

Mini Review

Viewing Gout as an Early Symptom of Sleep Apnea

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Submitted: 16 June 2017

Accepted: 08 August 2017

Published: 10 August 2017

ISSN: 2475-9155

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Abstract

The chronic intermittent hypoxemia which results from sleep apnea causes three effects which quickly elevate the concentration of serum uric acid, often leading to the precipitation of monosodium urate crystals, namely, gout: cell catabolism which culminates irreversibly in the generation of excess uric acid fed into the blood; serum acidosis and hypercapnia which reduces the solubility of uric acid in the blood; and gradual reduction of the kidneys' glomerular filtration rate so that the removal of serum uric acid is slowed. This physiologic connection of gout to sleep apnea leads to the view that gout is a symptom of sleep apnea, a view supported by epidemiologic studies, common comorbidities, and clinical evidence. The importance of this view is that the incidence of gout should be used to trigger diagnosis and treatment for sleep apnea, before its life-threatening consequences develop.

Keywords

- Etiology of Gout
- Gout flare
- Sleep apnea
- Monosodium urate
- Hypoxemia

ABBREVIATIONS

SA: Sleep Apnea; CPAP: continuous Positive Airway Pressure

INTRODUCTION

One aspect of gout which is too often overlooked in guidelines and in practice is that most gout flares are initiated during sleep. The sleep connection has been known at least since Sir Thomas Sydenham, MD, wrote about it in 1683. A recent study by Dr. Hyon Choi [1] et al., confirms Dr. Sydenham's observation. It is a very important clue to the etiology of gout whether or not it manifests with joint pain and inflammation, tophi, or urate kidney stones. The principal culprit is sleep apnea (SA), which is the frequent cessation of breathing for at least 10 seconds at a time, averaging at least 5 such events per hour during the sleep period. The strongest support for the view that gout is a symptom of sleep apnea is the physiology. In addition to the physiology, this mini review will present epidemiologic, shared comorbidities, and clinical evidence to date that support the view that gout is a symptom of SA.

PHYSIOLOGY

Many arthritic gout flares are a direct result of SA. Although Kelley's Textbook of Rheumatology [2] lists respiratory insufficiency as a cause of acidosis leading to hyperuricemia, the hypoxemia of SA actually has three effects which can lead to an overnight gout flare in short order. Effect #1 is cellular catabolism in which adenosine triphosphate degradation is accelerated, leading to nucleotide turnover which culminates irreversibly in the transient cellular generation of excess uric acid fed into the blood [3,4], faster than any food would cause. Effect #2 is transient hypercapnia and acidosis, so that the blood can hold

less uric acid in solution. Effect #3 is a long term deterioration of the kidneys' glomerular filtration rate [5] so that removal of uric acid from the blood is slowed. Thus, with SA there is an abrupt increase in the influx of uric acid in the blood, slowed efflux, and abruptly reduced storage capacity-perfect storm conditions for monosodium urate precipitation. The physiology suggests that gout, defined as the deposition of monosodium urate crystals in body tissues and fluids, starts early in the development of SA. Accurate measurement of these conditions is very elusive. After awakening and normal breathing is restored, the first two effects dissipate so that a blood test taken during waking hours misses their peaks. And if monosodium urate has precipitated recently, then the measurement of serum uric acid is greatly undervalued. The monosodium urate crystals are highly inflammatory [6], not only when they form in a joint, but anywhere in the body. They are a danger signal that alerts the immune system to many dying cells [7], leading to the maturation of dendritic cells and the stimulation of T cells that may be needed to combat invading pathogens.

EPIDEMIOLOGY

Two epidemiologic studies have found that gout was significantly more prevalent in a population which had been diagnosed with SA than in a population which had never been diagnosed with SA. Using data taken from nine UK general practices, [8] found that the odds ratio for SA was 2:1. A larger data base from the UK Health Improvement Network was used in [9], finding that the ratio of gout flare incidence over a one year period for those diagnosed with SA versus those never diagnosed with SA was 1.75:1, and that ratio held over population subgroups selected by age, sex, or body mass index.

SHARED COMORBIDITIES

Long term untreated SA is known to have many life-threatening conditions among its consequences, among which are cardiovascular diseases, diabetes, kidney disease, and hypertension [10]. These same diseases have been found to be comorbidities of gout [11]. The life-threatening diseases which are SA consequences have been shown to develop after years of untreated SA [12].

CLINICAL EVIDENCE

Rheumatologists reported in [13] that 54 patients were tested for SA by polysomnography, which is the gold standard for SA diagnosis. The result was that 89% were diagnosed with SA. However, the patient population selection was biased in that they were suspected to have SA by questionnaire prescreening.

One method to measure the effect of SA on uric acid was reported in [14], measuring uric acid concentration in urine excreted immediately after sleep, and normalizing its measurement to creatinine measured in the urine. These measurements were conducted on a cohort of twenty male patients diagnosed with SA by polysomnography on two successive nights of sleep - one during which they each slept without a nasal CPAP, followed by one during which they each slept using a nasal CPAP. The normalized uric acid excretion ratio from no CPAP to CPAP averaged among the participants was 1.8:1; the maximum was 6:1. These results are evidence that untreated SA induces the production of excess serum uric acid. In a telephone conversation with this author, the author of [14] opined that the average result was not higher because much of the uric acid went into urate stores.

DISCUSSION

The physiology described above suggests that gout occurs early in the development of SA, whereas its life-threatening consequences have been shown to develop after years of untreated SA. Thus an arthritic gout flare can be used to trigger diagnosis and treatment for SA, before its life-threatening consequences develop. After SA is successfully treated, Effects #1 and #2 no longer occur, and Effect #3 may reverse over several months of effective treatment for sleep apnea [15,16]. Thus successful SA treatment would be expected to minimize new gout manifestations, and may even reverse those previously occurring, because the SA-induced peaks in serum uric acid concentration no longer occur. In order to show that gout is indeed a symptom of SA, it is important to show that overcoming SA prevents additional gout manifestations without the use of urate lowering drugs. I know from my own experience and the experiences of others that overcoming SA prevents additional arthritic gout flares immediately and completely. What is needed is a two part clinical trial. Part 1 would test a randomly selected cohort of gout patients for SA to determine the prevalence of SA in the gout population. In Part 2, those found in Part 1 with SA should be treated for it to determine the degree of gout mitigation due to SA treatment. Because SA is so grossly under diagnosed [17], in both of the referenced epidemiologic studies a significant number of individuals in the group never diagnosed with SA may indeed have had that disease. Thus, the ratios found in both studies need

to be considered as lower bounds. If all members of both groups had undergone SA testing, the actual ratios may be much higher.

CONCLUSION

One of the first steps for treating gout should be screening and diagnosis for SA, followed by treatment of the SA where indicated. More importantly, gout should be considered to be an early warning of SA, which when heeded can lead to the early treatment of SA, thereby greatly reducing the risk for the development of SA's later developing life-threatening consequences. Using a gout flare as a sentinel event leading to the diagnosis and treatment of SA can save lives along with saving joints.

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Cite this article

Abrams B (2017) Viewing Gout as an Early Symptom of Sleep Apnea. *JSM Arthritis* 2(1): 1023.