International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Index Copernicus Value (2015): 78.96 | Impact Factor (2015): 6.391

Acute Vestibular Syndrome as Manifestation of an Acute Attack Chronic Tophaceous Gouty Arthritis in Obese Man: A Case Report and Literature Review

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Abstract: ***Acute Vestibular Syndrome (AVS) is a clinical condition characterized by vertigo or dizziness that develops acutely (over seconds, minutes, or hours) is accompanied by nausea/vomiting, gait instability, nystagmus, and head-motion intolerance; and persists for a day or more.Itwas estimated affect 2% of thepopulation. Gouty arthritis is a metabolic disease on joint due to crystal uric acid deposition. AVS as theinitial symptom of anacuteattack of gouty arthritis is a rare case. Here, we are presenting a 38 years old man, obese came with sudden onset of vertigo with nausea,vomiting,tinnitus, sweating and also pain his great toe. Physical examination findings were normal, except for a head tilt, downbeating rotatory nystagmus and also inflammation and tophy in metatarsal digiti I pedisdextra et sinistra. Blood test showed remarkable hyperuricemia. Patient was diagnosed with AVS and gouty arthritis and given intravenous fluid ringer lactate 20 drips per minute, betahistine mesylate 12 mg every 8 hours, flunarizine 5 mg every 12 hours, intravenous ranitidine 50 mg every 12 hours and intravenous ondansetron 8 mg every 12 hours and meloxicam 15 mg once a daily. The association between AVS and gouty arthritis remain unclear, but it is suggested through inflammation and oxidative stress which induced by monosodium urate level.***

Keywords: Acute Vestibular Syndrome, gout, obesity, vertigo, oxidative stress

1. Introduction

Vertigo is described as an illusionary sensation of movement of oneself or one's environtment.[1-4]It has an estimated lifetime prevalence of approximately 7%.and caused 3-5% of visits across clinical settings.[2] This translates to 10 million ambulatory visits per year in the United States for vertigo[3]with 25% of these visits to emergency departments.[2]It was estimated 10-20% of them whose presenting vertigo have an acute vestibular syndrome.Acute vestibular syndrome (AVS) is a clinical condition characterized by vertigo or dizzinessthat develops acutely (over seconds, minutes, or hours) is accompanied by nausea/vomiting, gait instability, nystagmus, and head-motion intolerance; and persists for a day or more.[5,6]

Gout is an increasingly common metabolic disorder of uric acid with substantial negative health and economic impacts that affect over 2% of the general population. In the USA, there are an estimated 5-6 million individuals were affected.[7-9] It is characterized by recurrent inflammatory arthritis associated with hyperuricemia and the tissue deposition of monosodium urate crystals. Gout can either manifest as acute arthritis or chronic arthropathy, which is also called tophaceous gout.[10,11]More recently, studies have shown its association with hypertension, cardiovascular disease, and cerebral vascular disease but its association with vestibular dysfunction still limited. Here, we report a patient who had no history of cochleovestibular disease whose developed acute vestibular syndrome as initial symptoms of acute attack of chronic tophaceous gout.

2. Case Presentation

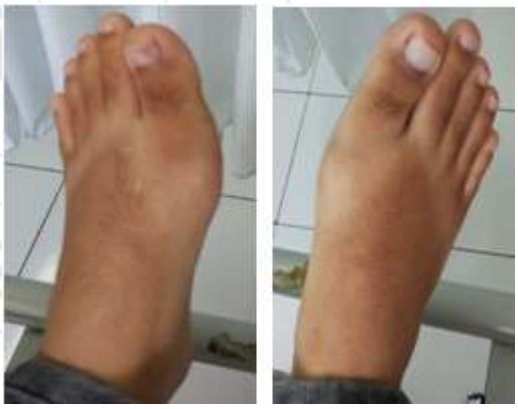

Figure 1: Patient left and right foot

A 38-year-old manattended Udayana Armyhospital Denpasar emergency unit due to dizziness with nausea, vomiting, tinnitus and sweating on his face. Hissymptoms had started 2 days before and worsen 2 hours before coming to the hospital. He also felt gait disturbance due to this symptoms. He experienced a sudden onset of dizziness with no other associated complaints of hearing loss, pressure sense, ear pain or ear fullness. He had neither previously been diagnosed with any peripheral or central audio vestibular pathologies. On the second day after onset of vertigo, he presented with an abrupt onset of severe pain, redness, and swelling in the area of both his great toe without morning stiffness. He complained of exquisite soft tissue tenderness to the point that he could not put on his

shoes. The painwas described as stabbing and lasting during the period. Within next few hours, the pain worsened, and he was unable to move the joint, which was tender, erythematous, and swollen on examination. He denies injury to these areas as well as fever. The patient had a history of hyperlipidemia. One day before the symptomsarisen, patient ate chicken curry and also "kripikemping" (melinjo nut crackers).He has been steadily gaining weight over the past few years.The patienthad takenmedications such asbetahistine, antimo (dimenhydrinate 50mg), voltadex (diclofenac sodium 50mg), ranitidine, miroxicam (meloxicam 15mg) and dexamethasone 1 hours before came to emergency unit. The patient had no history of gout or other rheumatological disorders but informed that his father was a long-term gout sufferer. He also had no history of urolithiasis and was not under any other medication. He had no habit of cigarette smoking and alcohol drinking. When asked particularly, he denied similar episodes in the past. He also denied any episode of swelling of the great toe in the past.

When the patient visited emergency department of our hospital on first physical examination, he was conscious, afebrile, and normotensive with head tilt position. The pain was 4/10 on the measurement due to his facial expression. Cardiovascular and respiratory system parameters were normal. The patient had average height and based on body mass index include as an obese man. Physical examination of locomotor system revealed first MTP joint iserythematous and very tender to even light touch. The patient has limited range of motion of these joints related to pain.Skin examination showed subcutaneous inflammatednodule, measuring 1–2 cm along metatarsophalangeal joints feet (Figure 1).There was no overlying edema or cellulitis. There were no other swellings or tophi noted especially on ears. Neurological examination were normal except downbeating nystagmus direction changing with alateral gaze.

Laboratory evaluation was remarkable for hyperuricemia (9 mg/dL; normal range 3.5-7.2mg/dL; uric acid urinary excretion was not measured). Serum uric acid had not been measured before the acute gout presentation. Complete blood count examination showed us red blood cells 79x10^12/L ,hemoglobin 14.3 g/dL, leukocyte counts of 8,300/µL, platelet counts of 241 x103/ µL, hematocrit 39,8%. Radiography of affected joints and diagnostic arthrocentesiswas not performed.

At the emergency room, the patient was given intramuscular 10 mg diphenhydramine and intravenous 8 mg ondansetron,but dizzinessremains. During hospitalization, the patient was given Intravenous fluid ringer lactate 20 drips per minute, betahistine mesylate12 mg every 8 hours, flunarizine 5 mg every 12 hours, intravenous ranitidine50 mg every 12 hours and intravenous ondansetron 8 mg every 12 hours and meloxicam 15 mg once a daily. After 2 days, patient's condition was improving and was allowed to be discharged. Follow-up of patient includes internal and neurological division.

3. Discussion

Acute Vestibular Syndrome (AVS) has rarely been reported in association with gouty arthritis. Our patient had neither history of audio vestibular problems nor gout before. Interestingly, he presented an acute vestibular syndrome associated with exquisite pain that lasted two days and went on to develop signs of a inflammated tophus, which is uncommon in patients without prior signs and symptoms of gout.

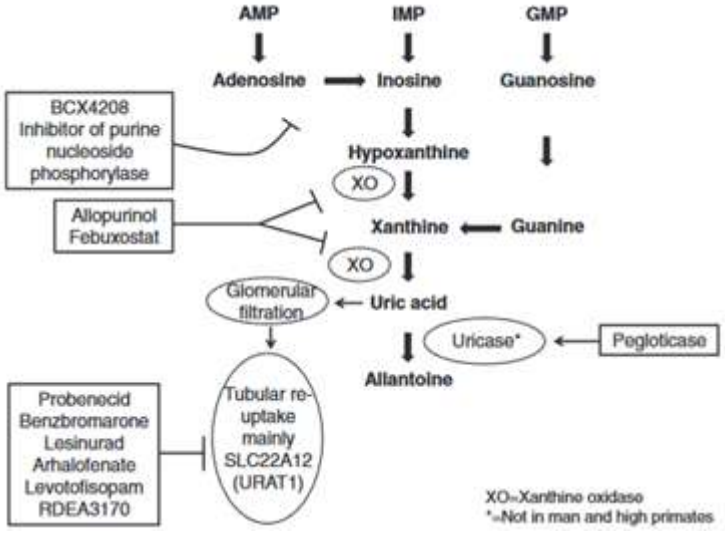

Figure 2: Schematic representation of uric acid formation and elimination.[19]

A diagnosis of AVS in this case is made based on clinical finding sudden, unprecipitated, vertigo with a subjective sensation of rotation, with unilateral loss of vestibular function (downbeating–torsional nystagmus with the fast phase directed away from the affected side). Patient also felt nausea, vomiting, tinnitus, sweating and pallor. Most peripheral vestibular disorders resolve in about 6–12 weeks, due to the effect of a number of different complex mechanisms collectively called vestibular compensation. These involve brain stem, cerebellar, cortical and spinal functions.[12-14] This symptomatic improvement does not parallel recovery of vestibular function, and accordingly the functional vestibular loss is often irreversible. In some patients, especially the elderly and those with central

nervous system (CNS) disorders, the vestibular compensation may not be as effective.

Our patient presented with tophi as an initial presentation of gout, which is very rare, but has been reported.[10]Investigational studies due to acute great toe pain is due to inflammatory of urate. A diagnosis ofchronic gouty arthritis but realized for this first time of acute attack based oninflammated metatarsophalangeal joint with pathognomonictophiwhich is supported by high-level uric acid on blood test.The diagnostic will be most accurate if visualization of uric acid crystals in a sample of joint or bursal fluid, or demonstrated histologically in excised tissue.Visible or palpable tophi, as this patient exhibited, are usually noted only among those patients who are hyperuricemic and have had repeated attacks of acute gout, often over many years. However, presentation of tophaceous deposits in the absence of gouty arthritis is also reported such as in this case.[10,11] Pain and inflammation are manifested when uric acid crystals activate the humoral and cellular inflammatory processes. Radiographic imaging on affected join is another simple diagnostic tools to investigate the gouty arthritis. Joint effusion (earliest sign), preservation of joint space until late stages of the disease, an absence of periarticular osteopenia, eccentric erosions, "punched-out" erosions with sclerotic margins in a marginal and juxta-articular distribution, with overhanging edges also known as rat bite erosions, punched-out lytic bone lesions, overhanging sclerotic margins, avascular necrosis, mineralisation is normal, tophi: pathognomonic, olecranon and prepatellar bursitis, periarticular soft tissue swelling due to crystal deposition in tophi around the joints is and also the soft tissue swelling may be hyperdense due to the crystals can be seen on plain photo of affected joint.[10-12]

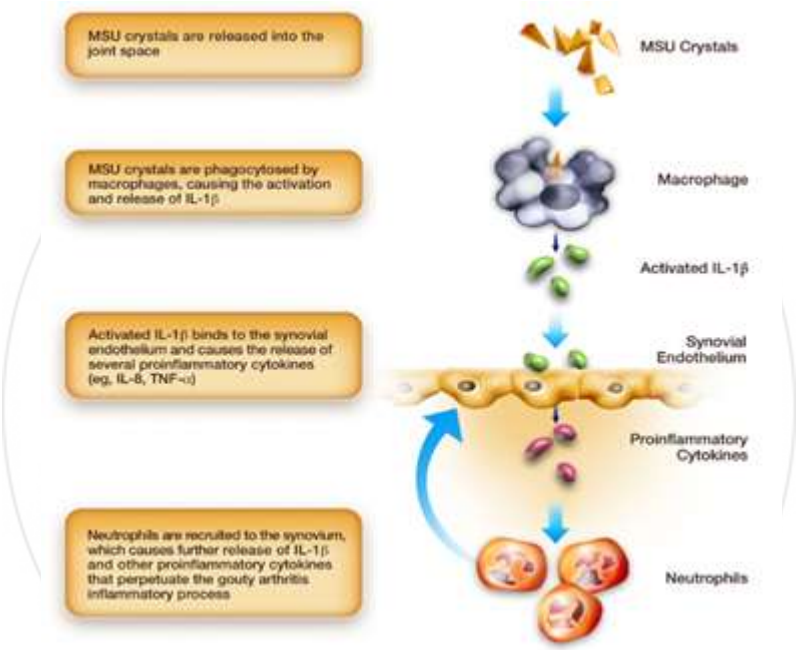

Figure 3: Il-1β signaling leads to recruitment of neutrophils and amplification of an acute inflammatory cascade[21]

Patient has several risk factor to develop gouty arthritis which is man, obese, history ofhyperlipidemia and also family history. Prevalence of gout was higher in man, increases dramatically with age, with almost 12% ofmales aged 70 – 79 years affected compared with <3% in men younger than 50 years and also associated with multiple comorbidities: up to 58% of patients with gout have comorbid hypertension, 45% with lipid disorder, 33% have both hypertension and a lipid disorder, and 20% have comorbid diabetes mellitus.[8,9,15,16]

Hyperuricemia in this patient was due to eating chicken curry and "kripikemping" one day before the symptoms arised. Curry is one of traditional Indonesian food that made meat, internal organ of animal and also coconut milk while "kripik emping" is a chips that made from melinjo (*gnetumgnemon*). Thus foods was contained of high purine. Urate levels in the body are balanced through diet, biosynthesis, and excretion, with overproduction or insufficient renal clearance leading to chronic hyperuricemia.[7,17]The pronounced increases in the plasma concentration of urate that occur during chronic hyperuricemia can lead to supersaturation, and at concentrations >6.8 mg/dL, precipitation of monosodium urate (MSU) crystals can occur (figure 2).[18]

Acute gouty arthritis develops when MSU crystal deposits around a joint are released into the joint space causing inflammation. Until recently, the molecular components of this inflammation were poorly understood. For example, not all individuals with elevated levels of uric acid develop gouty arthritis, there being other factors that potentially facilitate the process. However, recent research has revealed that interleukin (IL)-1β represents a key inflammatory mediator in this pathway which can be seen in figure 3. Given that the consumption of large meal, such as in this case, can lead to increases in free fatty acid concentrations, it stands to reason that the involvement of free fatty acids in triggering release of IL-1β may be an important factor in the development of gouty arthritis flares.[19,20]

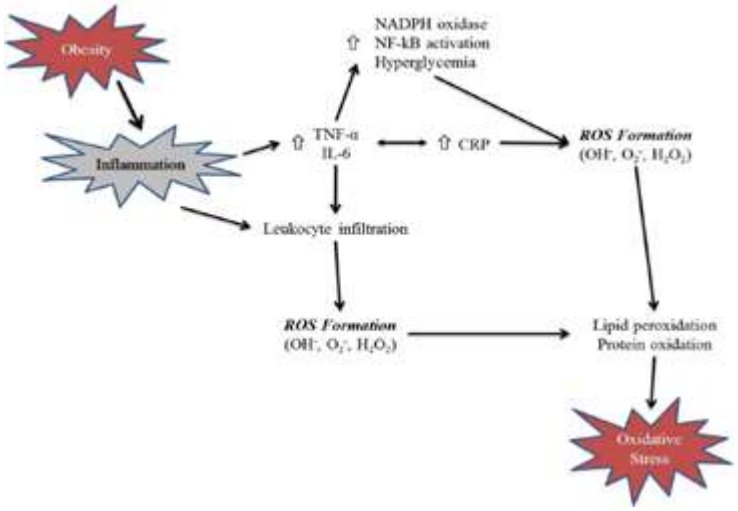

Figure 4: The link between obesity induced inflammation and oxidative stress, increased pro inflammatoryresponse and leukocyte infiltration in obese populations promote the formation of ROS, resulting in oxidative stress.[3]

Inflammation due to hyperuricemia has been suggested as underlying mechanism as acute attack in gouty arthritis and causing AVS as its initial symptoms. Hyperuricemia in the gout arthritis producing cytokines which is its mechanism has been shown in figure 3. In this case, the patient was obese based on body mass index measurement (BMI >30). Obesity can increasing stress oxidative which has also another suggested mechanism in the pathogenesis of symptoms of AVS. Although, the exact mechanisms for obesity-induced oxidative stress remain unclear, leptin, an adipocyte-derived hormone, has been considered as an important contributor.

Leptin is responsible for regulating energy intakeand expenditure and is also known to play a key role inmediating proinflammatory state in obese individuals. Korda et al.have shown that elevated leptin inducesoxidative stress (e.g., reduced NO and increasedO2− and ONOO−) in both human endothelial cells andthe endothelium of obese mice. Yamagishi et al.[22,23]have further demonstrated that leptin can increase intracellularreactive oxygen species (ROS) generation in microvascular endothelialcells. Thus far, two possible mechanisms have been proposedfor the leptin-induced oxidative stress: (i) thestimulation of mitochondrial oxidation of fatty acids[24]and (ii) the elevation of pro-inflammatory cytokines, which can be seen in figure 4.[25]In the study that was conducted by Mehmet Taylan Güçlütürk et at.showed us the level of total antioxidant status levels were lower in the BPPV group than in the control group (p=0.008). There was statistically significant decrease in the levels of IL-1β and IL-6 after Epley's repositioning maneuver in the vertigo group and also there was a statistically significant decline in IL-1β levels at the first and third month visits (p=0.014 for first month and p=0.013 for third month). These findings suggested that oxidative stress and inflammation may have a synergistic or complementary role in the pathogenesis of vestibular syndrome.[26]

The patientwas given ringer lactateintravenous fluid 20 drips per minute, betahistine mesylate 12 mg every 8 hours, flunarizine 5 mg every 12 hours, intravenous ranitidine 50 mg every 12 hours and intravenous ondansetron 8 mg every 12 hours and meloxicam 15 mg once a daily. Vestibular suppressants, such as antihistamines, sedatives or antiemetic can be used treating the symptoms of AVS. Vestibular suppressant such as betahistinemesylate and flunarizine was given to the patient. Betahistine mesylate, a structural analogof histamine with weak histamine H1 receptor agonist and more potent H3 receptor antagonist properties, increases the levels of neurotransmitters released from the nerve endings, stimulating H1 receptors thus augmenting the direct agonistic effects on the receptors. Flunarizine s is a selective calcium entry blocker with calmodulin binding properties and histamine H1 blocking activity. Both of them will cause vasodilatory effects in the inner ear, aiding to the treatment of vertigo. Flunarizine is contraindicated in patients with depression, in the acute phase of a stroke, and in patients with extrapyramidal symptoms or Parkinson's disease. It is also contraindicated in hypotension, heart failure and arrhythmia. Ondansetron is a 5-HT3 receptor antagonistare present both peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema,which can reduce nausea and vomiting while ranitidine is a competitive, reversible inhibitor of the action of histamine at the histamine H2 receptors found in gastric parietal cells. This results in decreased gastric acid secretion and gastric volume, and reduced hydrogen ion concentration thus relief the symptom.[27]

First-line treatments for an acute flare of gouty arthritisare either oral colchicine and non-steroidal anti-inflammatory agents. Systemic or intra-articular corticosteroids can also be used, and are equally effective, but with more side effects. Interleukin-1 inhibitors are still under investigation and are not approved for an acute attack of gout.In our case, thepatientwas given meloxicam 15 mg. NSAIDs and colchicine are the main treatment for an acute gout attack. The FDA has approved three NSAIDs for treatment of acute gout; indomethacin, naproxen, and sulindac. Colchicine reduces inflammation in the affected area however many patients do not tolerate it well due to gastrointestinal side effects. Acute gout will resolve in most patients within three to ten days with or without treatment. Early onset of treatment leads to improved outcomes. Patients with more than one attack of acute gout a year should be offered preventative therapy with Allopurinol. Allopurinol is

ineffective in acute gout attack but will help prevent future gout attacks by lowering uric acid levels. A diet low in purines can also help prevent future episodes of gout. Patients should avoid foods such as beer, red meat and seafood.[10,11]

Hyperuricemia is often present in patients with tophaceous gout, and they can benefit from uric acid loweringtherapy early during the course. In our patient, serum uric acid and 24-hour urine uric acid level were within normal limits when measured in the hospital before his discharge from the hospital. It was decided to follow him up in the clinic in two weeks, andthe measurementthese values again during 'interval gout' before deciding to start him on any particular medication to prevent further attacks of acute arthritis.

4. Conclusion

Inner ear disorders are common, and patients withaudiovestibulardisorders, especially vestibular disorder, may well present to a neurology clinic. A thorough history and examination will often provide a clear direction as to the diagnosis.From this case report, we suggest that the oxidative stress marker and the inflammatory mediators IL-1β, TNF-α and IL-6 may play roles in the pathogenesis of acute vestibular syndrome and these two mechanisms may have synergistic or complementary effects in which induced by hyperuricemia state in the acute attack of gouty arthritis. With additional studies, new systemic or intratympanic treatment protocols including antioxidant and/or anti-inflammatory medications may be used in the treatment of acute vestibular syndrome patients. Gout is a painful disease and can significantly affect a patient's quality of life. Treatment of acute gout must be initiated promptly. In patients with recurrent gout, providers must discuss diet and medication to prevent future attacks.

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