

## **REPORT**

# **A case report of Meige syndrome-like blepharospasm caused by ingestion of allopurinol**

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**Abstract:** One case of allopurinol-caused rare adverse reactions was reported. One male 51-year-old patient presented blurred vision, streaming eyes, photophobia and blepharospasm sequentially 1 week after oral administration of allopurinol. Complete remission was obtained after Botulinum toxin was locally injected. Allopurinol may cause Meige syndrome-like blepharospasm, the mechanism of which may be related to the inhibition of dopamine activity by affecting adenosine level in the brain.

**Keywords:** Allopurinol, Meige-syndrome, diagnosis, pathogenesis

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## **INTRODUCTION**

Allopurinol is the preferred medication in the clinical treatment of urinary calculi caused by chronic gout hyperuricemia, tumor associated hyperuricemia and hyperuricemia. It may reduce the serum level of uric acid primarily by inhibiting the activity of xanthine oxidase and preventing the conversion of hypoxanthine and xanthine into uric acid. Adverse reactions have been frequently observed over more than 50 years of clinical applications. Here, we report a case that vision-dependent blepharospasm occurred after allopurinol ingestion. To our knowledge, this is the first time to report a symptom of neuromuscular disorder induced by allopurinol.

### ***Case report***

One male patient, 51 years old, had a history of gout for 3 years, with no history of other diseases and treatment. Laboratory examination indicated serum uric acid of 644 $\mu$ mol/L, serum creatinine of 141.7 $\mu$ mol/L, urea nitrogen of 8.3mmol/L, normal urine routine, normal liver function, triglyceride of 2.20mmol/L and total cholesterol of 7.57mmol/L, with normal ECG. This patient was diagnosed as gout and uric acid nephropathy, with stage 3 chronic kidney disease. Initially, Allopurinol tablets (100mg per tablet) were administered orally 100mg twice daily, after developing blurred vision 1 week later, he was referred to our hospital and stopped allopurinol. The results of diagnosis tests showed serum uric acid of 466 $\mu$ mol/L, serum creatinine of 162.0 $\mu$ mol/L, urea nitrogen of 7.2mmol/L, normal urine routine and normal liver function; ophthalmic examination revealed mild conjunctival congestion of the right eye, normal cornea of both eyes, equal pupil size and no significant changes in

refractive media and ocular fundus of both eyes. The diagnosis was chronic conjunctivitis with ametropia and sulfacetamide sodium eye drops and diclofenac sodium eye drops as well as glasses were prescribed. After the medication, the patient felt blurred vision improved. Then continued oral allopurinol three days later, symptoms for both eyes developed, including difficulty in eye-opening, photophobia, tearing, blepharospasm with no muscle spasm of jaw and mouth. Nevertheless, symptoms like paresthesias of skin, rash, joint pain, and fever were not observed. Despite of normal central nerve system and facial sensory examinations, both eyes could not be completely opened with force, orbicularis muscle contraction, and paroxysmal tics of the upper and lower eyelids. Mecobalamin tablets, artificial tears, recombinant bovine basic fibroblast growth factor, and ofloxacin eye drops were prescribed, and symptoms were not improved. Botulinum toxin A was injected into eyelids 15 days later, and the patient perceived that the difficulty in eye-opening was improved 1 day after injection and could open the eyelids himself, but only for a few seconds. No additional treatment was given and the patient was discharged for observation. The symptoms were gradually relieved, and he could open his eyes three months later. Facial nerve and axillary nerve EMG and chest CT examination were taken during this period and the results were normal. Thymoma and myasthenia gravis were excluded. The spasm disappeared and normal eyes restored after six months.

## **DISCUSSION**

Meige syndrome, also known as the Brueghel syndrome, is a syndrome with blepharospasm as the initial manifestation in combination with involuntary spasm of facial, head and neck muscles as the main presentation.

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Definite diagnosis of Meige syndrome is generally made according to the clinical manifestations with the exclusion of other diseases that may cause blepharospasm. This patient perceived blurred vision after medication, followed by typical bilateral symmetry blepharospasm with photophobia and tearing that is similar with Meige syndrome. The symptoms gradually worsened with the Tricks phenomenon and myasthenia gravis and thymoma were excluded. Pathogenesis of Meige syndrome is complicated and not very clear yet. Some proteins expressed in the central nervous system can interfere with the actions of nuclear transcription factors, leading to the occurrence of the disease (Bressman *et al*, 2000; Bressman *et al*, 2009; Makino S *et al*, 2007; Xiao *et al*, 2004; Carbon and Eidelberg, 2011; Vander Heyden *et al*, 2009); Abnormal pathways between stem neurons and excitability of sensory motor areas in the cerebral cortex are also one of the mechanisms of pathogenesis (Berardelli *et al*, 1985; Pauletti *et al*, 1993; Currà *et al*, 2000). Some drugs, including antiemetic drugs (such as metoclopramide), antipsychotics (such as haloperidol), and anticonvulsant drugs can also induce dystonia, which is usually caused by the inhibitory effects of these drugs on the dopamine receptors in the brain (Ananth *et al*, 1988).

The adverse reactions of allopurinol include rash, liver damage, bone marrow suppression, gastrointestinal symptoms, and kidney damage, etc. But severe hypersensitivity syndrome also is a major adverse reaction with low incidence and high mortality. The mechanism for the adverse reactions is related to the structure of the thiol group, which can induce a series of immune response and biochemical reactions (Jaffe, 1986). In this case, the patient developed renal dysfunction due to uric acid nephropathy is accompanied with higher risk in the usage of allopurinol. The sequence of the symptoms onset and ingestion of allopurinol leads to the consideration of its rare side effect in nerve system. To our knowledge, several cases of aseptic meningitis (Greenberg *et al*, 2001), peripheral neuritis (Azulay *et al*, 1993), and muscle injury (Escousse *et al*, 2002) have been reported. However, Allopurinol-induced Meige syndrome-like blepharospasm have not been reported. The clinical manifestations were different from allergic reactions and no presentations such as distal limb paresthesias and muscle fatigue and pain were indicated, so we hypothesize the mechanism under the side effect may be distinct from the previously known one. In 1991, Ferre *et al*. found that stimulation of adenosine A2a receptor could reduce the affinity of dopamine D2 receptor agonist binding site in striatal neurons plasma membrane (Ferre *et al*, 1991). Dopamine can also play a regulatory role through A2a receptors (Lester *et al*, 2010). Adenosine A2a receptor and dopamine D2 receptor coexist in the cerebral cortex, hippocampus and striatum, regulating dopaminergic neurotransmission (Ferre, 1997).

These studies indicate a close relationship between adenosine A2a receptor and dopamine D2 receptor, with mutual influence. Meanwhile, studies have demonstrated that allopurinol may increase the level of adenosine in the brain (Marro *et al*, 2006) and adenosine receptor agonists have been proved to have similar properties of dopamine receptor antagonist (Weiser *et al*, 2014). Therefore we may speculate that allopurinol can inhibit the activity of dopamine in the brain, which may explain the Meige syndrome-like symptoms in this case. For this patient, injection of botulinum toxin A is effective. Symptom of blepharospasm was immediately improved after injection although completely recovered 6 months later. Thus, we conclude that allopurinol induce rare side effect of Meige syndrome-like blepharospasm in this case, although the mechanism under which is not well clarified, the conventional treatment for Meige syndrome is applicable and effective.

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