

Higoumenakis' sign in the diagnosis of congenital syphilis in anthropological specimens

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ABSTRACT

Higoumenakis' sign (HS) is a diagnostic criterion referring to the enlargement of the sternal end of the (right) clavicle, frequently observed in patients with late congenital syphilis. Although indexed for several years in clinical medicine textbooks, it has not been extensively applied for the diagnosis of congenital syphilis among anthropological specimens. This is highly significant, since the other major palaeopathology findings refer almost exclusively to the skull and diagnosis thus becomes difficult if only peripheral skeletal remains are available for evaluation. The potential effectiveness of the proposed use of HS as a marker of syphilis in anthropology appears adequate, since descriptions very similar to that of HS have been reported for certain findings, although no attempt has been made to correlate them with the presence of the disease. Higoumenakis himself originally observed this sign in 86% of his patients with congenital syphilis, and this report was subsequently verified by other independent researchers. His attempt to explain the pathophysiology of the sign and its localization, on the basis of anatomical, biological, and mechanical reasons, however, has been questioned. On the other hand, the application of the remaining markers of congenital syphilis is also problematic, due to sensitivity and/or specificity limitations, and other signs may not be detected due to inability to retain soft tissue samples in anthropological populations and a lack of reliable techniques for treponematous DNA amplification in such old samples. Thus, the fact that the onset of any of the signs of syphilis is not a constant finding justifies the authors' suggestion that HS should be checked for in any available anthropological specimen, because it is highly indicative of possible infection by *Treponema pallidum*.

HIGOUMENAKIS' SIGN IN THE DIAGNOSIS OF CONGENITAL SYPHILIS IN ANTHROPOLOGICAL SPECIMENS

INTRODUCTION: SYPHILIS AND CONGENITAL SYPHILIS

Syphilis is a sexually transmitted disease whose causative agent is the spirochete *Treponema pallidum*. Syphilis seems to have appeared in Europe soon after Columbus returned from America, but the origin of the disease still remains a debatable issue, as a number of authors support the concept of a Pre-Columbian presence of the disease in the Old World [1]. In addition, some European anthropological specimens have already been reported in an attempt to verify this hypothesis [2, 3]. Regardless of its exact natural history, the disease has been a major morbidity factor, with a variable clinical picture depending on whether it is acquired during an individual life or it is congenitally transferred to the foetus. The local environmental conditions, treatment availability, immunological status and the exact characteristics of the pathogen (some species are now known to actually cause completely different disease variants) may also influence the clinical outcome.

Congenital syphilis is a special form of the disease and a patient suffers from it when the mother suffered from syphilis during pregnancy and transmitted the spirochete to the foetus *in utero*. *T. pallidum* crosses the placental barrier in the maternal circulation to infect the foetus, which subsequently develops a series of signs and symptoms. These clinical manifestations may appear first during gestation, infancy, childhood, or even adult life [4] and are normally divided in early signs which include all aspects of the disease from prenatal infection to the end of the second year of life, and late congenital syphilis thereafter [5]. Congenital syphilis affects almost all the organs. Bone involvement (periostitis, cortical demineralization, osteochondritis), occurs in 60-80% of cases, a fact that makes bone lesions significant for anthropological studies. If untreated, periostitis leads to many permanent signs [5].

DIAGNOSIS OF CONGENITAL SYPHILIS IN ANTHROPOLOGY

The diagnosis of congenital syphilis in living humans is suspected based on their clinical presentation and confirmed by direct identification of treponemata in clinical specimens or by positive serologic findings. Methods available for direct identification of *T. pallidum* in lesion exudates are dark field microscopy or a direct fluorescent antibody test. Syphilis is diagnosed serologically by two types of tests: treponemal specific tests (e.g., the Treponema pallidum Hemagglutination Assay [TPHA] or Treponema pallidum Particle Agglutination Assay [TPPA] or FTA-ABS) and cardiolipin or nontreponemal-tests (e.g., Venereal Disease Research Laboratory test [VDRL], rapid plasma-reagin test [RPR]) [5-7].

In anthropological specimens (bones), diagnosis by these means is not possible. The diagnosis of congenital syphilis on bones is based on osseous evidence, making osseous signs of congenital syphilis very important for the differential diagnosis of the disease [2, 8, 9], especially when ancient treponemal DNA is considered impossible to detect in archaeological specimens [10]. Dental stigmata, such as Hutchinson's incisor and mulberry molar, are very important for the diagnosis of congenital syphilis in archaeological populations but are not always sensitive / specific enough for a definite diagnosis [2, 11]. On the other hand, if other signs are present on the bones of the remaining skeleton, this is very helpful in making the differential diagnosis in favour of congenital syphilis. In addition, this may be the only way to detect the disease if cranial and soft tissue remains are not available. Table 1 gives a brief description of congenital syphilis signs.

(Table 1 Here)

HYPOTHESIS

Our hypothesis suggests the inclusion of Higoumenakis' sign (HS) as a standard diagnostic criterion for congenital syphilis detection in anthropology, used as a

verification tool in conjunction with other markers (Table 1). We particularly emphasize this sign because it is not widely known among physicians, nor has it ever been mentioned by anthropologists as a sign indicative of congenital syphilis diagnosis in bone specimens. This sign should garner further interest in light of the recent biography of Higoumenakis that provides material supporting the hypothesis being proposed in the current paper [14, 15].

First point of evidence: Higoumenakis Sign

Higoumenakis first described the enlargement of the sternal end of the clavicle as a sign of late congenital syphilis in the late 1920s [16]. This sign's frequency among patients with congenital syphilis was 86% (170 out of 197 patients) and was noticed predominantly on the right side (157 patients), while it appeared mostly between the ages of 15 and 56 years [17, 18]. However, clavicular thickening has been noticed in other diseases as well, including sternoclavicular hyperostosis, sternoclavicular osteoarthritis, low-grade chronic osteomyelitis, condensing osteitis of the clavicle and Tietze syndrome [19].

Nevertheless, Higoumenakis gave radiological evidence of the sign and an explanation for its production, associating the side of the thickening with the preferred hand of the patient. The anatomical reason for this is that the sternal (medial) end of the clavicle is preformed out of connective tissue and ossifies between 11 and 22 years of age by a secondary ossification centre. The body of the clavicle is ossified from two primary centres, one medial and another lateral, which appear during the fifth and sixth weeks of intrauterine life. The biological reason is that *T pallidum*, carried in the blood stream of the foetus, becomes as readily localized in the connective tissues as in the lymphatic spaces and other organs of the foetus and may remain in the connective tissues and bones without manifestation in childhood. The mechanical reason is that later in life, the frequent movements of the arms during heavy work and the constant friction of the clavicle against the sternum causes

irritation; the treponemata are reactivated and through their toxins produce chronic periostitis that results in hyperostosis. The enlargement of the sternal end of the clavicle reaches a permanent stage about the age of puberty and thus becomes a valuable permanent stigma of prenatal syphilis. Histologically, it is a case of sclerotic bone involvement, representing the permanent residue of prior bony inflammation [4, 20].

Later authors confirmed the presence of the sign, with some in agreement as to its significance and mode of production and others less supportive of this idea. Dome and Zakon [21] presented 12 patients with confirmed congenital syphilis, and all bore the HS, whereas Yang [22], in his studies of six patients, remarks that "it is interesting to note that clavicle sign was present in all of them." Dax and Stewart [23] examined 64 patients with congenital syphilis and found enlargement of the sternal ends of the clavicles in 29.7% of their patients. They did not notice any association between the dominant hand and the side of clavicle enlargement. Higoumenakis, in fact, also noted that the enlargement appeared a few times on the left side of patients who were right-handed, but considered it a normal variation [24]. Over 30 authors commented on this sign during the period from 1930 to 1980, leading to its general acceptance, and texts as old as 1851 describe the same findings [15].

Second point of evidence: A recent specimen

Erdal [2] recently described the skeleton of a child approximately 15 years old, excavated from Bursa, Turkey in Western Anatolia (Nicaea), and dating back to the Late Byzantine period (13th century AD). The Nicaea specimen, as the author named it, displayed many common features with congenital syphilis specimens, such as Hutchinson's incisor, mulberry molar, darkened enamel, a radial scar on the frontal bone, sabre tibia, syphilitic dactylitis, and gummatous and non-gummatous osteomyelitis on almost every post-cranial bone. Interestingly though, he gave a description of a lesion in the right clavicle compatible to that of the HS, noting that

“there are signs of hyperplastic periostitis in the anterior concavity of the sternal end of the right clavicle” ([2], p. 22). HS, however, has never been described in archaeological specimens, nor has it been given scientific status. In the discussion section of his article, Erdal concludes that his specimen suffered from congenital treponematosi. This conclusion was based on the simultaneous presence of many stigmata of late congenital syphilis, including the lesions present in the clavicle.

Third Point of Evidence: Museum of London Specimens

The Centre for Human Bioarchaeology at the Museum of London, UK curates the Museum’s extensive holdings of human remains. It has developed the Oracle WORD database which includes a fairly comprehensive database of osteological specimens excavated from the City of London and Greater London area [25]. Among its specimens, there are 17 specimens with congenital syphilis and possible congenital syphilis from the medieval cemetery *St Mary Graces*, and the post-medieval cemeteries *Cross Bones*, *St Benet Sherehog*, *St Thomas’ Hospital* (See supplementary material). These specimens show varying degrees of inflammation in their clavicles, which could support the hypothesis that HS is indicative of congenital syphilis in archaeological specimens. For example, Specimen REW92_Context.58.2 from *Cross Bones* cemetery, dated to 1598-1853, comes from a sub-adult perinatal skeleton, and was given the following description: “*Possible Congenital syphilis. Severe porous new bone plaque formation to all extant long bones including clavicles & scapulae also. Indicative of possible chronic systemic infection. However, frontal not present*” (Figure 1). Specimen NLB91_Context.66 from *St Thomas’ Hospital* cemetery is a skeleton specimen belonging to a female adult 26-35 years old, dating between 1540-1714. It is described as “*Treponematosi (Treponema sp.), Probable Tertiary Syphilis - extravagant new bone to clavicles, distal right humerus, proximal ulnae, distal left femur, tibiae & fibulae. Frontal bone shows new bone growth. The area is very porous & lytic lesions are starting to*

appear. The inner table of the frontal bone is also very porous. Right zygomatic bone is totally covered in new bone which is very porous. The bone is given the appearance of thickening. The left bone is not available for comparison” (Figure 2). There is no reason that this could not be tertiary congenital syphilis, since a comprehensive study of HS in anthropological specimens is still lacking.

(Figure 1 here), (Figure 2 here), (Supplementary material here)

CONCLUSION

In the last 70 years, the evidence has shown that the enlargement of the clavicle in patients with congenital syphilis is a common finding which may assist in disease diagnosis. This observation is also supported by the inclusion of the criterion in several major reviews of disease clinical diagnosis [4, 5, 26]. The additional fact that dental stigmata of the disease, such as Hutchinson’s incisors and mulberry molars, are only observed in about 30% of all patients [2, 11, 27], allow us to advocate evaluating the clavicle sign in osteoarcheological studies, especially when cranial data evaluation is missing or remains inconclusive. In fact, even within the clinical scenario, the disease is so diverse (*la grande simulatrice*) that no single criterion can be independently applied for a clinical diagnosis and the actual definite decision can only be provided via serological / molecular testing, which, however, is not available in archaeological / anthropological samples [6, 7, 10]. In addition, HS may also be significant for the definite establishment of the presence of congenital syphilis in the pre-Columbian ancient Greek world and the Old World in general, as well as for the differential diagnosis between syphilis and other variants of treponemal / spirochete infections [2, 3, 11, 28]. A thorough osteoarcheological study of the specimens at the Museum of London is very likely to yield an answer to this hypothesis.

REFERENCES

- [1] Baker BJ, Armelagos GJ. The origin and antiquity of syphilis: paleopathological diagnosis and interpretation. *Curr Anthropol* 1988;29:703-737.
- [2] Erdal YS. A pre-Columbian case of congenital syphilis from Anatolia (Nicaea, 13th century AD). *Int J Osteoarchaeol* 2006;16:16-33.
- [3] Henneberg M, Henneberg RJ. Treponematoses in an ancient Greek colony of Metaponto, Southern Italy, 580-250 BCE. In: Dutour O, Pálfi GY, Bérato J, Brun JP, eds. *L'origine de la syphilis en Europe: avant ou après 1493? Actes du colloque international de Toulon; 1993 Nov 25-28*. Paris: Ed. Errance, 1994:92-98.
- [4] Crissey JT, Denenholz DA. Congenital syphilis. *Clin Dermatol* 1984;2:143-161.
- [5] Woods CR. Syphilis in children: congenital and acquired. *Semin Pediatr Infect Dis* 2005;16:245-257.
- [6] Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines. *MMWR* 2006;55(RR-11):30-32.
- [7] Wöhrl S, Geusau A. Clinical update: syphilis in adults. *Lancet* 2007;369:1912-1914.
- [8] Rothschild BM, Rothschild C. Congenital syphilis in the archaeological record: diagnostic insensitivity of osseous lesions. *Int J Osteoarchaeol* 1997;7:39-42.
- [9] Hutchinson DL. L'origine de la syphilis en Europe: Avant ou après 1493? (The Origin of Syphilis in Europe : Before or after 1493?). *Int J Osteoarchaeol* 1998;8:128-133.
- [10] Barnes I, Thomas MG. Evaluating bacterial pathogen DNA preservation in museum osteological collections. *Proc Biol Sci* 2006;273:645-653.
- [11] Hillson S, Grigson C, Bond S. Dental defects of congenital syphilis. *Am J Phys Anthropol* 1998;107:25-40.

- [12] Robinson RCV. Congenital syphilis. *Arch Dermatol* 1969;99:599-610.
- [13] Fiumara NJ, Lessel S. The stigmata of late congenital syphilis: an analysis of 100 patients. *Sex Transm Dis* 1983;10:126-129.
- [14] Frangos CC, Damanakis A, Frangos CC. Das turbulente Leben von Giorgos (Georg) Higoumenakis (1895-1983), Entdecker des Higoumenakis-Zeichens in später kongenitaler Syphilis und Pionier in der Forschung zur Leishmaniose. *Aktuelle Derm* 2010;36:385-391.
- [15] Frangos CC, Frangos CC. George Higoumenakis (1895-1983): Greek dermatologist. *J Med Biogr* 2009;17:64-72.
- [16] Higoumenakis G. A new stigma of hereditary syphilis. *Proc Med Soc Athens* 1927:687-699.
- [17] Higoumenakis G. Un nouveau stigmatte de syphilis héréditaire: l' hyperostose de l'extrémité sternale de la clavicule droite. *Revue française de dermatologie et de venereologie* 1928;4:213-221.
- [18] Higoumenakis GK. Neues Stigma der kongenitalen Lues. *Dtsch Z Nervenheilkd* 1930;114:288-299.
- [19] Jurik AG, De Carvalho A, Graudal H. Sclerotic changes of the sternal end of the clavicle. *Clin Radiol* 1985;36:23-25.
- [20] Glickman LG, Minsky AA. Enlargement of one sternoclavicular articulation: a sign of congenital syphilis. *Radiology* 1937;28:85-86.
- [21] Dorne M, Zakon SJ. Enlargement of one sternoclavicular articulation as a valuable clinical sign of late prenatal (congenital) syphilis. *Arch Derm Syphilol* 1935;32:602-604.
- [22] Yang KL. Clavicle sign of late congenital syphilis. *Arch Derm Syphilol* 1940;41:1060-1065.
- [23] Dax EC, Stewart RM. The sign of the clavicle. *Br Med J* 1939;1:771-772.
- [24] Higoumenakis G. "Clavicle Sign" and its diagnostic value in hereditary syphilis. *Urol Cutaneous Rev* 1937;41:799-809.

- [25] WORD database, Museum of London. URL:
<http://www.museumoflondon.org.uk/English/Collections/OnlineResources/CHB/Resources/Medievaldatadownloads.htm>, Accessed 29/03/2011.
- [26] Parish JL. Treponemal infections in the pediatric population. *Clin Dermatol* 2000;18:687-700.
- [27] Condon K, Becker J, Condon C, Hoffman JR. Dental and skeletal indicators of a congenital treponematosiis. *Am J Phys Anthropol Suppl* 1994;37:70.
- [28] Pálfi G, Dutour O, Borreani M, Brun J-P, Berato J. Pre-Columbian congenital syphilis from the late antiquity in France. *Int J Osteoarchaeol* 1992;2:245-261.

FIGURES

Figure 1. Right and left clavicles from specimen REW92_Context.58.2. Severe porous new bone plaque formation to clavicles.

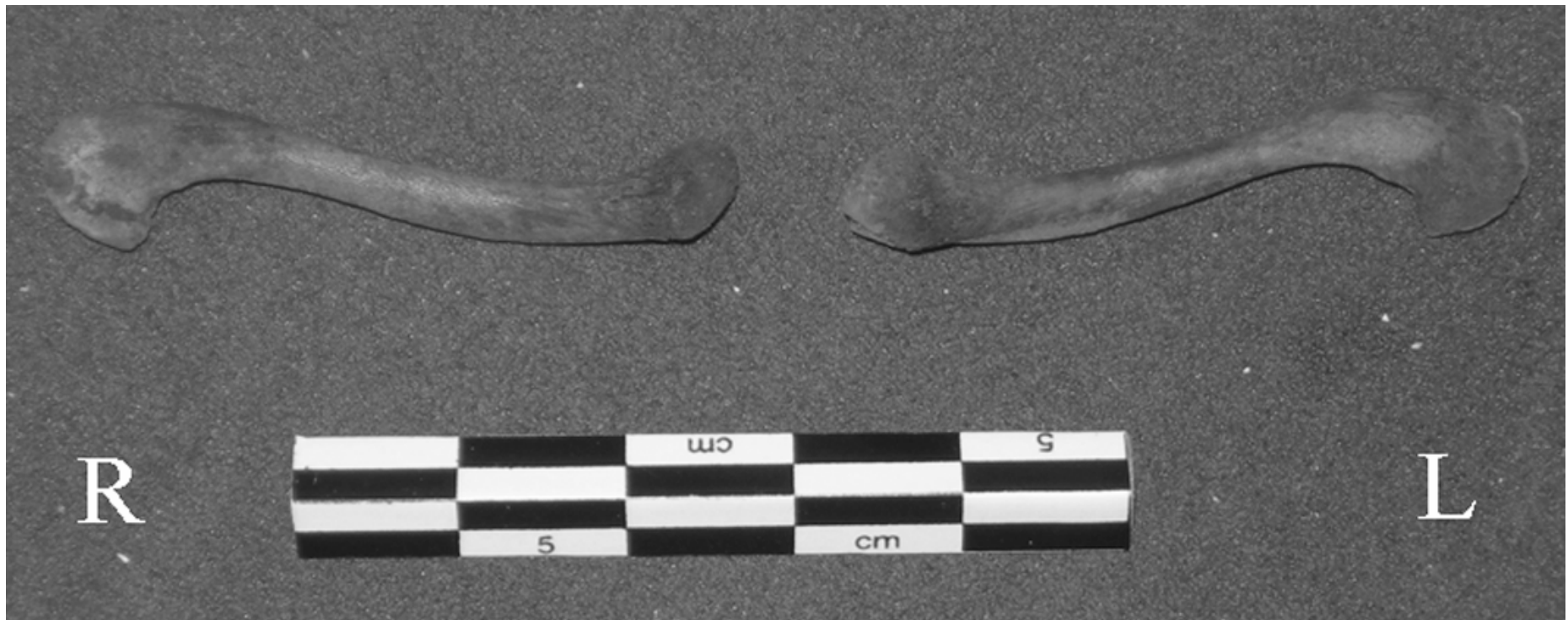
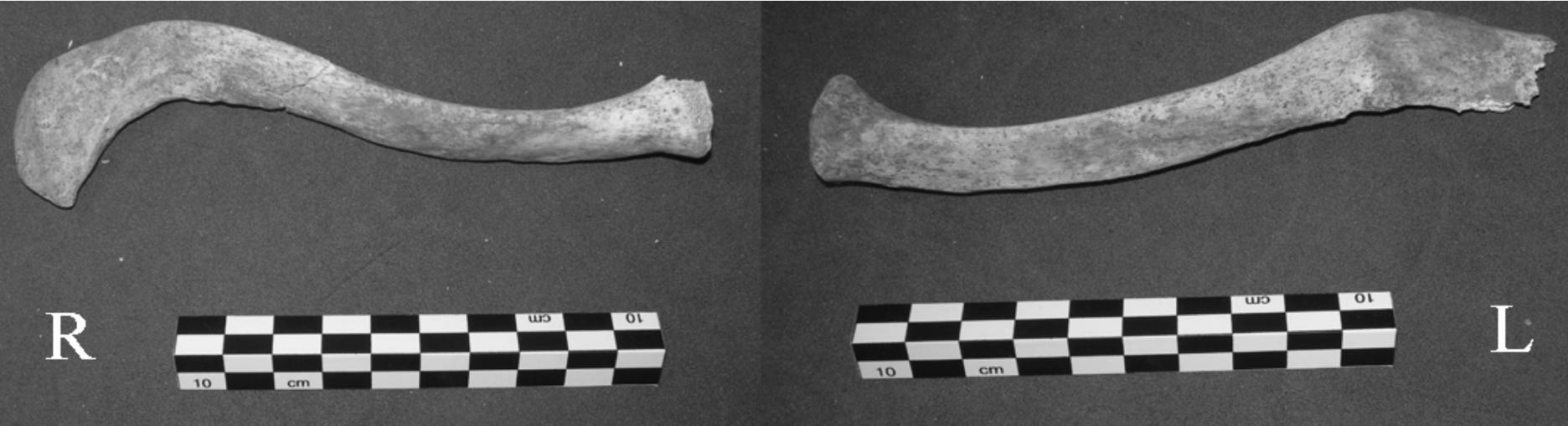


Figure 2. Right and left clavicles from specimen NLB91_Context.66. Extravagant new bone to clavicles.



TABLE

Table 1. Clinical findings consistent with the diagnosis of congenital syphilis. Those markers that may be used in anthropological material are indicated in the third column, along with an average estimation of their diagnostic value, based on current experience (the downwards pointing arrow symbolizes the major limitation in each marker's diagnostic value). Main sources are references [2, 4, 12, 13].

| Sign Name | Type of Finding | Applicability for Anthropological Specimens |
|-----------------------------------|-------------------------------------|--|
| <i>Dental Markers</i> | | |
| Hutchinson's incisors | Hutchinson's triad | Recognized (↓sensitivity) |
| Moon's molars | Permanent damage | Recognized (↓sensitivity) |
| Fournier molars | Hypoplastic defect | Limited (↓specificity) |
| Fournier canines | Hypoplastic defect | Limited (↓sensitivity) |
| <i>Skeletal Markers</i> | | |
| Osteitis- Periostitis | Long bone damage- tibia | Limited (↓specificity) |
| Higoumenakis' sign | Clavicle inflammation | Limited (so far) |
| Parrot's Osteochondritis | Bone-cartilage connection damage | Recognized (↓specificity) |
| Clutton's joints | synovial distortion | Limited (if any) |
| <i>Organic-Systemic Markers</i> | | |
| Neurosyph.-tabes dorsalis | Hutchinson's triad | None |
| Interstitial keratitis- ocular | Hutchinson's triad | None |
| Snuffles – saddle nose | Nasal cavity distortion | Limited (↓sensitivity) |
| Mucocutaneous disease | Facial distortion, gumma | None |

Supplementary material
SPECIMENS OF CONGENITAL SYPHILIS (OR POSSIBLE CONGENITAL SYPHILIS) AT THE MUSEUM OF LONDON.

At the Museum of London there are the following specimens of congenital syphilis:

Medieval St. Mary Graces (MIN86)

Context: MIN86 **5279**

Website: pictures of mandible + incisors

Diagnosis: Congenital Syphilis

Post-Medieval Cross Bones (REW92)

Context: REW92 **58.2** (age: sub-adult perinatal)

Clavicle R: +

Clavicle L: +

Diagnosis: Possible congenital syphilis or chronic vitamin C deficiency (scurvy)

Context: REW92 **73** (age: sub-adult perinatal)

Clavicle R: +

Clavicle L: +

Diagnosis: Chronic vitamin C deficiency (mainly) or scurvy, but we cannot rule out congenital syphilis due to clavicle lesions.

Context: REW92 **74** (age: sub-adult perinatal)

Clavicle R: +

Clavicle L: +

Diagnosis: Chronic vitamin C deficiency (mainly), but we cannot rule out congenital syphilis.

Context: REW92 **77** (age: sub-adult 1-6 months)

Clavicle R: +

Clavicle L: +

Diagnosis: Chronic vitamin C deficiency (congenital syphilis can also be considered)

Context: REW92 **79** (age: sub-adult 1-6 months)

Clavicle R: +

Clavicle L: +

Diagnosis: Chronic vitamin C deficiency or congenital syphilis

Context: REW92 **82** (age: sub-adult perinatal)

Clavicle R: +

Clavicle L: +

Diagnosis: Congenital Syphilis

Context: REW92 **84** (age: sub-adult perinatal)

Clavicle R: +

Clavicle L: +

Diagnosis: Congenital Syphilis or chronic vitamin C deficiency

Context: REW92 **99** (age: adult 18-25 years)

Clavicle R: +

Clavicle L: +
Diagnosis: Tertiary syphilis, most possibly congenital because tertiary has an incubation period over 20 years

Context: REW92 **103** (age: sub-adult perinatal)
Clavicle R: -
Clavicle L: +
Diagnosis: Possible congenital syphilis or vitamin C deficiency (scurvy)

Context: REW92 **113.1** (age: sub-adult perinatal)
Clavicle R: +
Clavicle L: -
Diagnosis: Possible congenital syphilis or vitamin C deficiency (scurvy)

Context: REW92 **119.2** (age: sub-adult perinatal)
Clavicle R: +
Clavicle L: -
Diagnosis: Possibly Congenital Syphilis

Context: REW92 **126** (age: sub-adult perinatal)
Clavicle R: +
Clavicle L: +
Diagnosis: Chronic vitamin C deficiency (mainly), but we cannot rule out congenital syphilis.

Context: REW92 **148** (age: sub-adult perinatal)
Clavicle R: +
Clavicle L: +
Diagnosis: Chronic vitamin C deficiency (mainly), but we cannot rule out congenital syphilis.

Post-Medieval St. Benet Sherehog (ONE94)

Context: ONE94 **138** (age: sub-adult 1-5 years)
Clavicle R: +
Clavicle L: -
Diagnosis: possibly congenital syphilis

Context: ONE94 **846** (age: sub-adult 1-6 months)
Clavicle R: +
Clavicle L: -
Diagnosis: Non-specific osteomyelitis or congenital syphilis or Histiocytosis-X

Post-Medieval St. Thomas' Hospital (NLB91)

Context: NLB91 **66** (age: adult 26-35 years)
Clavicle R: +
Clavicle L: +
Diagnosis: Tertiary syphilis (note: if she was 27, she might have tertiary congenital syphilis). Osteochondritis disseacans.