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Insights on the paleoepidemiology of ancient tuberculosis from the structural analysis of postcranial remains from the Ligurian Neolithic (northwestern Italy)

Vitale Stefano Sparacello[a,b,*], Charlotte A. Roberts[a], Alessandro Canci[c], Jacopo Moggi-Cecchi[d], Damiano Marchi[e]

[a] Department of Archaeology, Durham University, Durham DH1 3LE, United Kingdom
[b] UMR5199 PACEA, Université de Bordeaux – CNRS, Batiment B8, Allée Geoffroy Saint Hilaire, CS 50023, 33615 Pessac cedex, France
[c] Department of Archaeology, University of Padua, Piazza Capitaniato 7 35139 Padua, Italy
[d] Laboratory of Anthropology, Department of Biology, University of Florence, Florence, Italy
[e] Department of Biology, University of Pisa, via Derna, 1 56126 Pisa, Italy

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ABSTRACT

The aim of this research is to gain insights on the progression timeline of osteoarticular tuberculosis (TB) in people from the Neolithic period by using skeletal traits that are independent of the bony lesions. The body proportions and postcranial mechanical strength of bones from two individuals from Liguria in northwestern Italy (Arene Candide 5, adolescent, and Arma dell'Aquila 1, adult), were compared with the rest of the Ligurian Neolithic skeletal series (45 individuals). If TB led to wasting of the skeleton and lack of normal function that endured for years, as often happens today, a clear signature of postcranial gracility and disruption of development should be apparent. Conversely, rapid progress of the disease would leave little systemic macroscopic change in the skeleton, except for the bony lesions directly caused by the TB pathogen, suggesting a different level of bacterial virulence in the past. The extreme biomechanical gracility observed in the lower limb of Arene Candide 5 suggests a period of compromised diaphyseal periosteal apposition during ontogeny due to metabolic disturbances likely linked to TB. Results suggest that, in Neolithic Liguria, TB in humans saw a slow, chronic progression, which is characteristic of diseases with long histories of host-pathogen co-evolution.

1. Introduction

In skeletal analyses of ancient disease, in particular tuberculosis (TB), it often has to be assumed that the pathogen acted with a virulence comparable to modern times (i.e. the ability of the organism to invade the tissues of the host and cause disease). The purpose of this paper is to test this assumption by evaluating two Neolithic skeletons (6th–4th millennium BCE) with tuberculous spondylitis from Liguria (Italy). This new approach takes into account changes in skeletal properties that are independent of the osteolytic lesions observed in the skeletons. Through comparisons with the rest of the Neolithic skeletal series from Liguria (Parenti and Messeri, 1962), possible systemic reactions due to chronic TB leading to alterations in normal expected growth are assessed (stature, body mass, and body mass index – BMI), along with the presence or absence of a decrease in the mechanical competence (or 'gracilization') of the postcranial skeleton (evaluated via cross-sectional geometric analysis of the diaphysis, CSG – Ruff et al., 2006). By analyzing systemic changes in bone structure, insights on the timing of progression and virulence of TB in the past are explored to gain new information on the paleoepidemiology of this reemerging disease (Roberts and Buikstra, 2003; http://www.who.int/topics/tuberculosis/en).

Tuberculosis is a mammalian infectious disease caused by bacteria of the *Mycobacterium tuberculosis* complex (MTBC). It is mainly the human and bovine forms that affect humans, which are transmitted via the respiratory and gastrointestinal routes, respectively. The disease has had a long history, as seen in bioarchaeological studies. Skeletal evidence, usually consisting of destructive lesions in the spine (Pott's disease), has been documented in both the Old and New Worlds. Tuberculosis, as seen in human skeletal remains, became more common in Europe as population density increased and people started to live in permanent urban settlements supported by a farming economy. The earliest evidence derives from

* Corresponding author at: Department of Archaeology, Durham University, Durham DH1 3LE, United Kingdom.
E-mail addresses: vitale.sparacello@durham.ac.uk, vitosparacello@gmail.com (V.S. Sparacello).

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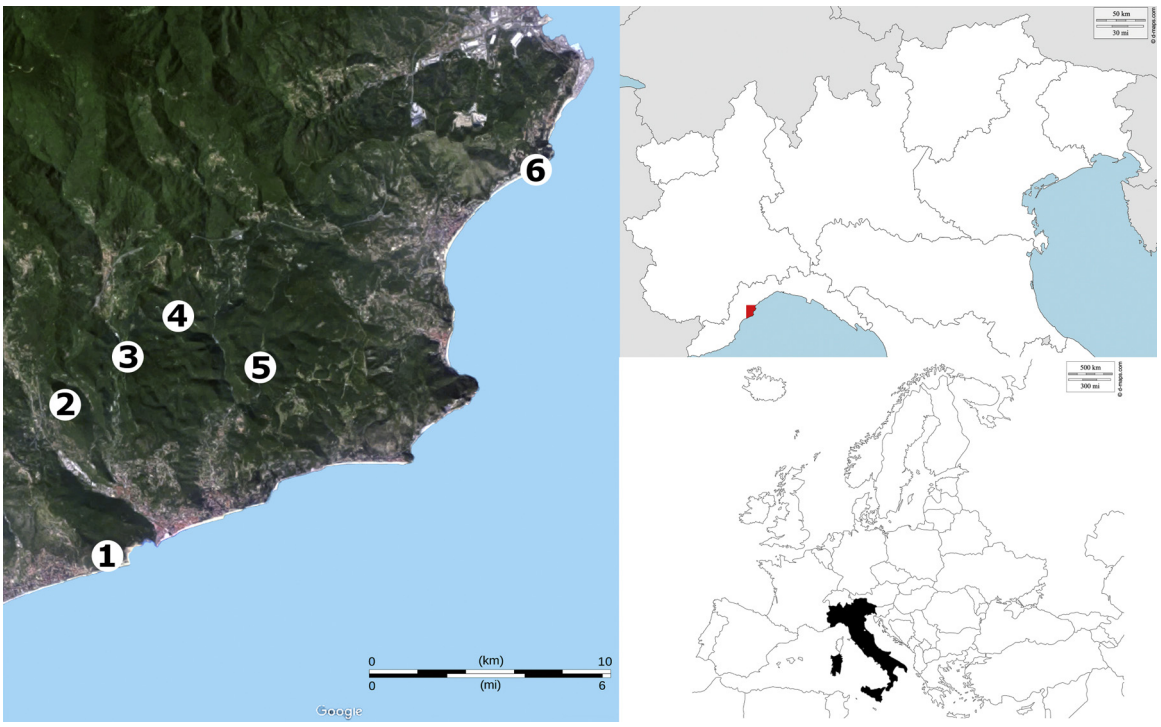

Fig. 1. Geographic collocation of Liguria, and distribution of the Neolithic sites from which skeletal remains included in this research have been unearthed. 1: Arene Candide; 2: Pollera; 3: Arma dell'Aquila; 4: Boragni; 5; Pian del Ciliegio; 6: Bergeggi. Created with Google Maps™ and d-maps.com.

archaeological sites in Germany, Hungary, Israel, Italy and Poland, with the Israeli evidence dating back to the 8th millennium BCE (see summary in Roberts, 2015).

The first Italian skeleton with a diagnosis of TB was reported by Formicola et al. (1987) from Arene Candide, a cave on the Ligurian coast (Fig. 1). Several inhumations from Neolithic levels have been excavated from caves in the area since the mid-19th century (Del Lucchese, 1997; Maggi 1997a,b; De Pascale, 2008). The skeleton Arene Candide 5 (abbreviated from now on as AC5) was a crouched inhumation, lying on their left side in a stone cist, and directly dated to 7571–7420 cal BP (99.7%; KIA-28340, Le Bras-Goude et al., 2006). Another skeleton with TB in the spine (Arma dell'Aquila 1, abbreviated from now on as AQ1; Canci et al., 1996) was found among the skeletal remains excavated by Zambelli in 1936 (Parenti and Messeri, 1956) at Arma dell'Aquila, a cave in the same area (Arobba et al., 1987; Fig. 1), and was directly dated to 6929–6310 cal BP (99.7%; GrN-17730, Paolo Biagi, personal communication). Individuals AC5 and AQ1 have different ages, the former being an adolescent (about 15 years old; Formicola et al., 1987), and the latter an adult (around 30 years old; Canci et al., 1996). Both individuals display a collapse of the spine due to lytic lesions affecting the lower thoracic and lumbar vertebral bodies. The lesions are typical of tuberculous spondylitis, a form of osteoarticular TB affecting the spine (Spiegel et al., 2005). Individuals who survive spinal TB enter a stage of repair and eventual ankylosis, with re-mineralization of the destroyed vertebrae that often results in a spinal deformity (i.e. kyphosis, Tuli, 2013). Minimal osteoblastic reaction (new bone formation) was noted, suggesting that death occurred while TB was still destroying the vertebral bodies, and therefore that it was still in the active phase.

2. Rationale of the study

Today, the progression of TB is slow and chronic. A recent meta-analysis suggests that the active phase of untreated pulmonary TB from the onset of symptoms to cure or death lasts for, on average, three years, but with considerable variation (Tiemersma et al., 2011). About 90% of modern human TB infections are clinically latent, with the pathogen being contained within granulomatous lesions at the site of the primary infection (Ulrichs et al., 2005). Spinal involvement occurs in only a small fraction of patients with TB (e.g. 1%, Turgut: 2001; 3–5%: Vigorita, 2008; 10% of patients with extra-pulmonary TB: Garg and Somvanshi, 2011), and has been reported to develop within two to three years after primary infection (Girling et al., 1988). Bone changes become apparent after three to five months from initial spinal involvement (Spiegel et al., 2005), with average disease duration ranging from 4 to 11 months to a few years (Garg and Somvanshi, 2011). Compared to pyogenic hematogenous bone diseases, lesions in skeletal TB develop slowly, with gradual decalcification of the bone and slow 'poisoning' of the cells (El-Najjar, 1981; Meghji et al., 1997).

The presence of osteoarticular lesions in Neolithic skeletons, if evaluated following modern standards, would therefore suggest a slow and chronic course for the disease. However, it is not safe to model past disease progression based on clinical evidence from patients treated with antibiotics. Changes in the pathogen as well as host immunity may significantly alter TB morbidity and virulence over a relatively short period of time (Palkovich, 1981). In particular, murine models suggest that the chronic slow progression of TB is not due to slow replication of the bacterium itself, but to the ability of the localized immune response to maintain equilibrium and latency (Munoz-Elias et al., 2005; Ulrichs et al., 2005; Gill et al., 2009). There is also clinical evidence suggesting that the host response plays a major role in restricting intracellular mycobacterial growth and therefore in determining the clinical manifestations of the disease (Schluger and Rom, 1998). It is therefore possible that, in Neolithic times, populations with no previous exposure to TB might have had not only a greater susceptibility but also a more rapid negative outcome. It is generally expected that this would result in no traces in the skeleton. However, lack of host resistance could imply a lesser ability to contain the spread of the disease from the lungs to the rest of the body. In the skeleton, this inability to

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