



MEFV Gene Mutation may have a Culprit Role in the Pathogenesis of Gout

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ABSTRACT

This paper is about an interesting case that presented with gastrointestinal system amyloidosis due to poorly controlled, polyarticular tophaceous gout. We aim to emphasize the culprit role of Mediterranean Fever (MEFV) gene mutations in such cases to prevent long-term poor complications, due to the unfavorable course of gout.

Keywords: MEFV mutation, Gout, Amyloidosis

INTRODUCTION

We read an interesting case that presented with Gastrointestinal System (GIS) amyloidosis due to poorly controlled, polyarticular tophaceous gout [1]. The patient was the first reported gout case with GIS amyloidosis without overt renal involvement. The authors also noted that they investigated other underlying immune-mediated diseases such as rheumatoid arthritis, chronic infection, including tuberculosis, and primary light chain amyloidosis, and ultimately did not find important evidence of any underlying disease except gout.

Gout is a common inflammatory disease, but it is rarely associated with secondary amyloidosis. This condition has been explained by the short and self-limited inflammatory activity and the use of colchicine [2]. Familial Mediterranean Fever (FMF) is the main cause of secondary amyloidosis in Turkey, and its relationship with Mediterranean Fever (MEFV) gene mutations is well-known [3]. Activation and migration of neutrophils seem to be associated with locally produced cytokines in both gout and FMF. It is well-known that interleukin-1 beta (IL-1 β) plays an important role in the pathogenesis of both diseases. A mutated MEFV gene allele may cause an elevation in IL-1 β and may be associated with the phenotype of gout. Based on this hypothesis, a few trials were designed. Firstly, Sari, et al. reported any major role of MEFV mutations in gouty arthritis in the Turkish population [4]. On the contrary, Karaarslan, et al. detected a high rate of MEFV gene mutations in gouty arthritis compared with a healthy control group [5]. In 2018, Balkarlı, et al. investigated the effects of MEFV variant alleles on manifestations of gout. The number of gout attacks per year and incidence of tophus was significantly higher in gout patients with a MEFV variant allele [6]. Besides these trials from our country, Druyan, et al. also investigated MEFV carriage in 50 gout patients and 23 hyperuricemia patients. A comparison of gene carriage has resulted without any difference between the hyperuricemia group and gout patients. Also, the activity of the gout disease was similar between MEFV mutation carriers and non-carriers [7]. We think that a lack of a comparison with a healthy group without hyperuricemia may change the result. In another study, although there was not any significant association between MEFV gene mutations and gout arthritis, E148Q was the most detected mutation [8]. This mild mutation may not be a causative factor in phenotypic change and/or presenting with arthritis.

Recent studies focused on the genetic background of the gout disease in addition to the MEFV gene. Vernerova, et al. emphasized familial transition and noted a 7 year and a 10 year history of gout disease in two brothers with the genetic defects of purine metabolism. Despite the treatment with colchicine, one of them progressed to end-stage-renal disease due to gouty nephropathy and amyloidosis [9]. Genome-wide association studies showed that some urate transporter genes in the kidneys and gut, including SLC2A9, SLC22A12, and ABCG2 regulate serum levels of uric

acid, and functional mutations in these genes may increase the development risk of gout [10]. Although genes related to the NLRP3 inflammasome pathway also play a role, genetic variants that increase penetrance, predict responsiveness to therapies, or patients who will progress from hyperuricemia to gout are not clear today [11].

Many simple and convenient fluorescence methods are under investigation to detect serum, urine, and/or salivary uric acid levels in recent studies [12]. The newest one is a highly sensitive electrochemical sensor that is successfully used to determine serum uric acid in real human specimens [13]. It should not be forgotten that not all patients with hyperuricemia develop gout. The demonstration of Monosodium Urate (MSU) crystals in synovial fluid or tophus aspirates is necessary to diagnose patients with gout to our current knowledge [14]. New classification criteria for gout have a good sensitivity of over 80% in the detection of the early disease [15]. These criteria set are based on a scoring-system and include ultrasound findings due to widespread use of ultrasound. Also, Dual-Energy Computed Tomography (DECT) has improving evidence in detecting MSU crystals in early phases [16]. Early clinical examination, a look for tophi on physical examination, screening MSU crystals, and/or double contour signs with imaging methods may provide early detection in those patients with suspected genetic defects and/or family history.

The main step in preventing gout attacks is the management of the disease. Comprehensive lifestyle changes include a low-purine diet, weight loss, restrictive consumption of alcohol and sweetened beverages, and regular exercise programs [17]. Urate lowering therapy is still the cornerstone of preventing recurrent gout attacks in which serum uric acid levels are uncontrolled. Concomitant anti-inflammatory prophylaxis with colchicine is strongly recommended for at least 3-6 months when initiating urate-lowering therapy [18].

Although there is still no clear data about the frequency and relationship of MEFV mutations in gout patients with amyloidosis due to a rare occurrence, MEFV gene mutations could be checked in such cases due to the unfavorable course of gout and the relatively short disease duration. Regular use of colchicine for longer than the recommended time may change the course of the disease in poorly controlled resistant gout cases. Nevertheless controlling the gout attacks and the underlying inflammation is still the most important policy to prevent secondary amyloidosis in patients with gout disease.

DECLARATIONS

Conflicts of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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