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Dental developmental defects due to mercurial treatment in a child from Late Middle Age Getap (Armenia)*

• Anahit Yu. Khudaverdyan, Husik A. Melkonyan, Inessa A. Karapetyan, Hasmik Z. Margaryan •

Institute of Archaeology and Ethnography, National Academy of Science, Republic of Armenia

Address for correspondence:

Anahit Yu. Khudaverdyan
Institute of Archaeology and Ethnography, National Academy of Science, Republic of Armenia
E-mail: ankhudaverdyan@gmail.com

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Abstract

The morphology of teeth can vary due to genetic factors, infectious diseases and other environmental stresses. In the past, treatment of congenital syphilis with mercury also interrupted dental processes. This resulted in very different dental characteristics. An incomplete skeleton of a 3–4-year-old child with suspected congenital syphilis was found in the Getap Monument in Armenia. One child had remarkable dental anomalies due to mercury treatment. The left 1st and 2nd molars (not erupted) are consistent with Hutchinson's descriptions and illustrations of the types of abnormalities that can result from mercury treatments. The case presented provides evidence of some of the highest levels of mercury recorded in osteoarcheological remains to date, making the individual the youngest patient documented in the palaeopathological literature to show signs of mercury treatment.

Keywords: Armenia; Late Middle Age; Getap; congenital syphilis

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Introduction

There are three human treponemal diseases that can cause skeletal lesions: syphilis, bejel and yaws (1, 2). Unsuccessful attempts to detect treponemal aDNA (3, 4, 5, 6) and shaken assumptions about genetic relationships (7, 8, 9, 10, 11) highlight the value of a macroscopic approach to identifying treponematoses in ancient skeletal material. Treponema pallidum subsp. pallidum is thought to be the only treponeme that causes congenital infection in the unborn child (12, 13, 14, 15, 16). Several systems are affected in the neonate. The pathology occurs in two stages. Early skeletal manifestations include periosteal reactions, osteochondritis and osteomyelitis (17), while late signs may include frontal bossing, short maxilla, high palatal arch, saddle nose, Higoumenakis sign, diaphysitis, metaphysitis and sabre toe (18, 19). The disruption of tooth formation (odontogenesis) is the best-known aspect of the disease. The characteristic dental signs of congenital syphilis are seen in the permanent teeth (upper central incisors, canines and first molars) which erupt at around 6-8 years of age; the dental abnormalities in these teeth are produced in the early stages of the disease, when infection and fever occur around the time of birth and affect the initial crown formation. Many people with congenital syphilis did not reach adulthood. The effect of syphilis on the developing foetus often results in miscarriage or severe fetal impairment, leading to increased mortality early in life (i.e. before the child has a chance to develop permanent teeth).

The palaeopathological evidence of congenital syphilis is of great importance: It leads to the inescapable conclusion that venereal syphilis must have been present in the archaeological sample examined (20, 21). In clinical practice, cranial or postcranial changes are known to occur (22, 23, 24). However, these symptoms are too non-specific to identify congenital syphilis in an archaeological setting (25, 26). Furthermore, bony lesions such as metaphysitis often heal without evidence of palaeopathology (17, 27). The importance of dental lesions in the diagnosis of congenital syphilis lies in their (partly) pathognomonic nature (28), their relation to dental development (29) and the general durability of enamel compared to bone (30, 31). With regard to congenital syphilis, four dental manifestations derived from clinical practice (32-38) have been identified in an archaeological setting (39-42). Permanent upper central incisors shaped like a screwdriver or barrel with a central incisal notch are called Hutchinson's incisors (43-46). Fournier's molars (or mulberry molars) are permanent first molars with hypoplastic cusps (47). This feature has often been confused with the moon or bud molar, which has crowded cusps giving a dome-shaped appearance (48-50, 22). Permanent canines may have a fang-like appearance with a circumferential groove in the occlusal third of the crown (47, 51).

Mercury was used for medicinal purposes in China in the 27th century BC (52). Mercury and its compounds were most commonly used to treat syphilis (47, 53-55, 52, 56, 57). The Persian physician Abu Ali al Hussein is thought to have used mercury to treat syphilis in the 11th century (58). It was recognised as a form of treatment for venereal disease before the introduction of salvarsan (59, 60) and penicillin in the 20th century (61).

Mercury caused widespread severe enamel hypoplasia not only in first molars but also in incisors and some canines (54). These were caused by disturbed amelogenesis, resulting in deep irregular pits and irregular enamel with exposed dentin. Throughout Europe, mercuric compounds were administered in various forms, including tablets, ointments, vapours and intramuscular injections. Mercuric treatments contained from 1 to 20 grains (1 grain equals 64798.9 µg) of solution (55). This is significantly higher than the tolerable weekly intake of methylmercury established in 2004, which is 1.6 µg per kilogram of body weight for children and pregnant mothers (to protect the foetus), and double that (3.2 µg per kilogram of body weight) for adults (62). The large amounts of mercury administered would be expected to disrupt odontogenesis and amelogenesis in children. The dental defects observed in these individuals do not resemble those caused by other infectious diseases, genetic conditions, vitamin deficiencies or elemental toxicities (63-67, 68, 26, 69-73).

The purpose of this case study is to report on a skeleton from Getap (Armenia) that exhibits a pattern of dental and cranial malformations that may be caused by congenital syphilis. The lesions are discussed and compared with clinical and palaeopathological evidence.

Material and methods

In autumn 2007 the expedition of the Institute of Archaeology and Ethnography, National Academy of Sciences, Republic of Armenia started excavations at the Getap Monument (expedition leader H.A. Melkonyan, archaeologists I.A. Karapetyan, H.Z. Margaryan, etc.). Getap is a village in the Yeghegnadzor

Municipality of Vayots Dzor Province in Armenia (Figure 1). It is located about 1-2 kilometres west of the provincial centre, along the lower reaches of the Yeghegis River. The Getap fortress and cemetery is located 1.5 km north of the village, on the right bank of the Yeghegis River, on a hill with abrupt slopes and an egg-shaped peak, 50 m high. The fortress or citadel occupies an area of 2050 m2 along the summit, outside which is the settlement (about 2 ha). So far, no traces of the settlement wall have been found at the foot of the hill, because in the Soviet period the neighbouring territory was turned into farmland and gardens. Sixteen graves were discovered. Most of them were dug into the ground, while for others parts of the old walls were used, with the addition of one-row sections. The deceased, of various ages, were buried on their backs, in a stretched position, with their hands on their chests, their heads to the west and their faces to the east (towards the house of prayer). The burials are Christian, mostly single and in one case double. Very few objects were found to accompany the deceased, only a few carnelian beads and a copper earring. A ruined tomb with a silver coin of the Hulaguid ruler Abu-Said (1317 - 1335) had already been discovered during the survey of the site in 2006 and the study of the archaeological levels (74). This helps us to date the burials more accurately and to conclude that they belong to a relatively late period (Late Middle Ages), when the fortress had lost its importance and had been abandoned. The child in this study (burial 1) was part of a sample of 9 individuals.

Bone remains and dentition were examined using standard macroscopic methods. Most of the skeletal remains are in a poor state of preservation (Figure 2). Surface erosion and some post-depositional fractures are present on the bones. Based on tooth eruption (75), the individual was approximately 3-4 years old. The sex of the individual is unknown.

Papers describing dental abnormalities in congenital syphilis and mercurial treatments were reviewed (76). The lesions were compared with the macroscopic and radiological diagnostic criteria of treponemal disease (see 1, 2, 26). There have been numerous descriptions of dental signs (51) in an attempt to establish a standardised method for determining dental signs of disease that would aid in the diagnosis of syphilis. Hillson et al (28) developed a standardised method which is now widely used. Known changes in the permanent dentition associated with congenital syphilis include (1) Hutchinson's incisors, affecting mainly the permanent upper central incisors and occasionally some lower incisors, (2) Moon's molars, (3) Fourier's molars with a defect that cuts into the base of the cup, and (4) canines with a groove-like defect around the apex of the crown (28). Dental changes are important in archaeological and palaeopathological collections because enamel does not change. Signs that are by definition characteristic of a disease (pathognomonic) cannot occur as a result of other diseases, so their presence alone provides a reliable diagnosis.

The inclusion of the effects of mercury as a diagnostic method is very important to paleopathologists as it may add further diagnostic features to the disease. Dental abnormalities associated with congenital syphilis may occur as (1) a sign of the disease alone, (2) a sign of the treatment alone, or (3) a combination of the two (77). Molars affected by mercury show enamel defects on the occlusal surface and appear to varying degrees rough, pitted and soiled (54). In some cases, dentin is observed with multiple discoloured nodules or spines (74). The entire occlusal surface may be affected or affected in patches. All of these abnormalities caused by congenital syphilis and its treatments should be considered in the diagnosis of the disease, as they are not present in any other disease.

Diagnostic features of syphilis also include 'caries sicca', sclerosis and pitting of the outer table of the skull resulting from the accumulation of stellate scars (26), giving a 'worm-eaten' appearance (78), tibial bowing known as 'sabre shin' (26), and expansion of the long bones with nodules with superficial cavitation (78). The specimen was examined by macroscopic examination. X-ray (Portable Digital X-ray Radiography System) was used at the Institute of Archaeology and Ethnography of NAS RA to assess the condition of the skeleton.

Results

Skeleton 1-1 belongs to a child aged 3-4 years. The deciduous teeth showed no evidence of abnormal enamel formation (Figure 2). The permanent dentition showed pathological changes. The individual has dental signs that fall within the wide range of dental abnormalities seen in individuals with congenital syphilis. Note the fracture of the thin and unprotected dentin of the upper left first and second molars (not erupted) (Figure 3). The occlusal surface of the teeth has an irregular appearance. It feels as if the occlusal surface of the molars (with many thin spikes) has been broken into many pieces.

Figure 1. Location map of the Getap cemetery. Getap monument.

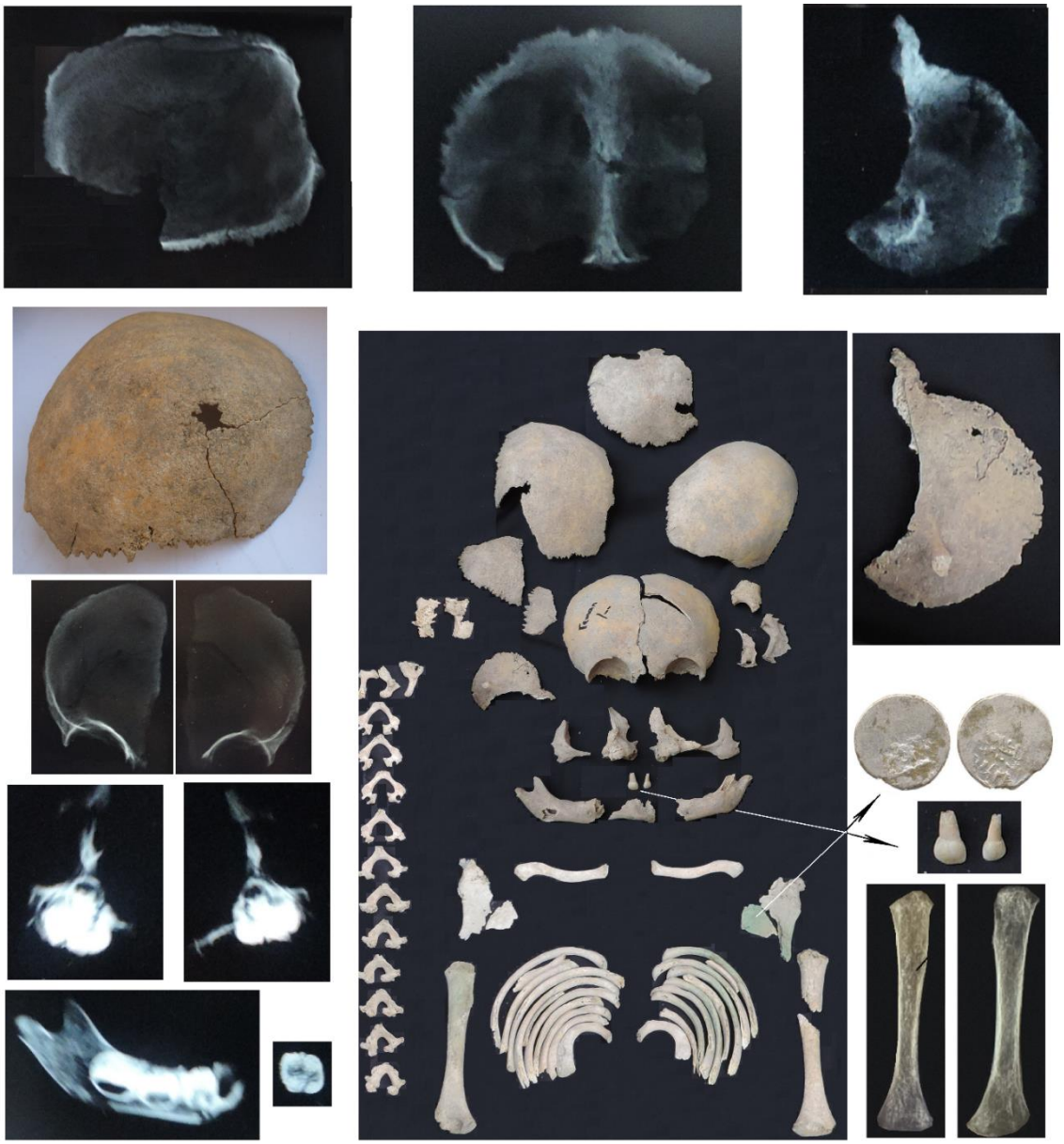

Figure 2. The preservation of a child skeleton from Getap.

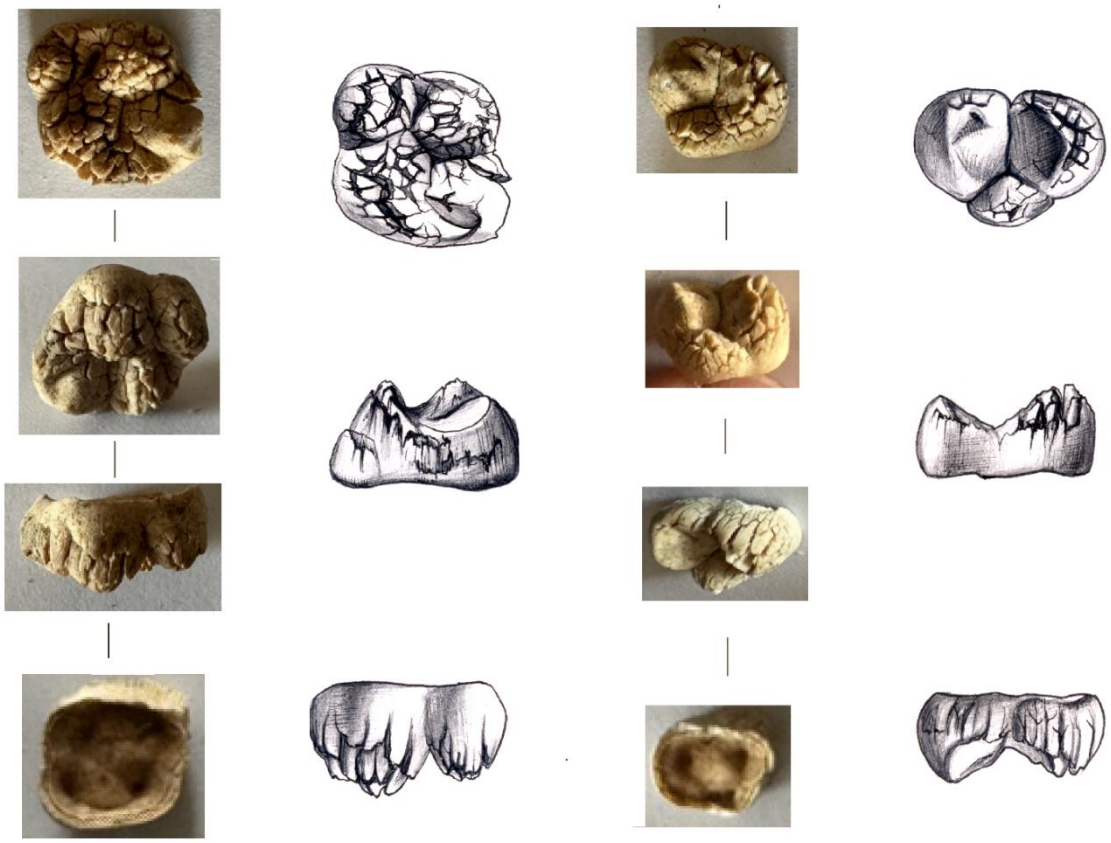

Figure 3. The upper left first and second molars (not erupted). The occlusal surface of the molars (with multiple thin spikes) has been split into many pieces.

This malformation of the occlusal surface does not occur in any other disease and is therefore considered pathognomonic for congenital syphilis. The left 1st and 2nd molars (not erupted) are consistent with Hutchinson's descriptions and illustrations of the types of abnormalities that can result from mercury treatments. Dental defects associated with congenital syphilis show greater variation than is generally known. Another characteristic of the molars is that they have multiple spines, which are fragile and easily broken.

The skull vault on the parietal, temporal and occipital bones shows several possible osteolytic lesions in the form of circumvallate depressions with fine scar lines radiating within the shallow depressions (Figure 2). A radiograph of the cranial bones shows several lucent areas of surrounding sclerotic bone. The fine superficial pitting on the surface of these lesions may be secondary to post-mortem erosion.

Mild cribra orbitalia was observed on the orbital roofs, but these lesions are unlikely to be related to infection. There is no evidence of pathology in the cervical, thoracic or lumbar vertebrae, clavicles, ribs, scapulae or humerus. The remaining bones were lost post-mortem (see Figure 2).

Discussion

The excavations of the Getap fortress show that it was founded in the Urartian period, continued to exist in the ancient Armenian period and then, after a long interval, was inhabited for a short period (12th-13th centuries). In the 13th-14th centuries it was abandoned and used as a cemetery. The material culture of the Getap Fortress is mainly represented by a rich assortment of Urartian, post-Urartian (ancient and medieval Armenian) pottery, found both on the surface and during excavations. Along with the Urartian pottery, fragments of ancient

Armenian pots with fine rims, polished jars, basins, bowls, jugs and millstones with levers have been discovered. Medieval culture is represented by more or less typical pottery and funeral ornaments (74). The Getap sample is characterised by the presence of pathological changes often associated with stressful episodes, such as anaemia, malnutrition, infectious diseases and the presence of parasites (data not yet published). The Getap child had severe mercury poisoning, suggesting prolonged exposure in early childhood. This child's dental defects could be partially interpreted as the result of congenital syphilis. Crowning of the first permanent molar is known to begin around birth, with completion at 2 1/2 to 3 years of age. Crowning of the second permanent molars occurs between 3 and 7 years of age (79). Therefore, any insult, either syphilitic fever or treatment with mercury, during initial crown formation would have a detrimental effect on the development of the occlusal surface. The case presented here illustrates how dental defects associated with congenital syphilis can vary. The idea that only the first permanent molars can be affected by mercury is contradicted by our data. The second permanent molar is also affected by mercury.

Congenital syphilis results from transplacental infection with the spirochete Treponema pallidum subspecies pallidum when an infected woman becomes pregnant or a pregnant woman becomes infected during pregnancy. It is important to stress that congenital treponematosis of any kind is rare. A woman must usually become infected around the time of her first pregnancy for transplacental transmission to occur. Transmission is much less likely once syphilis has reached the chronic stage, although it can occur if the woman is immunologically compromised for any reason, but this is probably even rarer. Although there are controversial reports on fetal morbidity and mortality, approximately 50% of cases result in in utero death, premature birth, stillbirth or death shortly after birth (26). The early death of 50% of infected infants means that congenital syphilis is rarely diagnosed in skeletons (80). Therefore, the number of congenital syphilis diagnoses made from pre-Columbian skeletons in the New and Old Worlds is very small. Both were from the New World. The first was found in Virginia (1, 26) and the second in Peru (Machu Picchu Candeleria cave, circa 1100-1200 AD; 81). Studies show that cases of congenital syphilis have also been discovered in the Old World. These include a 7-month-old foetal skeleton found at Costebelle in southern France (300-500 AD) (82) and two individuals aged 15-19 years found at the ancient Greek colony of Metaponto (580-250 BC) in southern Italy (83). The skeleton of an approximately 15-year-old child from the late Byzantine period (13th century AD) in Nicaea (Anatolia) also shows symptoms common to the majority of people with congenital syphilis (40).

Macroscopic analysis of the skeletal remains from Tigranakert (jar burial no. 6, year 2018, individual 2) also revealed a case of syphilis. The characteristics of the lesions are consistent with the diagnosis of venereal syphilis. The lesions observed are of the non-gummatous type. Affected bones are thickened due to periosteal new bone formation (lower leg bones) (data not yet published A.Yu. Khudaverdyan).

The arguments, based on data ranging from biblical references to ancient sources and from linguistic evidence to rumours and myths that continue to this day, gained momentum in the 20th century and focused on the origin of treponemal diseases, especially syphilis, and the possibility of their existence in the Old World before 1493 (84, 85, 40). Paleopathological and epidemiological studies of many skeletons with good specimens that leave no doubt about the diagnoses prove that treponemal diseases were present in the New World before Columbus (e.g. 86, 1). In contrast to the New World, specimens proving the existence of treponemal diseases in the Old World are rare (83, 82, 87, 40).

Human odontogenesis is regulated by genetic factors, but also depends on interactions with pathogens and the quality of the nutritional and physical environment. The tooth crown is formed by amelogenesis, which has two stages: the secretory stage and the maturation stage. Disruption of enamel matrix formation tends to result in hypoplastic defects such as pits, grooves and thin or even absent enamel (88). Their appearance on the crown surface depends on the stage of tooth development affected and the duration of the insult. The location of the defect on the enamel is a good indication of the approximate time of the insult (88). Congenital syphilis is known to disrupt tooth and enamel formation, resulting in specific dental characteristics. Hutchinson (45, 55), Moon (89) and Fournier (47) described specific dental characteristics (notched incisors, domed molars and nodular molars) that they observed in individuals with congenital syphilis in the 19th century. However, variations in these features can occur, resulting in dental signs that are "not

typical" of the disease (54). Because enamel does not re-form, dental changes are important in archaeological and palaeopathological collections. Mercury caused widespread severe enamel hypoplasia not only in the first permanent molars but also in the incisors and in some cases in the canines (54). These changes were the result of disturbed amelogenesis, producing deep irregular pits and irregular enamel with areas of exposed dentin. The dental abnormalities caused by mercury were so different from those caused by congenital syphilis itself that Hutchinson (54) and later Moon (89) considered them worthy of documentation. However, the effects of treatment, the 'mercurial' changes, have not been used as a diagnostic method in paleopathological diagnosis until recently (76, 90, 77). The new approach of using dental defects caused by congenital syphilis and its treatments together as criteria of differential diagnosis can now be applied to evaluate the oldest paleopathological cases suggested in the literature as those of congenital syphilis.

Dental and cranial abnormalities are essential in the differential diagnosis. The gingival and non-gingival lesions of treponemal diseases, as described by Ortner (26), are mainly observed in skeletal areas close to the skin surface, such as the skull and long bones. It is well known that in syphilis only 1/3 of patients in the tertiary stage develop bone lesions (91).

We have already noted that mercury was used in China as early as the 27th century BC (52). The use of mercury in medicine was also incorporated into Egyptian, Greek, Armenian and Arab medical practice (52, 92, 93). The Arabs used it to treat various dermatological conditions such as ulcers, pediculosis, herpes and scabies. For example, Albucasis (940-1013) practised friction with a combination of mercury and laurel oil, a very toxic mixture that often-caused ulcers in the patient's mouth (94). In 1393, Guy de Chauliac (c. 1300-1368), writing in his Grande Chirurgie, recommended the use of an ointment to treat scabies. The ointment, called 'Unguentum Saracenium' because of its Arabic origin, consisted of gum resin, wild delphinium, mercury and pig fat (95).

Mercury has been administered to mothers during pregnancy (96), to children and infants at doses of 10 grains or 648.0 mg in the form of ointments, calomel teething powder (46, 54, 97, 96) and injections (104), with adverse health effects in individuals. Mercury poisoning was noted by Sir Hutchinson (46, 54) to have a gross effect on dental development, causing abnormalities in enamel formation. The changes caused by mercury treatment were described mainly in the permanent dentition, where large amounts of enamel may be lost completely, especially on the occlusal surfaces, where "the dentine grows through and shows a number of discoloured tubercles or spines" (46, p. 53).

Mercury was administered in four ways, usually starting with a high dose for 4 to 6 weeks (98, 99):

- Mercury ointment rubbed into different parts of the body (friction).
- Mercury plasters applied every 2 or 3 days.
- Fumigation in a hot cupboard with cinnabar (crude mercury sulphide) (95). Patients were placed in an overheated room or barrel and forced to inhale vapours of heated cinnabar and metallic mercury; treatments could last from weeks to months (100).
- Oral administration, for example in the form of the so-called Barbarossa pills. These pills, containing a mixture of mercury, perfume essences and fruit flavours, were named after the Turkish admiral who gave them to his soldiers suffering from venereal syphilis in the 15th century (101).

Several factors can influence the appearance of mercurial teeth, including the dosage of mercury administered to the individual, the rate of mercury excretion, and the overall duration of treatment. In addition, the variability of dental abnormalities in congenital syphilis and in cases of congenital syphilis treated with mercury must be taken into account. These considerations suggest that the effects of mercury treatment on the teeth may vary considerably depending on a number of factors.

Although side effects can include death, mercury has been widely recommended as the main treatment for syphilis (102, 92).

Other diseases and chemicals can affect odontogenesis and amelogenesis. They should be considered in the differential diagnosis. Diseases include rickets, fluorosis and amelogenesis imperfecta. Chemicals include mercury, arsenic, potassium iodide and bismuth. Rickets is a disease caused by vitamin D deficiency that affects bone mineralisation and enamel formation. Dental abnormalities associated with this disorder include caries and enamel hypoplasia in the form of pits and linear grooves (103). Pinhasi et al (104) found no significant association between enamel abnormalities and skeletal rickets in the Broad Gate population, and the types of enamel hypoplasia seen in rickets are not comparable to Getap.

Fluorosis refers to changes in tooth enamel during tooth development caused by the ingestion of large amounts of fluoride over a long period of time. In people with dental fluorosis, the enamel may appear with opaque white bordered areas on parts or all of the tooth, depending on the severity, and/or be pitted or porous, and may be yellow or brown in colour (105). The dental signs seen in fluorosis are not seen in the child described here.

Amelogenesis imperfecta can cause enamel discolouration, delayed tooth eruption, tooth sensitivity, congenital missing teeth and enamel hypoplasia and hypoplasia (106). Dental abnormalities caused by amelogenesis imperfecta are not apparent in the cases described in this study, and syphilis and treatments containing mercury affect specific teeth, unlike amelogenesis imperfecta. Amelogenesis imperfecta is therefore excluded as a diagnosis.

In addition to its association with disease, the presence of mercury in ancient bones and teeth has been linked to mining, metallurgical practices and the consumption of contaminated food in prehistoric Spain (107-108), the use of mercury-based cosmetics in medieval Russia (109), atmospheric mercury pollution (110, 111), work in mercury mines in Mesoamerica (112), and the effects of volcanic emission treatment in post-medieval Iceland (113).

The present study reports one of the most severe paleopathological cases of mercury poisoning; moreover, the Getap child is the youngest individual with evidence of mercury treatment documented in the literature to date.

Conclusions

In this study, for the first time, an incomplete skeleton of a child (Getap, burial 1) with features of congenital syphilis was analysed.The data show that cortical porosity and dental malformations are the most prominent morphological features in syphilitic bone disease and teeth.The child has the most significant dental malformations. This is a characteristic sign associated with mercury treatments. It is possible that the child was treated soon after birth. It is plausible that a high dose of mercury was administered due to the extensive damage to the enamel of the first and second maxillary molars. In particular, clinical complications in the form of abnormalities in the development of the permanent teeth were observed only in the infant who received 10 grains or 648.0 mg of mercury (55). The child was not fully cured and later died of syphilis despite the administration of mercury. Mercury was a known treatment for syphilis in medieval Armenia (92). A major limitation of this study is that not all limb bones were preserved for examination.

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Declaration of Interest

None

Author Contributions

The study was designed and conceivedby Anahit Yu. Khudaverdyan. The fieldwork was carried out by Husik A. Melkonyan, Inessa A. Karapetyan, Hasmik Z. Margaryan. The manuscript was written by Anahit Yu. Khudaverdyan. No artificial intelligence was used in the preparation of this manuscript.

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