On the history of gout: paleopathological evidence from the Medici family of Florence

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Abstract

Objective

Throughout history, gout has been referred to as the "disease of the kings", and has been clearly associated with the lifestyle of the aristocratic social classes. According to the written sources, several members of the famous Medici family of Florence suffered from an arthritic disease that contemporary physicians called "gout".

A paleopathological study carried out on the skeletal remains of some members of the family, exhumed from their tombs in the Church of San Lorenzo in Florence, offered a unique opportunity to directly investigate the evidence of the arthritic diseases affecting this elite group.

Methods

The skeletal remains of several members of the family were examined macroscopically and submitted to x-ray investigation.

Results

The results of the study allowed us to ascertain that the so-called "gout of the Medici" should be considered the clinical manifestation of three different joint conditions: diffuse idiopathic skeletal hyperostosis, rheumatoid arthritis and uratic gout. In particular, uric acid gout was diagnosed in the Grand Duke Ferdinand I (1549-1609). Recently, a new case of this disease was diagnosed in Anton Francesco Maria (1618–1659), a probable illegitimate member of the family.

Conclusion

With this new case, uratic gout was observed in 2 out of 9 adult males, leading to suppose that the disease should have been a common health problem within the family. The aetiology of the disease has to be searched in environmental factors, since both historical and paleonutritional studies demonstrated that the diet of this aristocratic court was rich in meat and wine.

Key words

gout, Renaissance, Florence, Medici

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Gout through history

Gout has been a well recognised disease since Graeco-Roman times, although confusion with other pathological conditions of rheumatic origin was probably common. The first clinical description of gout is attributed to Hippocrates (5-4th century BC), who named the affliction in the big toe with the term *podagra*, from *pous* "foot" and *agra* "hunt, catch", on the basis of the classic localisation of the illness rather than on its aetiology. The father of medicine regarded gout as being the result of an excessive accumulation of one of the bodily humours, probably phlegm, which painfully distended the affected joint (1). In Roman medicine the Hippocratic theory largely prevailed; the disease was in fact indicated with the Latin word *gutta* "drop", which refers to the aetiology of gout, as caused by bad humours entering the affected joint, drop by drop (1). During the Medieval and Early Modern Age the beliefs on the humoral causes of the disease remained unchanged.

The word gout was first attested in the 13th century: it was used by the Dominican monk Randolphus of Bocking (1197–1258), who perpetrated the confusion between gout and other arthritic diseases: *gutta quam podagram vel artriticam vocant* "the gout that is called podagra or arthritis" (2). The distinction between gout and rheumatism was introduced later, in the 17th century, by Thomas Sydenham (1624–1686), who was himself attacked by gout and renal disease (3).

Throughout the centuries gout has been associated with a rich diet, in particular in meat, and with alcohol consumption, and has been referred to as the "disease of the kings", being clearly associated with the lifestyle of aristocratic social classes. Furthermore, gout has been considered primarily a male disease (2).

The paleopathological study of the members of the Medici family, exhumed from their tombs in the church of San Lorenzo in Florence, offered a unique opportunity to directly study the evidence of the arthritic diseases affecting this elite group of Renaissance and Early Modern Age Florence (4). As a matter of fact, according to the historical records, several members of the Medici family are claimed to have been affected by a disease that contemporary physicians called "gout", but only a paleopathological study can clarify the true nature of this nosological entity.

Gout and the Medici family: historical and paleopathological evidence

The Medici of Florence were one of the most important and powerful families of the Italian Renaissance history; from a fortunate commercial and banking activity, they built a lasting social power and political prominence, initially in Florence, but later in entire Tuscany. The Medici were patrons of several great artists of the period, promoting the art and the sciences.

The clinical vicissitudes of the members of the family are well known from the extremely rich archives, also including the reports of the ambassadors and court physicians (5). According to the written records, several personages suffered from arthritic diseases, constantly named gout, whose symptomatology includes violent pain in the shoulders, hands, knees, feet, and thoracic-lumbar spine (5). Early in the 15th century the nickname "the gouty" was attributed to Piero (1416-1469); gout was reported in the clinical history of several personages, all of male sex, including Cosimo I (1519–1574), Ferdinando I (1549–1609), Cardinal Carlo (1596–1666), Prince Lorenzo (1599–1648), Cosimo II (1590–1621), Cardinal Giovanni Carlo (1611–1663), Prince Mattias (1613-1667), Cardinals Leopoldo (1617–1675) and Francesco Maria (1660–1711) (5). Still in the 17th century Gastone of Orléans (1608–1660), son of Maria de' Medici, Queen of France, said to the Tuscan Resident in Paris: "I come from the Medici House, and I am honored, despite the podagra which I took from it" (5), indicating that gout or arthritis was considered an unavoidable problem connected to the family.

The burials of 24 members of the family were explored during the "Medici Project", a multidisciplinary archaeological, anthropological and paleopathological investigation of the funer-

ary depositions of the Medici Grand Dukes and of their relatives (4). Cosimo I, Ferdinando I and Cardinal Carlo are among the personages who in the written sources are claimed to have been affected by gout; they were exhumed, and their skeletal remains were submitted to a paleopathological study, which clarified the nature of their diseases (6).

In Cosimo I gout was to be identified with degenerative osteoarthritis, as no traces of true gout or of other rheumatic diseases were found, except for diffuse idiopathic skeletal hyperostosis (DISH) (7).

Ferdinando I suffered from true gout, as demonstrated by a typical osteoarchaeological seen at the interphalangeal joint of the big left toe. Furthermore, gout was associated with DISH, in a more advanced stage than that observed in his father Cosimo, since more vertebral elements were involved (7). Accurate examination of the skeletal remains of Cardinal Carlo Carlo revealed that he had suffered from a severe ankylosing disease, diagnosed as an advanced case of rheumatoid arthritis (8, 9).

Features compatible with rheumatoid arthritis were also observed in Cosimo the Elder (1389–1464) in a previous paleopathological study carried out at the half of the 20th century by Costa and Weber (10). Finally, examination of the son of Cosimo the Elder, Piero, surnamed "the Gouty", revealed another probable case of rheumatoid arthritis in advanced stage, with features very similar to those observed in Cardinal Carlo (10).

A new case of true gout: Anton Francesco Maria (1618-1659)

Recent restauration works at the Medici Chapels in the Church of San Lorenzo in Florence have brought to light a new burial. The tomb belonged to Anton Francesco Maria (1618–1659), as reported on the coffin inscription, son of Antonio de' Medici (1576–1621) and Artemisia Tozzi (?-1643). He was probably an illegitimate member of the Medici family, as the true lineage of Anton Francesco Maria's father, hidden by the intrigues and plots of the

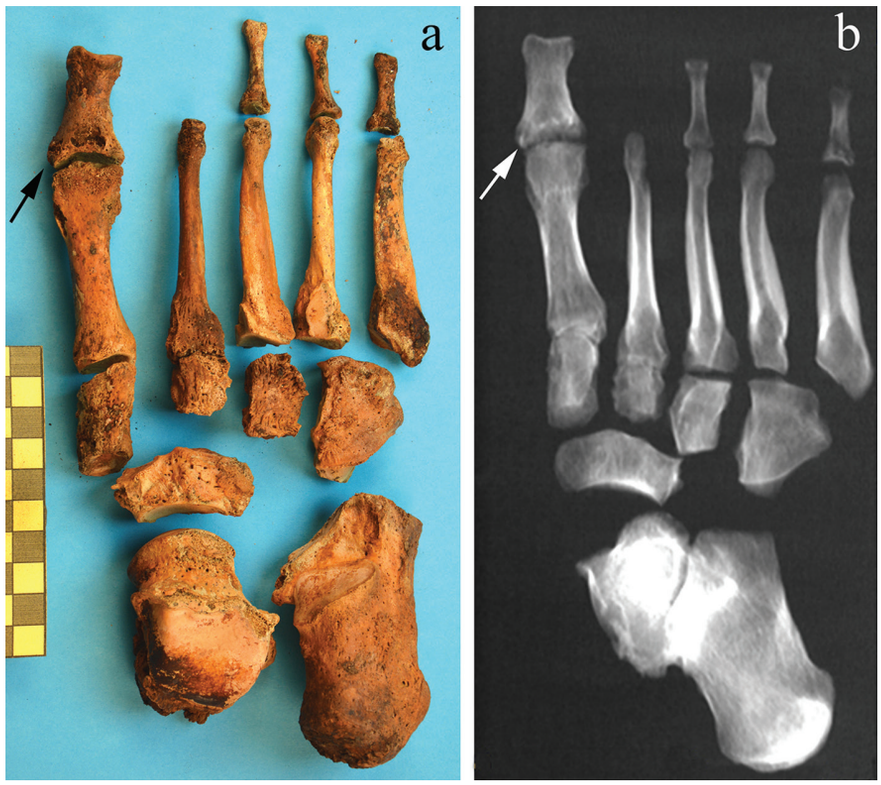

Fig. 1. The gout of Anton Francesco Maria: **a**) right foot with lesion at the level of the metatarsophalangeal joint of the hallux (arrow); **b**) x-ray of the right foot, showing sclerotic margins of both the bones of the joint (arrow).

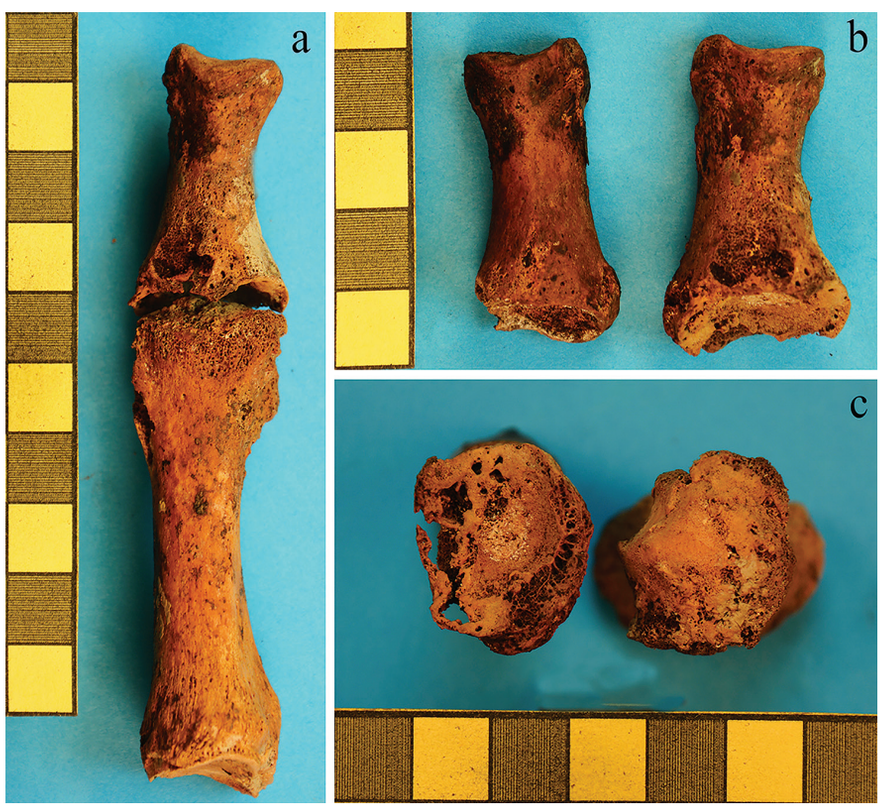

Fig. 2. Detail of the lesion of Anton Francesco Maria: **a**) the right hallux; **b**) right and left proximal phalanx of the halluces: the left one is normal; **c**) articular surfaces of the metatarsophalangeal joint of the right hallux with partial destruction of the sub-chondral plate.

Fig. 3. The gout of Ferdinando I: **a**) left foot with lesion at the level of the interphalangeal joint of the big toe; **b**) x-ray of the left big toe, showing sclerotic margins of both the bones of the joint; **c**) articular surfaces of the interphalangeal joint with partial destruction of the subchondral plate.

palace, has indeed never been clarified. Antonio was the only son of the Granduke Francesco I (1541–1587) and his second wife Bianca Cappello (1548–1587). Francesco, still married to his first wife Giovanna of Austria (1547–1578), fell in love with the beautiful Bianca engaging himself in an illegal relationship. Antonio was born in 1618, but rumours indicated him as having been adopted by the couple. When Giovanna died, Francesco could finally marry Bianca (5), but Antonio, opposed by the Medici family, was excluded from the succession. He was always kept in the shade by his uncle, the Grand Duke Ferdinando I (1549–1587), who forced him to give up all claims on the legacy of his father. After having been appointed Prior of the Knights of Malta in 1594, Antonio had five sons: two illegitimate daughters and three sons from Artemisia Tozzi: Paolo (1616–1656), Giulio (1617–1670) and Anton Francesco Maria (11).

Only a few records about the life of Anton Francesco Maria are known. After the death of his father, he was educated at the court of the Medici, while his mother Artemisia was confined in the Florentine monastery of San Clemente. Anton Francesco Maria cultivated humanistic and literary studies in Pisa. Initially buried in the Sagrestia Nuova, he was later translated among the members of his family in the Medici Chapels, where he was found in 2013 (12).

The opening of the tomb of Anton Francesco Maria revealed the skeletonised remains of an adult male with a high stature over 185 cm. The craniotomy of the skull and the cuts of the ribs demonstrate that autopsy, a current practice reserved to the aristocracy to allow embalming of the corpse, was carried out (13). The skeleton of Anton Francesco Maria shows a peculiar lesion in the right foot (Fig. 1). The base of the first phalanx presents several erosions and cavitations, mainly in correspondence of the superior margin (Fig. 2). These cavitations range from 1.5 to 18.3 mm; the largest one is the result of several confluent defects, and the major erosion has a raised margin. The distal articular surface is normal. The head of the first metatarsal appears irregular for the presence of erosions and of cavitations. Fusion of the second cuneiform with the proximal epiphysis of the second metatarsal is also observed. The other bones of the right foot are affected by degenerative joint disease. In the left foot, besides arthritic changes, erosions affect the calcaneus, the scaphoid and the base of the fifth metatarsal. The first cuneiform is fused with the proximal epiphysis of the first metatarsal, also showing erosions and cavitations.

Discussion

Gout is currently the most common inflammatory rheumatic disease in the Western world; it is characterised by elevated uric acid levels in serum, deposition of uric acid crystals in the joint, and acute inflammatory arthritis (14). Chronic gout is characterised by poly-articular arthritis and articular and extra-articular deposits of monosodium urate, called tophi. The most common affected joint is the metatarso-phalangeal joint of the hallux; other frequent locations are, in addition to the feet, hands, wrists, elbows and knees (15). In the pathogenesis of gout both diet and genetic factors play a role. Environmental factors, in particular diet, are clearly involved, and are related to the consumption of alcohol, meat, and seafood (16-17). Recent studies have evidenced that inheritance also plays a part; genes SLC2A9, SLC22A12 and ABCG2 have been found to be commonly associated with gout (18).

In skeletal remains, the crystal deposits are generally lost, and the diagnosis of gout depends on the localisation and on

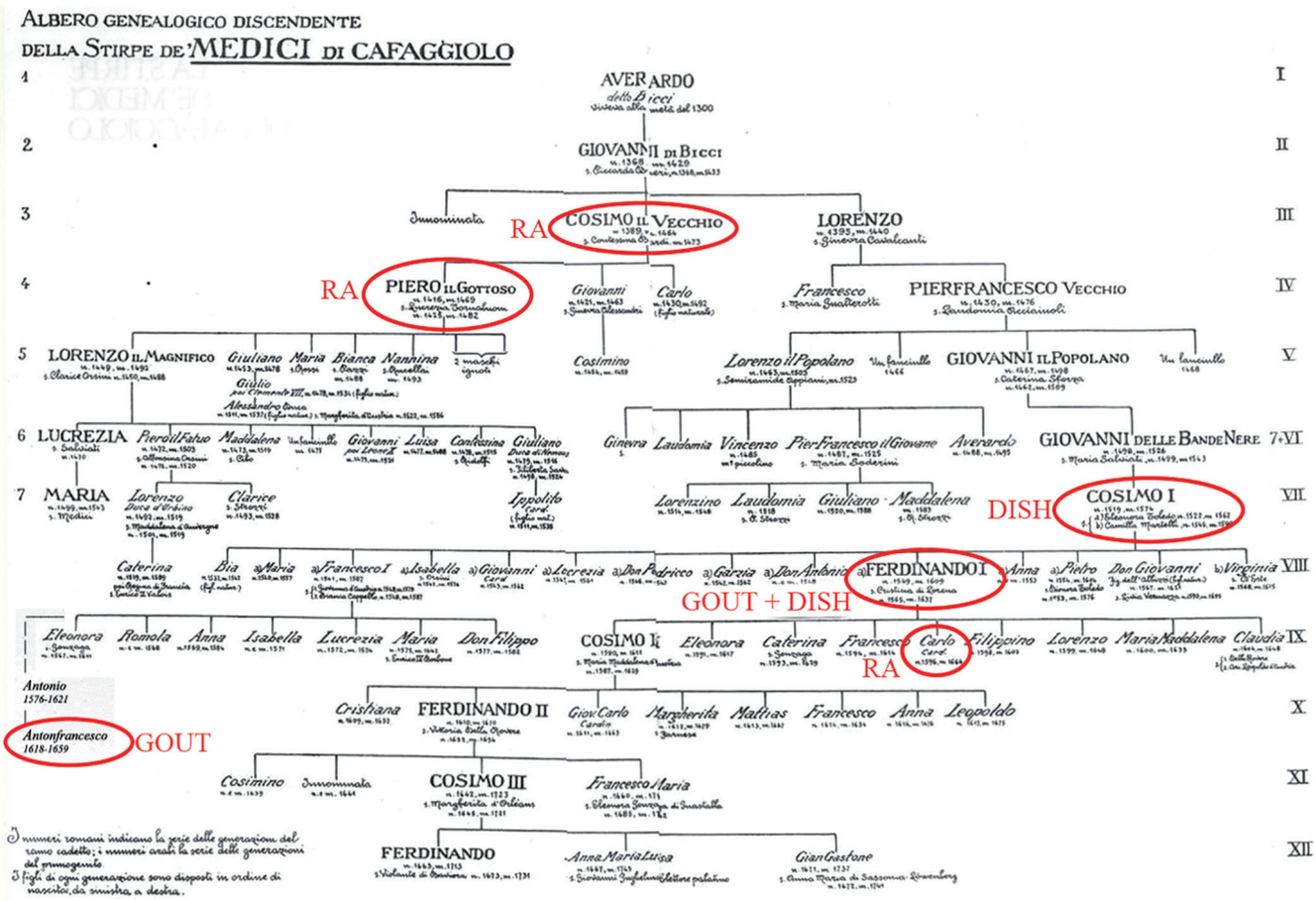

Fig. 4. The genealogic tree of the Medici family. The personages affected by rheumatic diseases are encircled in red.

the features of the bone lesions typical of gout. The para-articular tophi pressure produces erosions on the articular surface or at its margins or even at a distance from the joint, and affects both the bones of the involved joint. These scooped-out defects are asymmetrical and, despite they penetrate into the bone, they remain separated from the marrow cavity by a thin layer of bone. A proliferative reaction can produce hook-shaped projections at the margins of the lesion, known as Martel's hook sign (19). On x-ray examination, a sclerotic margin around the lesion and the overhanging edges are the most commonly observed features (20-21).

Gout seems to be underestimated in osteoarchaeological remains in comparison to what is expected especially from the Modern Age, when the disease was common. Although the skeletal features may result in a confident diagnosis, they are likely to remain unobserved, as the aetiology of lytic lesions is probably not recognised after the removal of urate crystal by groundwater. Therefore, only a few cases of gout are reported in paleopathological literature (22-26).

Despite the Arno flooding of 1966, the skeletal remains of the Medici were in excellent state of preservation, allowing to observe the characteristic lesions of gout. Anton Francesco Maria showed a defect typically localised at the metatarsofalangeal joint of the hallux; in particular, the raised margin of the major erosion presented Martel's hook sign, pathognomonic of gout (19). Therefore, he was affected by a severe form of chronic gout in his right foot.

This finding is of particular interest, not only because there is very little evidence of this rheumatic disease in paleopathology, but also because the macroscopical and radiological aspect of the lesions of Anton Francesco Maria is very similar to that observed in his putative uncle Ferdinando. The allux is classically involved in both cases and the features of the lesion are similar. In fact, the interphalangeal joint of the big toe of Ferdinando presented cavitations, erosions and osteophytic margins, with a "scooped-out" defect at the peri-articular and articular surface of the joint and partial destruction of the sub-chondral plate (7) (Fig. 3).

Up until now, the adult members of the family submitted to paleopathological investigation have been 11, of whom 7 were males; to these Cosimo the Elder and his son Piero "The Gouty", exhamined previously by Costa and Weber (10), can be added. The paleopathological study demonstrated that 4 cases diagnosed by court physicians as gout were not true gout: in fact, Cosimo the Elder, Piero and Cardinal Carlo were affected by rheumatoid arthritis, whereas Cosimo showed the features of DISH. In total, 2 out of 9 male individuals of adult age presented paleopathological evidence of uratic gout, Ferdinando, who was also affected by DISH, and Anton Francesco Maria (Fig. 4).

Therefore, the new case of gout diagnosed in Anton Francesco Maria sug-

gests that the disease should have been common in the family. Its aetiology has to be searched in environmental factors. According to the historical data, the Italian Renaissance diet of the upper classes was largely based on wine and meat, and occasionally enriched with eggs and cheese and, on penitential occasions, by fish. The consumption of vegetables was scarce, and fruit was almost totally absent from alimentation (27). The paleonutritional study performed on the skeletal samples of the Medici members, showed high $\delta^{15}N$ values at the level of the carnivores, confirming a diet very rich in meat. The consumption of fish, revealed by the $\delta^{13}C$ values, attested a 14–30% intake of marine proteins (28). Therefore, both the historical and paleonutritional data demonstrate that the diet of the Medici family could have exposed its members to the risk of developing uratic gout, further supporting the evidence that it was a "disease of the kings". In particular, the present study highlights the environmental origin of gout in the Medici family. Although a probably illegitimate member of the family, Anton Francesco Maria enjoyed the lifestyle and privileges of the court, and was thus exposed to the same risk factors. As to the genetic predisposition, up until now no molecular investigations concerning gout have been carried out on ancient skeletal remains. The most modern advances in paleopathology may find evidence of gout in the future and demonstrate a genetic basis among the members of the Medici family.

Conclusions

According to paleopathological data, the so-called "gout of the Medici" mentioned recurrently in the clinical history of several personages of the family could be considered the manifestation of three different and rather common joint diseases: DISH, rheumatoid arthritis and uratic gout. DISH was diagnosed in Cosimo I and Ferdinando I; rheumatoid arthritis in Cosimo the Elder, Piero "the Gouty" and Cardinal Carlo; uric acid gout in Ferdinando I and Anton Francesco Maria. In the absence of a paleopathological study, the nature of the arthropathy reported in the clinical history of Cosimo II, Prince Lorenzo, Antonio, Cardinal Giovanni Carlo, Prince Mattias and cardinals Leopoldo and Francesco Maria remains unclear.

The new case of true gout observed in Anton Francesco Maria supports the evidence that it should have been a common disease within the family and that it was a "disease of the kings". The risk factors predisposing to uratic gout in this elite group of the Renaissance and Early Modern Age were linked to a diet rich in proteins and wine. Genetic factors are also likely to have played a role in uratic gout, although the disease has not yet been investigated in paleopathology with a molecular approach.

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