CHAPTER 26

PATHOGENESIS AND PREVENTION OF AVIAN GOUT

Wei Chen, Ning Li, Mengbing Ding, Guanming Tian and Xiaoquan Guo*

Provincial Key Laboratory for Animal Health, Institute of Animal Population Health, College of Animal Science and Technology, Jiangxi Agricultural University, Nanchang 330045, PR China
*Corresponding author: xqguo20720@jxau.edu.cn

INTRODUCTION

Avian gout is a disease of urate deposition in poultry caused primarily by Sodium urate crystals (Dalbeth et al. 2019). Due to excessive uric acid production and uric acid metabolism disorder, a large amount of uric acid is excreted through the kidney, causing kidney damage and dysfunction, further blocking uric acid excretion, and resulting in uric acid poisoning and uric acid crystal deposition, leading to gout. Gout can occur in chickens, turkeys, pigeons, geese and pheasants, and mainly in caged chickens. The main features of avian gout are loss of appetite, light crown color, depressed, white semi-mucus-like feces containing large amounts of uric acid and reduced or zero egg production in adult hens. There are two general types of avian gout: one is arthritic gout and the other is visceral gout (Guo et al. 2005; Hong et al. 2020). The joint type of gout is the deposition of uric acid in and around the joint cavity. At first, the joint is swollen. The swelling is soft and the boundary is not obvious. After that, the area gradually becomes hard and forms nodules. The nodules are large, similar to the size of a bean, and later rupture. There is cheese flow out, forming ulcers. The sick bird is often in a squatting or one-legged standing position, with slow movement and lameness. Visceral gout is the deposition of uric acid in the viscera, which is not easy to diagnose clinically, and can be seen in the pleura, peritoneum, lungs, pericardium, liver, spleen, kidneys, intestines and intestinal lining with lime-like, flocculent, crumbly white uric acid crystals on the surface. The most distinctive phenomenon is the "tinea kidney", in which the kidney is covered with snowflake patterns formed by urate deposits. Gout is one of the most common mammalian and avian metabolic diseases, and is an arthritic form of hyperuricemia (Yang et al. 2020). Due to the lack of uric acid oxidase and glutamine synthetase in poultry, it is difficult for ammonia to be converted into urea through the guanine cycle and it is difficult to be excreted. Therefore, poultry are prone to hyperuricemia and gout (Zhang et al. 2018). In order to improve egg production and growth rate of broilers as soon as possible, farmers usually give broilers high-fat and high-protein feeds, which are rich in nucleoproteins and purine bases, easily inducing avian gout. Poor feeding conditions and improper feed ratios have made poultry gout a common disease in poultry, causing great economic losses to farmers. Gout involves a variety of mechanisms, such as increased synthesis and decreased metabolism of uric acid caused by abnormal purine metabolism and astrovirus infection (Shao et al. 2017; Zhang et al. 2018). When the level of uric acid in the blood exceeds the saturation of the blood, the excess uric acid forms crystals deposited in the joints and tissues of the body, causing recurrent inflammation in the surrounding area. This chapter reviews the causes, mechanisms and prevention of avian gout with the purpose that it can provide reference for the prevention and treatment of avian gout.

Causes of the Disease

There are many causes of gout. The cause of gout is usually complicated and difficult to be determined. Existing studies have shown that there are more than 20 causes of avian gout, which can be divided into two categories. One category is the excessive production of uric acid in the body, and the other is the disturbance of urate excretion.

Hereditary Factors

There is a genetic susceptibility to gout for certain strains of chickens. Certain breeds of chickens have defective renal tubular secretion of uric acid, which can cause gout even when fed on the diets with normal protein levels. Some researchers have also bred some hereditary hyperuricemia chickens (HUA chickens) from chickens with high incidence of joint gout, and hereditary factors are often the main factors of joint gout. Studies have shown that long-term feeding of high-calcium diets can cause kidney damage and induce gout in chickens.

Nutrient Metabolic Factors

Excessive protein content in feed, especially too much animal protein, can easily produce excessive uric acid. Common ones include animal offal, meat and bone meal, fish meal, meat scraps, etc. In addition, it also contains plant-based feeds such as soybeans and mushrooms. It has been reported that gout can be caused when the addition of fat-free horsemeat and 5% urea to the Turkey diet increases the protein content of the diet to 40%. All hens developed gout after 3 to 5 months of continuous feeding with fat-free horsemeat. Studies have shown that, under the condition of normal kidney function, feeding diets with slightly higher protein level will temporarily increase plasma uric acid level, but will not cause gout. Other studies have found that high-protein diet can promote the occurrence of articular gout in HUA chickens.

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Infectious Factors

All pathogenic microorganisms that are nephrophilic and can cause renal function damage may block the excretion of urate, thereby causing chicken gout, such as nephropathogenic infectious bronchitis (IB), infectious bursal disease (IBD), inclusion body hepatitis in chickens, avian egg drop syndrome, avian influenza, Marek's disease (MD), avian mycoplasmosis, pullorum disease, staphylococcus, aspergillus, pneumocystosis, Eimeria, and histo-trichomoniasis (Pegram et al. 1981; Slemons et al. 1990; Trampel et al. 2000). At present, nephropathogenic infectious bronchitis is the most studied and reported (Xu et al. 2019). Guo et al. (2005) found that the pathogenesis of nephropathogenic infectious bronchitis virus induced avian gout, which indicated that nephropathogenic infectious bronchitis virus infection induced the change of global transcriptomic and metabolomic profiles of kidney and Fabricius (Xu et al. 2019; Kuang et al. 2020). In addition, NIBV mediated endoplasmic reticulum stress and apoptosis in kidney, which were closely related to the occurrence of chicken gout (Fung et al. 2014; Chen et al. 2021).

In addition, gosling astrovirus (GoAstV) is also believed to be the main causal pathogen of gout, but the full-blown disease of gout cannot be well reproduced by infecting the goslings with GoAstV. Therefore, Liu et al. (2020) studied the changes in GoAstV and GPV infection in goslings by PCR and DNA sequencing. The HE staining demonstrated that the kidneys were congested with renal tubular necrosis, abscission of renal tubular epithelial cells, and eosinophilic protein-like substance in the renal tubules. The ureteral lumen was enlarged with necrotic debris and basophilic staining of urate deposits. The liver, spleen and lung were markedly congested and edematous. The hyperemia and hemorrhage of the cerebrum, cerebellum, and trachea were present. The necrosis and dissolution of cells and hemorrhage in blood capillaries in the heart and leg skeletal muscle were also observed. Basophilic intranuclear inclusion bodies were found in kidney, liver, harderian gland, bursa of fabricius, lung, and spleen (Liu et al. 2020). Studies have shown that different varieties of geese can be infected with GoAstV. New type of goose stellate virus infection leading to gout in goslings mainly occurs in 5 to 20 days old goslings, goslings infected at about 5 days old onset, incidence of about 80-90% and mortality of about 20-30%, and the highest can reach 50% (Monroe et al. 1993; Niu et al. 2018). Goslings in the early onset of infection appear slow action, close eyes, shrink neck spirit, drooping double wings, drooping feathers, fluffy messy, and other clinical symptoms. As the condition gets worse, sick young appetite decreases gradually. Excretion of stone ash cinder looks white and thin dung appears claddy. Serious conditions can cause paralysis until the death. Young goose growth is retarded, and body resistance is reduced. The typical clinical symptom of gout occurrence of young goose is obvious joint swelling. In the late stage of the disease, white urate crystals are precipitated at the eyelid (Zhang et al. 2018).

Coccidiosis of Eimeria tender occurs mostly in chickens aged from 3 to 6 weeks. The parasite parasitized in the cecum and rectum mucosa epithelial cells, and had an incubation period of 4 days after infection. At the beginning of the disease, the patient was listless, with feathers inverted, head curled up, eyes closed, loss of appetite, and feces sparse. From the end of the 4th to 5th day, the chick suddenly excreted a large amount of blood stool, showing obvious anemia. Studies have shown that the serum uric acid content in tender chickens with Eimeria coccidiosis is significantly increased, which may be related to excessive ammonia and nucleic acid removal, especially the intensified tissue destruction and accelerated nucleic acid decomposition, but whether it is related to local destruction of cecum or other systemic toxin effects remains to be studied. However, according to Ruff et al. (1981), chest RNA was significantly reduced on day 4 of *E. tenella* infection. In addition, the study found changes in kidney structure and uric acid clearance in young chickens with Eimeria coccidia. Padmavathi and Witlock (1981) proved that the cause of death in tender chickens caused by Eimeria infection was renal tubular dysfunction caused by elevated uric acid levels.

Toxic Factors

Toxic factors mainly damage the kidneys and reduce uric acid excretion, thereby causing visceral renal gout. Some nephrotoxic drugs combine with plasma proteins to produce antigenicity, which can cause allergic reactions in the body and diffuse kidney damage. For example, improper medication and excessive use of nephrotoxic drugs such as antibiotics, sulfonamides, furans, and chlorocyclic hydrocarbon pesticides in the process of prevention and control of poultry diseases can easily reduce renal function, weaken the ability to excrete uric acid, and cause a large accumulation of uric acid which causes gout. In addition, the excretion of sulfonamides in an acidic environment can easily cause crystals to be precipitated from the urinary tract, while the renal excretion capacity of crystalline sulfonamides is extremely low, resulting in obstruction of the renal tubular lumen. The mycotoxin poisoning factors are more harmful, which can seriously damage the kidneys and cause hyperuremia and visceral gout. Nephrophilic chemical poisons such as Potassium dichromate, cadmium, thallium, zinc and lead can also cause gout. Visceral gout in birds can be caused by intoxication with allopurinol drugs used to treat hyperuricemia in humans.

Unbalanced Vitamin Content

Long-term lack of vitamin A in the diet can lead to keratinization of renal tubular and ureteral epithelium, and impaired urate excretion after kidney injury, leading to gout. Lack of vitamin D can make the body mineral especially calcium phosphorus metabolism disorder and cause gout. Lack of pantothenic acid, biotin, choline can directly or indirectly lead to kidney diseases and cause gout. For example, high levels of vitamin D can enhance the absorption of calcium in the gut, which can cause hypercalcemia.

Other Factors

Cold and wet environments function in the development of gout. The lowering of the ambient temperature can promote the crystallization of urate. When uric acid is at a high level in the body of avian animals, cold temperatures and humidity will cause local microvascular contraction, thus slowing down the blood flow and promoting the deposition of large amounts of urate in the joint cavity of avian joints, resulting in gouty arthritis.

Lack of drinking water can also promote the deposition of urate. The rotation and absorption of nutrients in the body and the excretion of wastes in the body require water as a medium. When the lack of water is too long, the concentration of uric

acid and other minerals in the blood and renal tubules will increase. Then urine is concentrated and urate is continuously deposited in the ureter, which finally causes gout.

Pathogenesis

Avian gout spreads all over the world, with an incidence of 85% and a mortality of 30%. Urate overproduction and underexcretion of urate can be considered to lead to hyperuricemia in the body of birds and monosodium urate crystal deposition to form avian gout.

Urate Overproduction

There is no arginase in the livers of avian animals, so that protein cannot be excreted through the ornithine cycle into urea, and only through the purine nucleotide cycle to form purines (Lee et al. 2013). Purine is a nitrogen-containing ring structure substance, which is widely present in the nucleic acid of plant tissues. Purine can be produced by the decomposition of nucleoprotein in food, or it can be formed by the decomposition of the core protein. Urate is the end-product of purine nucleotide degradation, so diet therapy occupies an important position in this disease. Purines can be produced by the decomposition of nuclear proteins in food (exogenous), and in the body (endogenous) (Li et al. 2021). Hence, with excessive intake of protein, purine substances increase serum urate and the risk of incident gout. High uric acid combines with calcium and sodium ions to form uric acid salts. The stability of urate is easily affected by the environment. It is protected from deposition in the blood by massive plasma proteins that maintain stability. However, high urate levels in the blood form ultrafiltration urate colloidal particles, which are filtered into tissues with low protein content, destabilizing them and causing deposition. Urate deposited in the joint cavity can act as a damage-related molecule to stimulate innate immune pathways, and activate the nuclear transcription factor NF-κB through TLR4 and TLR2, promoting the synthesis of pro-IL-1β and inflammasome components, and eventually leading to gouty arthritis. Xi et al. (2019) studied the expression levels of inflammatory factors and inflammatory signaling molecules in the kidneys of goslings with gout and found that TLR2/TLR4, MyD88, NF-κB, IL-1β, IL-8 and TNF-α in the kidneys of goslings with gout are significantly increased, resulting in severe renal inflammatory damage, which further exacerbates renal excretory dysfunction (Xi et al. 2019).

Uric Acid Excretion Disorder

The only organ for excretion of uric acid in poultry is the kidney, so that the normal excretion of uric acid in poultry depends on the structure and function of kidney (Shideman et al. 1981). Under normal circumstances, uric acid is excreted through renal tubule secretion and reabsorption, both of which directly affect uric acid levels in the body. If the secretion of uric acid by the renal tubules is reduced, it will cause the obstruction of uric acid excretion and induce hyperuricemia. Previous studies have shown that New Hampshire chickens exhibit an innate genetic susceptibility to articular ventilation due to an impaired uric acid transport mechanism and a defective gene for uric acid secretion in renal tubules (Cole et al. 1980). In addition, some researchers selected inherited hyperuricemia chickens from the chickens with high-incidence of jointed gout (Austic et al. 1976). If the serum uric acid concentration in poultry keeps increasing, it will cause persistent excessive excretion in the kidney, which in turn induces up-regulation of URAT1 (uric acid anion exchanger 1 encoded by SLC22A12) and GLUT9 (glucose transporter 9 encoded by SLC2A9), leading to kidney damage (Liu et al. 2015; Qin et al. 2018). At the same time, uric acid deposits in the way of urate in the blood on the joints, cartilage, soft tissue, and visceral surface. URAT1 and GLUT9 also mediate the reabsorption of uric acid in the proximal tubules, which in turn seriously hinder the excretion of uric acid (Le et al. 2008). On the contrary, OAT1 (organic anion transporter 1 encoded by SLC22A6) participates in basolateral urate excretion, helping the kidney to regulate excess excretion of uric acid (Habu et al. 2005). Therefore, changes in the functions of different urate transporters can directly cause changes in uric acid excretion.

Another major cause of uric acid excretion disorder in poultry is the accumulation of hyperuricemia and sodium urate crystals, which leads to the formation of gout (Hong et al. 2020). Uric acid is slightly soluble in water and can form urate deposition with cations such as Na^+, K^+ and Ca^{2+} under certain pH conditions (Kanbara et al. 2012). In other words, the stability of urate colloid is closely related to electrolyte balance and acid-base balance of body fluid. Many studies have reported that a high calcium diet and long-term vitamin A or vitamin D deficiency are important causes of gout in poultry (Guo et al. 2008). High dietary calcium levels can cause hypercalcemia, which leads to metabolic alkalosis and increased parathyroid secretion (Konstantinov 1970). Then it can increase calcium ion concentration and deposition in renal tubular epithelial cells, leading to the formation of kidney stones and chronic renal insufficiency. By this time the nephron is continuously destroyed, so that it is not enough to compensate for all renal function, resulting in blocked excretion of uric acid, and deposition on the serous membrane surface of the kidney, heart, liver, mesentery, air sac and peritoneum, eventually causing gout and renal failure (Marcocci et al. 2011; Ding et al. 2019). In addition, when the poultry body is in a state of high calcium, the ratio of calcium to phosphorus will be unbalanced, and low phosphorus can promote the occurrence of gout. Relevant studies showed that when the calcium content in gosling's diet reaches 3.1% (the normal requirement is 0.8~1%), the ratio of calcium to phosphorus reaches 7.8:1.0 (the normal ratio is 1.1:0.7), and gout occurs in gosling (Alagawany et al. 2021). It is worth mentioning that vitamin A can maintain mucosal integrity and protect mucosal barrier by regulating the proliferation and differentiation of epithelial cells (Miyaishi et al. 1992). But long-term vitamin A deficiency can lead to keratinization of renal tubules and ureteral epithelium, which is not conducive to the excretion of uric acid and phosphorus, which eventually could lead to urate deposition and renal failure (Chandra et al. 1984). Another cause of metabolic disorder of avian fluid electrolyte is insufficient intake of vitamin D. Lack of vitamin D can lead to the mineral metabolism disorder, proportion imbalance, and excretion obstacles, especially calcium and phosphorus. However, when dietary vitamin D supplementation is excessive, it will cause intestinal absorption of more calcium, which is easy to cause hypercalcemia and indirectly lead to the occurrence of gout.

Similarly, any nephrophilic protomicroorganism can cause renal function injury and urate excretion obstruction, such as new astrovirus, avian nephritis virus (ANV), aspergillus nephritis,

and nephropathogenic infectious bronchitis virus (NIBV) (Jin et al. 2018). These pathogens act on renal tissue directly or indirectly, causing functional lesions at the early stage and organic lesions at the later stage. Wu et al. (2020) found that GoAstV infection in goslings caused an increase in uric acid produced by purine metabolism, and a decrease in uric acid excreted by the kidneys, resulting in the accumulation of uric acid in goslings, and eventually leading to hyperuricemia and the occurrence of gout (Wu et al. 2020). Trampel et al. (2000) reported the first case of urethral cryptosporidiosis in adult hens. Under the influence of cryptosporidium parasitism, ureteral epithelial cells of infected birds prolifically shed, resulting in partial ureteral obstruction and visceral gout. Some nephrotoxic drugs will produce antigenicity after combining with plasma proteins, which can cause allergic reactions in the body and diffuse damage to the kidney - degeneration, necrosis, shedding, agglutination of renal tubular epithelial cells, blocked excretion of uric acid, etc. In addition, the excretion of sulfonamides in acidic environment makes it easy for crystals to precipitate from the urinary duct, while the excretion ability of kidney to crystalline sulfonamides is very low, which leads to obstruction of renal tubule lumenage and reduces the ability of kidney to excrete uric acid.

Other Factors

Cold and wet environments play a role in the development of gout. The lowering of the ambient temperature can promote the crystallization of urate. When uric acid is at a high level in the body of avian animals, cold temperature and humidity will cause local microvascular contraction, thus slowing down the blood flow and promoting the deposition of large amounts of urate in the joint cavity of avian joints, resulting in gouty arthritis.

Lack of drinking water can also promote the deposition of urate. The rotation and absorption of nutrients in the body and the excretion of wastes in the body require water as a medium. Once the lack of water is too long, the concentration of uric acid and other minerals in the blood and renal tubules will increase. Then urine is concentrated and urate is continuously deposited in the ureter, which finally causes gout.

Prevention

Due to the complex causes of avian gout, there is no specific drug to treat it at present. The most effective way to prevent avian gout is to take different measures for different causes.

Pay Close Attention to Feed Management

Poultry have different nutritional needs at different feeding stages. High-calcium and high-protein feed is one of the main causes of gout in poultry, and regulating the content of calcium and protein in feed is the most effective method. After decades of development, the formula and technology in the feed industry have been very mature. The feed required by poultry at different growth and development stages is subdivided to make the feeding of farms more targeted. In the process of storing feed, we should pay attention to the warehouse environment to ensure that it is cool, ventilated and dry. For warehouses with relative humidity greater than 50%, quicklime can be sprinkled on the corner ground to absorb moisture in the air, reduce humidity and prevent mildew of feed. The technicians of many manufacturers can also come on site for disease diagnosis and treatment services, which is conducive to the control of the disease from the feed source.

Strengthen Disease Prevention and Control

Most gout is caused by diseases, most of which are nephropathogenic, infectious bronchitis virus, infectious bursal disease, Salmonella infection and other diseases (Choi et al. 2009; Lin et al. 2015). It is suggested that the vaccine immunization of infectious bronchitis and infectious bursal disease should be well done in the chicken stage, so that the body can produce effective titers of antibodies to resist wild virus infection. At present, there is no good vaccine for salmonellosis. It is recommended to use antibiotics, but pay attention to the rest period for broilers and eliminated chickens. Commercial chickens entering the laying period are prohibited from using antibiotics, and non-antibiotics materials such as traditional Chinese medicine, probiotics, phage feed additives, biochemical products and plant essential oils can be used for prevention and control of the disease.

Scientific Use of Drugs

Drug abuse can lead to liver and kidney damage, resulting in urate metabolism and excretion disorders (Jospe-Kaufman et al. 2020). Here we do not forbid the use of veterinary drugs, but use them in a proper way. Aminoglycosides have strong toxicity to the kidney, but they are basically not absorbed orally. Only when injected, the drugs can quickly reach the kidney through blood circulation and cause damage to the kidney. The drug administration method is very important. It is easy for sulfonamides to form crystalline urine when passing through the kidney, resulting in damage to the renal tubular wall and affecting the excretion of uric acid. When used, sulfonamides can be used together with baking soda to alkalize the generated urine, which can reduce the crystallization of sulfonamides. It is suggested that farms with frequent occurrence of this disease should consulted professional licensed veterinary doctors for clinical medication guidance, so as to reduce the incidence of the disease.

Treatment

For poultry gout with complex pathogenic mechanism, there is currently no particularly effective drug. Different types of gout need to be targeted differently.

High-calcium and high-protein feed is one of the main causes of gout in poultry, and reducing the content of calcium and protein in feed is the most effective method. Dexamethasone is currently the most effective drug for the treatment of avian gout. Dexamethasone belongs to the hormone class, increasing enzyme activity in the body to increase the rate of metabolism to achieve the purpose of reducing uric acid and urate deposition in the body to relieve gout. Relevant literature shows that the cure rate of dexamethasone for gout is as high as 91.8%. Allopurinol, as a competitive inhibitor of xanthine oxidase, is also useful in the prevention and treatment of avian gout. Allopurinol can effectively reduce the content of uric acid in the body, but attention should be paid to its side effects on gastrointestinal tract. In recent years, rapid progress has been made in the process of treating gout with Chinese herbal medicine, such as avian gout powder, and kidney kangning.

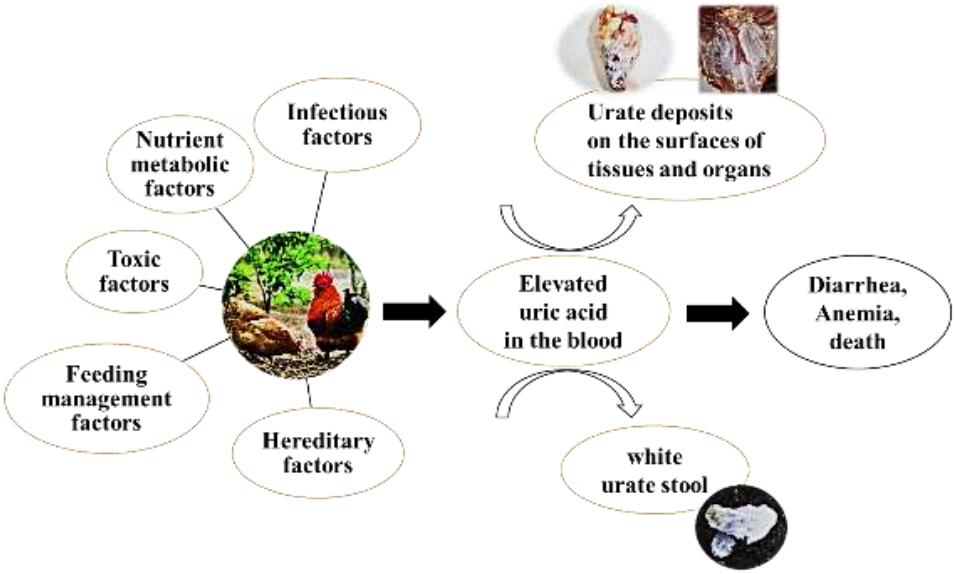

Fig. 1: The general process of avian gout

Relevant experiments show that, compared with allopurinol, Piper-betle-L showed significant efficacy in the treatment of avian gout (Chakravarthi et al. 2021). Probenecid is of great significance in the treatment of chronic avian gout. Probenecid reduces urate concentration by inhibiting urate reabsorption and promoting urate excretion, which accelerates the formation of urate dissolution. But benzosulfonate has no obvious effect on acute gout. Gout can also be treated by adding Sodium bicarbonate and Potassium chloride to drinking water to regulate the acid-base balance in avian. It works by alkalinizing urine, making uric acid less likely to accumulate and crystallize in urine. It has the advantages of quick effect and can greatly reduce the mortality of poultry. There are many other drugs to treat avian gout, such as colchicine, non-steroidal anti-inflammatory drugs, and utlopine. A recent study showed that pepper extract alleviates gout symptoms by increasing antioxidant capacity in broilers (Vikrama et al. 2022). Generally speaking, the cure rate of traditional Chinese medicine is higher than that of western medicine. Specific use of drugs should be selected according to the actual situation.

Thoughts on the Study of Avian Gout

Avian gout is highly similar to human gout. In terms of clinical manifestations, avian joint gout is very similar to human gout, mainly in joints. The manifestations of the disease are joint swelling, being soft and painful at the beginning, gradually hardening of swelling parts, aggravation of pains, the formation of not mobile or slightly mobile nodules, and presence of pain swelling occurs in distal joints, such as toe joints, and anterior toe joints, but it can also infringe on wrist joints, anterior wrist joints and other places. In terms of pathogenesis, both avian gout and human gout are caused by urate deposition due to increased uric acid production or decreased uric acid excretion. All are affected by factors such as heredity, diet, and environment. Excessive intake of purines and proteins can lead to an increase in the production of uric acid, which is easily deposited in the form of sodium salts and calcium salts, resulting in gout. The pathological basis is similar. The liver of poultry does not contain arginase, so the protein consumed can only generate purine, which forms uric acid insoluble in water under the action of xanthine oxidase, and easily forms urate with sodium or calcium, which leads to gout on the surface of renal tubules and joint cavities. However, humans lack in uric acid oxidase, which cannot metabolize purine into soluble urea and expel it from the body like other mammals (Hong et al. 2020). Uric acid is also the final metabolic product. At present, the commonly used animal models of gouty arthritis only simulate the pathological phenomenon of urate crystals precipitated in the joints, which is inconsistent with the pathogenesis of human gout. In addition, uric acid oxidase exists in rodents, which has a different metabolic pathway compared with purine in humans. Uricase-deficient mice obtained by gene knockout are expensive for basic research. However, there are many similarities between avian gout and human gout, and the avian gout has a high incidence and can be seen in many kinds of birds. Therefore, it is of great significance to establish an animal model of avian gout for the study of the pathological mechanism of human gout and drug screening.

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