or fad diet. Though the dietary intervention guidelines for patients with gout and hyperuricemia have evolved over time, it is still not known as to which combination of foods is the best. The following general dietary guidelines are to be explained to all aircrew with hyperuricemia.

- (a) High protein diet is associated with increase urinary uric acid excretion and may reduce the serum uric acid level. The amount of red meat and seafood however has to be reduced. Diet should include, consumption of more of low fat dairy product and complex carbohydrate which helps in reducing the serum uric acid levels [15]
- (b) Purine rich vegetables (peas, lentils,

spinach, mushroom, cauliflower) may not affect serum uric acid to desirable extent and hence purine restricted diet is rarely necessary. Vitamin C in dosages of 500mg/ day has mild urate lowering effect.

- (c) High-fructose corn syrup containing foods and drinks increase blood urate levels and are hence not recommended to be consumed [16]. Coffee may decrease the risk of gout attacks [17].
- (d) Alcohol increases the urate levels by increasing the production of uric acid as well as by impairing its excretion. Beer with its high purine content causes more elevation of serum urate levels than wine [18].

**What is the disposal of these cases?**

Asymptomatic hyperuricemia is not a disease in itself and as per the present Indian protocol for aviators, he is free to exercise unrestricted flying privileges. These aviators are explained the various life style changes required and are followed up at periodic interval. Cases of gout requiring medication will however require observation on ground for the assessment of the disease process and also to look for adverse effects of medication if any.

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