PhD DISSERTATION

EVALUATION OF ENDOCRANIAL BONY CHANGES IN RELATION TO TUBERCULOSIS IN THE ROBERT J. TERRY ANATOMICAL SKELETAL COLLECTION (WASHINGTON, DC, USA)

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To my beloved grandfather, in memoriam.

"We do not know a truth without knowing its cause."

–Aristotle

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ABVI: abnormal blood vessel impression

AIDS: acquired immune deficiency syndrome

APDI: abnormally pronounced digital impression

BCG: *Bacillus Calmette−Guérin* vaccine

CNS: central nervous system

CSF: cerebrospinal fluid

DI: digital impression

eICP: elevated intracranial pressure

GI: granular impression

HIV: human immunodeficiency virus

HPO: hypertrophic pulmonary osteopathy

MDR-TB: multidrug-resistant tuberculosis

MTBC: *Mycobacterium tuberculosis* complex

NMNH: National Museum of Natural History

NTB: non-tuberculous

PA: periosteal apposition

PNBF: periosteal new bone formation

RR-TB: rifampicin-resistant tuberculosis

SES: *serpens endocrania symmetrica*

TB: tuberculosis/tuberculous

TBM: tuberculous meningitis

WHO: World Health Organization

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1 INTRODUCTION

1.1 Aetiological agents, transmission, and pathogenesis of tuberculosis

Tuberculosis (TB) is an airborne infectious disease of both humans and animals that is caused by a number of pathogenic mycobacterial species belonging to the *Mycobacterium tuberculosis* complex (MTBC) (*i.e*., *M. tuberculosis*, *M. africanum*, *M. canettii*, *M. bovis*, *M. caprae*, *M. microti*, *M. pinnipedii*, *M. orygis*, *M. mungi*, *M. suricattae*, "dassie bacillus", and "chimpanzee bacillus"), with *M. tuberculosis* being the most common cause of TB in humans. TB bacteria enter the human body usually via the respiratory tract through inhalation of droplets expelled into the air by an individual with active pulmonary TB disease during sneezing, coughing or talking. Following inhalation, pathogens that reach the alveoli in the lungs may be eliminated by the host's immune system (*i.e*., rapid clearance) (Flynn & Chan, 2001; Flynn *et al*., 2011; Gideon & Flynn, 2011; Ernst, 2012; Gagneux, 2012; Gengenbacher & Kaufmann, 2012; Miranda *et al*., 2012; Bañuls *et al*., 2015; Brites & Gagneux, 2015; Fogel, 2015; Getahun *et al*., 2015; Clarke *et al*., 2016; Pai *et al*., 2016).

However, in most people, TB bacteria are able to escape elimination in the alveoli and invade into the lung parenchyma, where their presence triggers the recruitment of an increasing number of immune cells (*e.g*., macrophages, dendritic cells, and lymphocytes) to sites of infection, ultimately resulting in the formation of tuberculous granulomas, also known as tubercles. On the one hand, tubercles provide an isolated microenvironment in which host cells interact to control and prevent dissemination of the infection; whereas on the other hand, they function as a survival niche in which TB bacteria can replicate or persist in a dormant state within the lung tissue until opportunity arises for them to reactivate and spread. In the minority of people affected (~10%) – mainly in infants and children –, tubercles fail to contain the infection and TB bacteria can disseminate throughout the lung or into other parts of the body; thus, the infection progresses into primary active TB disease (*i.e*., the infected person becomes symptomatic and contagious), usually within the first 2 years after exposure. Nevertheless, in most cases (~90%) – defined as latent TB infection (*i.e*., the infected person is asymptomatic and not contagious) –, TB bacteria remain dormant within the tubercles for a long time (even for a lifetime), with subsequent reactivation occurring only when certain factors (*e.g*., malnutrition, HIV infection, and *diabetes mellitus*) compromise the host's immune system (Flynn & Chan, 2001; Flynn *et al*., 2011; Gideon & Flynn, 2011; Ernst, 2012; Gengenbacher & Kaufmann, 2012; Miranda *et al*., 2012; Fogel, 2015; Getahun *et al*., 2015; Pai *et al*., 2016).

Although tuberculosis primarily affects the lungs (*i.e.*, pulmonary TB), the haematogenous or lymphogenous spread of TB bacteria to other parts of the body, including the skeleton or the central nervous system (CNS), results in the development of different types of extra-pulmonary tuberculosis (*e.g.*, miliary TB, skeletal TB, and CNS TB) that together constitute about 15 to 20% of all cases with active tuberculosis (Golden & Vikram, 2005; Vanhoenacker *et al.*, 2009; Mohapatra *et al.*, 2011; Fuentes Ferrer *et al.*, 2012; Pai *et al.*, 2016; Held *et al.*, 2017).

1.2 Palaeoepidemiological and epidemiological aspects of tuberculosis

Tuberculosis is one of the oldest known infectious diseases that has been plaguing mankind for thousands of years: the earliest recognised and verified TB cases (*e.g.*, Nicklisch *et al.*, 2012; Spekker *et al.*, 2012; Köhler *et al.*, 2014, 2016; Baker *et al.*, 2015; Hershkovitz *et al.*, 2015; Masson *et al.*, 2015; Sparacello *et al.*, 2017) come from the Neolithic period. Apparently, TB remained relatively sporadic until the 1700's but – as a consequence of increased population density and unsanitary living conditions – started to reach epidemic levels during the *Industrial Revolution*. From the second half of the 19th century, a number of factors (such as the general improvement in living conditions, sanitation, and nutrition) have been attributed to a reduction in the number of TB cases in developed countries. Later, the decline in TB incidence rates was even more accelerated by the introduction of the *Bacillus Calmette−Guérin* (BCG) vaccine and the use of antibiotics (*e.g.*, streptomycin, isoniazid, and rifampicin). TB epidemic trends in Hungary followed those of Western Europe, with an approximately 75-year delay. The steady decrease in TB incidence in developed countries has led to predictions of the complete eradication of the disease by the end of the 20th century. Nonetheless, particularly fuelled by the growing human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) pandemic and the emergence of multidrug-resistant tuberculosis (MDR-TB), TB incidence started to increase again in the late 1980's. In 1993 (WHO, 1994), tuberculosis has been declared a global health threat by the World Health Organization (WHO) (Friend & Watson, 1998; Hutás, 1999; Pálfi *et al.*, 1999, 2015; Zumla *et al.*, 2000; Roberts & Buikstra, 2003; Smith, 2003; Golden & Vikram, 2005; Gagneux, 2012; Galagan, 2014; Bañuls *et al.*, 2015; David *et al.*, 2015; Fogel, 2015; Pai *et al.*, 2016).

In this day and age, more than 2 billion people – about one-third of the total population of the world – are latently infected with the causative agent of TB, of whom only 5 to 15% are at risk of eventually developing active TB disease during their lifetime (Golden &

Vikram, 2005; Flynn *et al*., 2011; Gengenbacher & Kaufmann, 2012; Miranda *et al*., 2012; Getahun *et al*., 2015; Esteves *et al*., 2017; WHO, 2017). According to estimates of the WHO (2017), in 2016, there were approximately 10.4 million new incident cases of active TB disease, of which about 10% were among HIV-positive people. Tuberculosis remained one of the top 10 causes of death and the leading cause of death from a single infectious agent (ranking above HIV/AIDS), with accounting for 1.3 million deaths among HIV-negative individuals and for an additional 374,000 TB-related deaths among people co-infected with HIV. Drug resistance surveillance data show that in 2016, there were an estimated 490,000 new incident cases of MDR-TB worldwide, of which 6.2% were extensively drug-resistant. An additional 110,000 people were susceptible to isoniazid but resistant to rifampicin (RR-TB), and a total of 240,000 deaths occurred due to MDR/RR-TB globally. Tuberculosis has been reported from all parts of the world but the majority of new incident cases and deaths (more than 95%) occurred in low-income and middle-income countries. In 2016, the most affected WHO region was the South-East Asia Region (~45%), followed by the African (~25%) and Western Pacific Regions (~17%). Seven countries comprised about two-thirds of new incident cases (in descending order): India, Indonesia, China, the Philippines, Pakistan, Nigeria, and South Africa.

The global health emergency presented by TB today has sparked a renewed interest and funding to the research of the disease and of its aetiological agents, including science projects concerning the origin and evolutionary history of the MTBC, as well as the palaeopathological diagnostics for TB (Pálfi *et al*., 2015; Pai *et al*., 2016; WHO, 2017).

1.3 Palaeopathological diagnosis of tuberculosis – Non-endocranial bony changes

Traditionally, the diagnosis of TB in ancient human bone remains relies on the identification of pathological lesions in the skeleton that are related to different forms of TB, such as pulmonary TB, osteoarticular TB, and CNS TB (Kelley & Micozzi, 1984; Aufderheide & Rodríguez-Martín, 1998; Ortner, 2003, 2008; Santos & Roberts, 2006; Pálfi *et al*., 2012; Mariotti *et al*., 2015).

Nowadays, skeletal tuberculosis occurs in less than 2% of all active TB cases and accounts for 10 to 35% of extra-pulmonary TB cases. Nevertheless, over the past two decades, the incidence of osteoarticular TB has increased worldwide, especially in low-income and middle-income countries, due in part to the HIV/AIDS pandemic. In high-TB-burden countries, skeletal TB affects more commonly children and young adults, mainly during the first three decades of life; whereas in low-TB-burden countries, the majority of

osteoarticular TB cases occur mainly in foreign-born younger adults (particularly between 20 to 30 years of age) from TB-endemic regions of the world or in native-born older adults (predominantly between 60 to 70 years of age). Similar to other forms of TB, predisposing factors for tuberculous involvement of the bones and/or joints include factors contributing to impairment of the host's immune system, such as HIV infection, immunosuppressive therapy, and alcohol or substance abuse (Houshian *et al*., 2000; Jutte *et al*., 2004; Golden & Vikram, 2005; Kumar, 2005; Sandher *et al*., 2007; Vanhoenacker *et al*., 2009; Garg & Somvanshi, 2011; Fuentes Ferrer *et al*., 2012; Rasouli *et al*., 2012; Pigrau-Serrallach & Rodríguez-Pardo, 2013; Patel *et al*., 2016; De la Garza Ramos *et al*., 2017; Esteves *et al*., 2017; Held *et al*., 2017).

Osteoarticular tuberculosis is usually secondary to haematogenous spread of TB bacteria from a primary location outside the skeleton (such as the respiratory, alimentary or genitourinary system) into the bone and/or synovial tissue during or shortly after the bacteraemic stage of primary infection or late reactivation of the disease; however, in the minority of TB cases, lymphogenous dissemination, contiguous spread from adjacent structures or direct inoculation of pathogens into a skeletal site can also occur. Any part of the skeleton can be affected by TB but areas containing large amounts of red bone marrow are most frequently predisposed to be involved because of the rich blood supply of the marrow; thus, the most preferential skeletal localisation of TB is the spine (50–70%), followed by the hip and knee joints (10–15% each). Deposition of TB bacteria into the skeleton can lead to the development of three main forms of osteoarticular TB: spinal tuberculosis or tuberculous spondylitis (*i.e*., combination of tuberculous vertebral osteomyelitis and arthritis), tuberculous osteomyelitis of the extra-spinal bones, and tuberculous arthritis of the extra-spinal joints, with the first being the most common type (~50%) (Aufderheide & Rodríguez-Martín, 1998; Lagier, 1999; Ortner, 2003; Golden & Vikram, 2005; Kumar, 2005; Spiegel *et al*., 2005; Vanhoenacker *et al*., 2009; Agrawal *et al*., 2010; Garg & Somvanshi, 2011; Fuentes Ferrer *et al*., 2012; Rasouli *et al*., 2012; Pigrau-Serrallach & Rodríguez-Pardo, 2013; Patel *et al*., 2016; De la Garza Ramos *et al*., 2017; Esteves *et al*., 2017).

Tuberculous spondylitis – also known as *spondylitis tuberculosa* or *Pott*'s disease in honour of English surgeon *Sir Percivall Pott* (1779) who first described this clinical entity in the modern era – is characterised by an insidious onset and a slowly progressive course, with disease duration generally varying from a few months to a few years. Any part of the vertebral column can be involved by tuberculosis but the most frequently affected regions

are the lower thoracic (40–50%) and upper lumbar (35–40%) spine; whereas the cervical region is involved in only approximately 10% of all cases with tuberculous spondylitis. Although spinal TB typically affects two or more contiguous vertebrae, multilevel non-contiguous involvement or solitary vertebral lesions may also occur in some patients. Based on the localisation pattern of tuberculous alterations in the vertebra, five main types of tuberculous spondylitis can be distinguished, namely the paradiscal, central, anterior subligamentous, posterior, and articular forms (Ortner, 2003; Kumar, 2005; Spiegel *et al*., 2005; Sridhar & Krishnan, 2009; Agrawal *et al.*, 2010; Garg & Somvanshi, 2011; Fuentes Ferrer *et al*., 2012; Rasouli *et al*., 2012; Pigrau-Serrallach & Rodríguez-Pardo, 2013; Acharya & Gibbs, 2016; Patel *et al*., 2016; De la Garza Ramos *et al*., 2017; Esteves *et al*., 2017).

The most common type of spinal TB, namely the paradiscal form, accounts for approximately 90 to 95% of all cases with tuberculous spondylitis. It arises from the anterior subchondral region of the vertebral body (adjacent to the superior or inferior cartilaginous endplates) that has a dense end-arteriolar network making it susceptible to bacterial seeding via the segmental arterial circulation (anterograde blood flow). Lodgement of TB bacteria into the subchondral region triggers the onset of granulomatous inflammation of the cancellous bone with tubercle formation in the red bone marrow, followed by secondary involvement of the bone trabeculae. Development and caseous necrosis of the gradually expanding and coalescing tubercles located in the marrow induce growth of the initial intra-vertebral abscess and establishment of additional intra-vertebral abscesses within the affected vertebral body, as well as deprivation of the blood supply to cancellous bone due to TB involvement of segmental artery branches with consequent thrombosis and arterial occlusion. Any or all of the aforementioned processes result in necrosis and resorption of bone trabeculae that ultimately lead to the formation of osteolytic lesions in the subchondral region **(Fig. 1A−B)**, with subsequent involvement of the entire vertebral body and occasionally of the posterior vertebral elements. Later, the intra-vertebral abscess extends towards the anterior and/or posterior longitudinal ligaments that – at least temporarily – resist the horizontal progression of its passage; thus, TB infection spreads vertically (upwards or downwards) beneath the ligaments from the primarily affected vertebra into a similar location at one or more contiguous vertebrae or beyond, with relative sparing of the adjoining intervertebral discs until more advanced stages of the disease, most likely due to lack of proteolytic enzymes in TB bacteria (Aufderheide & Rodríguez-Martín, 1998; Ortner,

2003; Kumar, 2005; Spiegel *et al*., 2005; Agrawal *et al.*, 2010; Garg & Somvanshi, 2011; Rasouli *et al*., 2012; Acharya & Gibbs, 2016; Esteves *et al*., 2017).

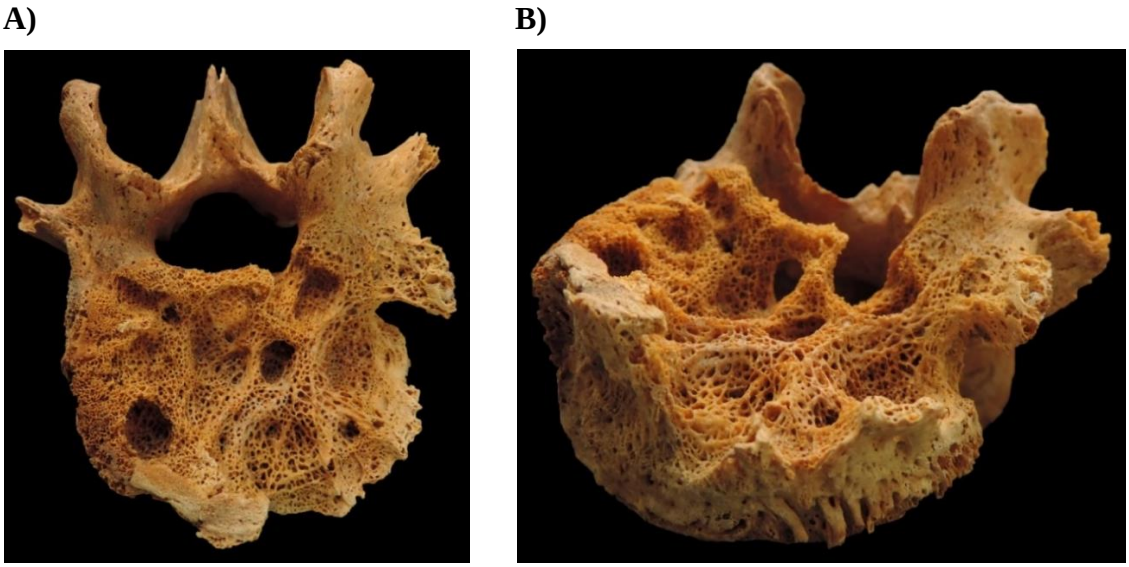


Figure 1: TB osteolytic lesions affecting the upper half of the L2 body: A) superior view and B) left antero-lateral view (Bácsalmás – Homokbánya, Hungary, 16th–17th century AD, Grave No. 115, *Juvenis*, male) (Maczel, 2003).

Nevertheless, progressive destruction of the subchondral region of two adjacent vertebral bodies may compromise nutrition of the intervertebral disc abutted by them that can lead to its degeneration or result in its herniation into the weakened adjoining vertebral bodies, with gradual diminution or eventual loss of the intervertebral disc space. Degenerated and/or herniated discs are more prone to seeding by TB bacteria from the subchondral cancellous bone either via subligamentous dissemination or contiguous spread through the cartilaginous endplate. In children, the intervertebral disc – because of its vascularised nature – can represent the initial site of tuberculous spondylitis; whereas in adults, the age-related avascularity of the intervertebral disc prevents it from serving as the primary focus of infection in the vertebral column; therefore, dissemination of TB bacteria from the infected intervertebral disc into the abutting vertebral bodies occurs scarcely (Aufderheide & Rodríguez-Martín, 1998; Agrawal *et al.*, 2010; Garg & Somvanshi, 2011; Rasouli *et al*., 2012; Esteves *et al*., 2017).

The weakening of the affected vertebral bodies due to TB osteolytic lesions may result in their consequent collapse under the weight of the trunk that is characterised by a wedge-shaped appearance, since cavitation of the infected vertebrae predominantly involves their anterior part, with intact or less destroyed posterior vertebral elements. Depending on its location in the spine, the collapse of one or more contiguous vertebrae may lead to the

development of different spinal deformity types, most frequently of a sharply angular kyphosis in the thoracic region (*i.e.*, *Pott*'s gibbus) with its severity particularly determined by the extent of vertebral destruction, the spinal region affected by TB osteolytic lesions, as well as the number of vertebrae involved by the pathological process **(Fig. 2A)**. Nonetheless, vertebral collapse occurring in the lumbar spine may terminate with telescoping of the affected area. Progressive vertebral destruction and consequent spinal deformity may be associated with mechanical instability of the vertebral column that may result in subsequent bony fusion of the remnants of collapsed vertebral bodies, bony ankylosis of the facet joints, as well as formation of bony extensions interconnecting the adjacent vertebrae (*i.e.*, bony bridges), in order to restabilise the spine. Destructive vertebral lesions very likely attributable to the paradiscal form of spinal TB were identified in a number of ancient human skeletons (*e.g.*, Bartels, 1907; Marcsik, 1978; Bennike, 1999; Blondiaux *et al.*, 1999; Gładykowska-Rzeczycka, 1999; Horáčková *et al.*, 1999; Marcsik *et al.*, 1999, 2009; Maczel, 2003; Suzuki & Inoue, 2007; Ősz *et al.*, 2009; Hajdu *et al.*, 2012; Arrieta *et al.*, 2014; Baker *et al.*, 2015; Balázs *et al.*, 2015; Kajdocsi Lovász, 2015; Molnár *et al.*, 2015; Sparacello *et al.*, 2017) and mummies (*e.g.*, Allison *et al.*, 1973; Nerlich *et al.*, 1997; Strouhal, 1999; Lombardi & Cáceres, 2000) from all parts of the world, and represent much of the evidence for tuberculosis in antiquity (Aufderheide & Rodríguez-Martín, 1998; Palmer, 2002; Ortner, 2003; Agrawal *et al.*, 2010; Jain, 2010; Garg & Somvanshi, 2011; Rasouli *et al.*, 2012; Esteves *et al.*, 2017).

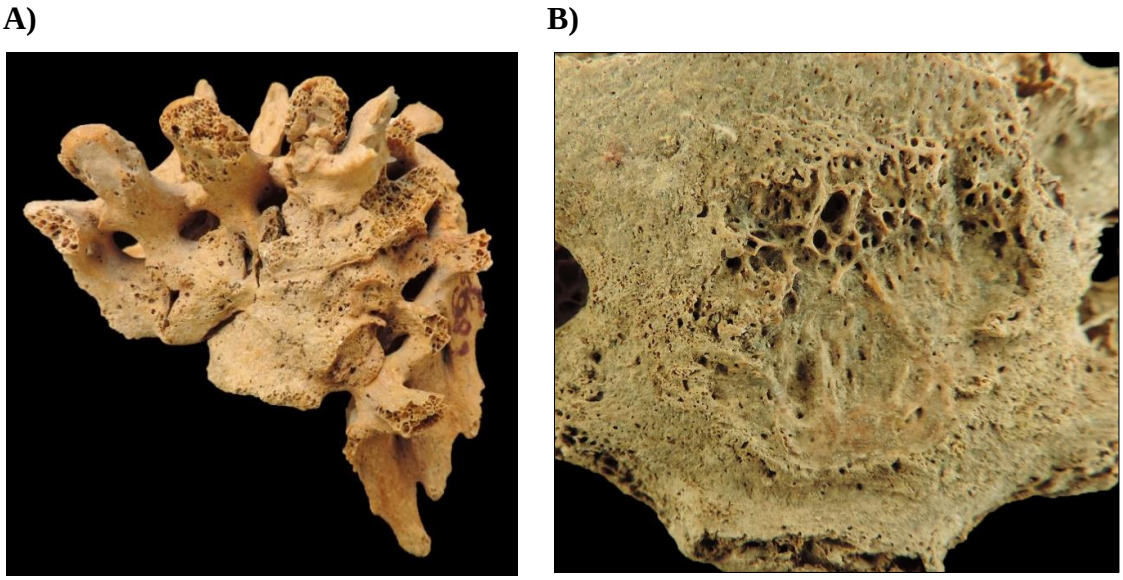


Figure 2: A) severe angular kyphosis (*Pott*'s gibbus) involving the upper thoracic vertebrae (C7–T8) (Sükösd – Ságod, Hungary, 7th–8th century AD, Grave No. 19, *Juvenis*, female) (Marcsik *et al.*, 1999) and B) probable traces of an overlying TB cold abscess on the anterior surface of the sacrum (Vésztő – Mágori-halom, 45th–49th century BC, Grave No. 6, *Maturus*, female) (Spekker *et al.*, 2012).

Formation of an extra-vertebral cold abscess or *abscessus frigidus* (*i.e.*, a slowly progressive abscess without characteristic signs of inflammation, such as heat, erythema or tenderness that may become encapsulated and calcified over time) around osteolytic vertebral lesions is a common complication of tuberculous spondylitis – occurring in about two-thirds of all cases with spinal TB – that is secondary to the extension of infection from the affected area of the vertebral column into adjacent ligaments and soft tissues. The TB material may be accumulated within the prevertebral and/or paravertebral spaces with the formation of prevertebral (*e.g.*, retropharyngeal abscess in the cervical region), as well as unilateral or bilateral paravertebral abscesses (*e.g.*, psoas abscess in the thoracolumbar region), commonly associated with fistulae. The TB cold abscess may remain localised at the initial site of infection; however, in most cases, it extends vertically (usually downwards) beneath the anterior and/or posterior longitudinal ligaments or along the fascial planes. In response to an overlying TB cold abscess, erosive cortical bone destruction, as well as reactive new bone formations, may occur on the adjacent surfaces of bones (*e.g.*, vertebrae, hip bones, and femora) **(Fig. 2B)**. The above-mentioned bony changes and/or remains of TB cold abscesses were occasionally observed during the palaeopathological examination of ancient human skeletal and mummified remains dated to different archaeological periods (*e.g.*, Dutour *et al.*, 1999; Marcsik *et al.*, 2009; Madkour, 2011a; Spekker *et al.*, 2012; Kajdocsi Lovász, 2015; Molnár *et al.*, 2015) (Aufderheide & Rodríguez-Martín, 1998; Ortner, 2003; Garg & Somvanshi, 2011; Rasouli *et al.*, 2012; Acharya & Gibbs, 2016; Ingole *et al.*, 2016; Patel *et al.*, 2016; Turliuc *et al.*, 2016; Esteves *et al.*, 2017).

Other types of spinal TB (*e.g.*, central, anterior subligamentous, posterior, and articular forms) all together comprise approximately 5 to 10% of all cases with tuberculous spondylitis. The central type, resulting from haematogenous dissemination of TB bacteria via the *Batson*'s paravertebral venous plexus into the spine (retrograde blood flow), arises from the mid-section of one or more distant or adjacent vertebral bodies instead of their subchondral region. Later, the infection extends centrifugally to involve the entire vertebral body without or with minimal involvement of the intervertebral disc. Destruction of the vertebral body by TB osteolytic lesions may lead to its subsequent ballooning and concentric collapse that resembles *vertebra plana* and indicates complete compression of the vertebral body under the weight of the trunk, with consequent development of spinal deformity (Kumar, 2005; Agrawal *et al.*, 2010; Garg & Somvanshi, 2011; Esteves *et al.*, 2017).

The anterior subligamentous form of spinal TB is characterised by erosive cortical bone destruction mainly affecting the anterior and lateral surfaces of the involved vertebral

bodies. It may be secondary to the development of an extra-vertebral TB abscess between the vertebral body and the anterior longitudinal ligament or periosteum that may extend vertically (upwards or downwards) over several contiguous vertebrae beneath the aforementioned fibrous structures. Subligamentous spread of the TB abscess results in stripping of the anterior longitudinal ligament and periosteum from the anterior and lateral vertebral surfaces that leads to deprivation of the periosteal blood supply to the vertebral body with consequent ischaemia. The combination of ischaemic and pressure effects caused by the presence and extension of the extra-vertebral TB abscess results in shallow erosion of the anterior and lateral surfaces of the affected vertebral bodies that produces a scalloped appearance (*i.e*., anterior "gouge defect" or "aneurysmal syndrome"). As the pathological process progresses, it may subsequently involve the anterior and lateral portions of the affected vertebral bodies, since avascular vertebrae are more susceptible to infection. Besides the erosive cortical bone destruction, interconnecting, stabilising bony extensions (*i.e*., bony bridges) may occur on the anterior and/or lateral aspects of the involved adjoining vertebral bodies that contribute to the preservation of the intervertebral disc spaces and prevention of the development of vertebral collapse and subsequent spinal deformity even in cases with severe bone loss (Sorrel & Sorrel-Dejerine, 1932; Reid, 1949; Aufderheide & Rodríguez-Martín, 1998; Palmer, 2002; Ortner, 2003; Kumar, 2005; Spiegel *et al*., 2005; Agrawal *et al.*, 2010; Garg & Somvanshi, 2011; Rivas-Garcia *et al*., 2013).

In one of the less frequent types of spinal TB (2–3%), namely in the posterior or appendiceal form, the granulomatous inflammatory reaction is isolated to the posterior vertebral elements, without or with secondary involvement of the vertebral body. The disease may result from haematogenous spread of TB bacteria via the posterior external venous plexus (retrograde blood flow) or by direct inoculation of pathogens into the posterior vertebral elements (*i.e*., the pedicles and laminae of the vertebral arch, and the transverse and spinous processes). In posterior tuberculous spondylitis, the TB osteolytic lesions mainly affect only one vertebra, with pedicles and laminae representing the most common sites of involvement. Destruction of the posterior vertebral elements only is rarely accompanied by spinal deformity, since barely affecting the stability of the vertebral column; however, it is often associated with severe neurological deficit (*e.g*., paralysis), due in part to the compressive effect exerted by the TB material on the spinal cord or *cauda equina* (Aufderheide & Rodríguez-Martín, 1998; Ortner, 2003; Sridhar & Krishnan, 2009; Garg & Somvanshi, 2011; Yazdi & Rahimizadeh, 2012; Al-Khudaira & Meir, 2014; Kumar, 2017).

Similar to the posterior type, the articular or synovial form of spinal TB occurs in only the minority of patients with tuberculous spondylitis (*e.g.*, the involvement of the atlanto-occipital joint can be observed in less than 1% of all cases with spinal TB). It is usually secondary to haematogenous dissemination of TB bacteria through synovial vessels into the synovial membrane of the atlanto-occipital, atlanto-axial or facet joints (anterograde blood flow), with subsequent development of TB arthritis of the affected intervertebral joints (Ortner, 2003; Garg & Somvanshi, 2011; Fuentes Ferrer *et al.*, 2012; Qureshi *et al.*, 2013; Mansukhani *et al.*, 2014; Kumar, 2017).

In addition, circumferential, multiple, smooth-walled resorptive lesions (pits) often connected by horizontal vascular impressions on the anterior and lateral aspects of the thoracic **(Fig. 3A−B)** and lumbar vertebral bodies – representing hypervascularisation of the involved vertebrae – were described in several palaeopathological and palaeomicrobiological studies on osteoarchaeological series and documented skeletal collections (*e.g.*, Ménard, 1888; Baker, 1999; Haas *et al.*, 2000; Maczel, 2003; Giacon, 2008; Spekker *et al.*, 2012; Baker *et al.*, 2015; Guichón *et al.*, 2015; Mariotti *et al.*, 2015; Masson *et al.*, 2015; Molnár *et al.*, 2015) as probable but not specific signs of early-stage spinal TB.

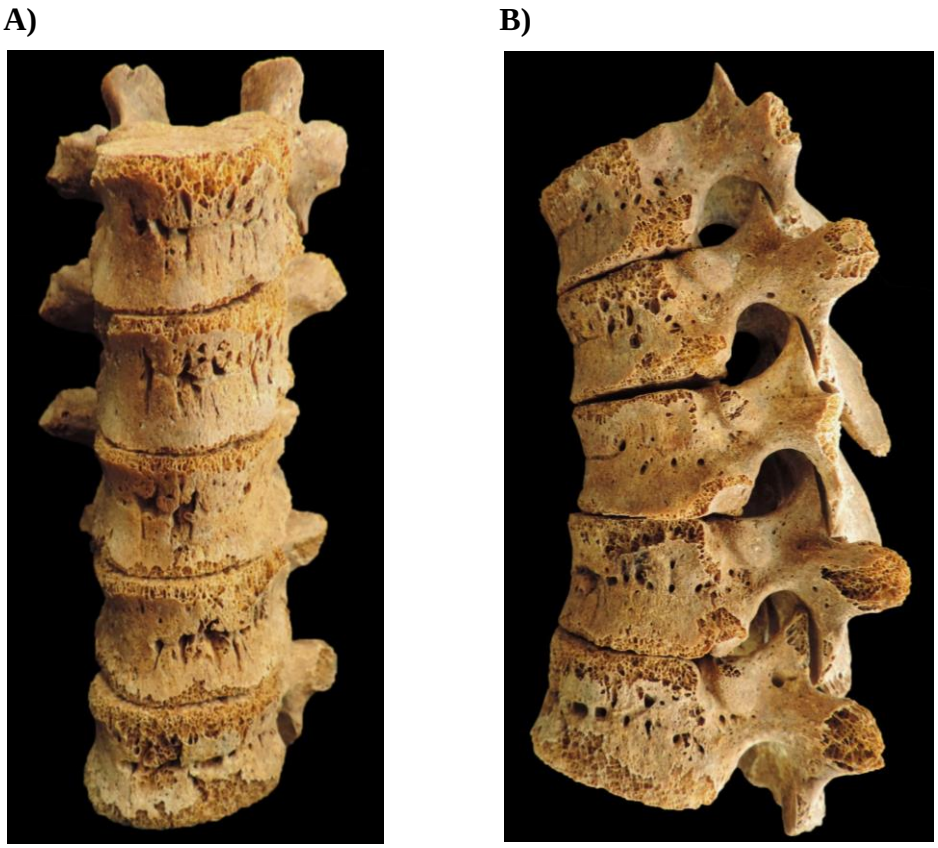


Figure 3: Circumferential, multiple, smooth-walled pits connected by horizontal vascular impressions on the A) anterior and B) left lateral aspects of the T5–9 vertebrae (Vésztő – Mágori-halom, Hungary, 45th–49th century BC, Grave No. 33, *Juvenis*, male) (Spekker *et al.*, 2012).

In this day and age, extra-spinal TB osteomyelitis **(Fig. 4A−B)** is a rare medical condition, accounting for about 2 to 3% of all cases with osteoarticular TB. Any bone of the extra-spinal skeleton (*e.g.*, sternum, ribs, as well as hip and cranial bones) can be affected by the disease but the metaphyses of short and long tubular bones are most frequently predisposed to be involved because of their rich blood supply. Similar to other forms of osteoarticular tuberculosis, extra-spinal TB osteomyelitis is generally secondary to haematogenous spread of TB bacteria from a primary location outside the skeleton into the bone. Lodgement of pathogens into the cancellous bone triggers the onset of its granulomatous inflammation with consequent formation of round or oval TB osteolytic lesions at sites of bacterial deposition. As the pathological process progresses, extra-osseous TB cold abscesses overlying the osteolytic lesions may develop that can be accompanied by fistulous perforation of the skin. Later, the infection may extend from the initial metaphyseal focus into the epiphysis, with subsequent TB arthritis of the adjacent joint. Although extra-spinal TB osteomyelitis typically affects only one bone in the skeleton, simultaneous involvement of multiple bones may also occur in some patients, with the TB osteolytic lesions in different stages of development, as bacterial seeding of the affected bones may occur at different times during the course of the disease. Signs of extra-spinal TB osteomyelitis were occasionally identified in different bones – such as the cranial bones (*e.g.*, Blondiaux *et al.*, 1999; Strouhal, 1999; Dawson & Brown, 2012; Colombo *et al.*, 2015), tibia (*e.g.*, Horáčková *et al.*, 1999), humerus (*e.g.*, Blondiaux *et al.*, 1999) or clavicle (*e.g.*, Spekker *et al.*, 2012) – during the palaeopathological examination of ancient human skeletons and mummies (Aufderheide & Rodríguez-Martín, 1998; Kam *et al.*, 2000; Ortner, 2003; Spiegel *et al.*, 2005; Vanhoenacker *et al.*, 2009; Madkour, 2011b; Wiratnaya *et al.*, 2017).

A) **B)**

Figure 4: Smooth-walled lytic lesions on the A) acromial (7x8x6 mm) and B) sternal (6x7x8 mm) ends of the right clavicle, probably representing TB osteomyelitis (Vésztő – Mágori-halom, Hungary, 45th–49th century BC, Grave No. 6, *Maturus*, female) (Spekker *et al.*, 2012).

The second most common form of skeletal TB is tuberculous arthritis of the extra-spinal joints, particularly of the large, weight-bearing joints, such as the hip (*i.e.*, *coxitis tuberculosa*) and knee (*i.e.*, *gonitis tuberculosa*) **(Fig. 5A−B)**. It typically affects only one joint (*i.e.*, monoarticular involvement) (~90%) and – similar to tuberculous spondylitis – has an insidious onset and a slowly progressive course. TB arthritis is usually secondary to seeding of TB bacteria into the synovial membrane of the joint capsule by haematogenous dissemination of pathogens through synovial vessels or into the subchondral bone by contiguous spread of microorganisms from an osteomyelitic focus in the metaphysis (more common in children) or epiphysis (more common in adults) of long tubular bones; therefore, the disease may begin in the synovial membrane (*i.e.*, TB synovitis), in the subchondral bone or in both concomitantly. When TB arthritis starts as a synovitis, granulomatous inflammation of the synovial membrane results in synovial effusion and hypertrophy over the articular cartilage, as well as studding of the inner surface of the synovial membrane with tubercles. Invasion of the articular cartilage by the pannus initially formed at the joint periphery leads to progressive marginal erosion of the underlying articular cartilage and subsequently of the subchondral bone on both sides of the affected joint. Later, spreading of the pannus across the joint (from the periphery to the weight-bearing central areas) results in ultimate loss of the articular cartilage and further bone erosion, with gradual diminution and eventual obliteration of the articular cavity. Progressive destruction of the joint with consequent instability may be associated with the development of subluxation or dislocation. In more advanced stages of TB arthritis, reactive new bone formations may occur along the periarticular bone, and the disease may terminate in bony ankylosis of the affected joint. Extension of the infection into adjacent ligaments and soft tissues may result in the formation of cold abscesses with associated fistulae. When TB arthritis starts in the subchondral bone, the granulomatous inflammation of the cancellous bone results in the development of osteolytic lesions that may erode into the articular cavity, with subsequent TB involvement of the synovial membrane. Articular changes very likely attributable to tuberculosis were detected in extra-spinal weight-bearing (*e.g.*, Blondiaux *et al*., 1999; Buzhilova *et al*., 1999; Gładykowska-Rzeczycka, 1999; Horáčková *et al*., 1999; Marcsik *et al*., 1999, 2009; Maczel, 2003; Ősz *et al*., 2009; Kajdocsi Lovász, 2015; Molnár *et al*., 2015; Paja *et al*., 2015; Cieślik, 2017) and non-weight-bearing (*e.g.*, Bennike, 1999; Gładykowska-Rzeczycka, 1999; Maczel, 2003; Kajdocsi Lovász, 2015) joints in a number of ancient human remains dated to different archaeological periods (Aufderheide & Rodríguez-Martín, 1998; Ortner, 2003;

Spiegel *et al*., 2005; Vanhoenacker *et al*., 2009; Al-Sayyad & Abumunaser, 2011; Mohapatra *et al*., 2011; Pigrau-Serrallach & Rodríguez-Pardo, 2013; Tseng *et al*., 2014; Shapiro, 2015).

A) **B)**

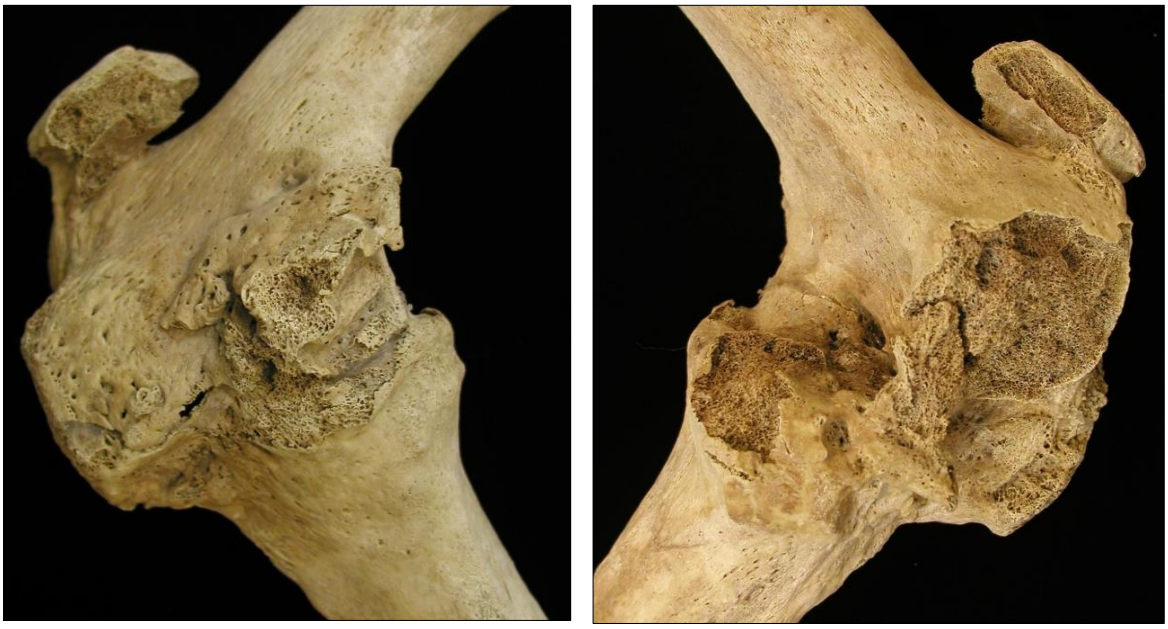


Figure 5: TB involvement of the right knee joint resulting in fusion of the adjoining surfaces of the right femur and tibia in a flexed position: A) antero-medial view and B) lateral view (Bátmonostor – Pusztafalu, Hungary, 12th–16th century AD, Grave No. 993, *Senium*, male) (photos by *László Paja*) (Paja *et al*., 2015).

Besides the above-mentioned lesions, periosteal new bone formations (PNBFs) affecting the visceral surface of ribs, as well as the shaft of short and long tubular bones, were associated with TB following examination of skeletons of known cause of death from modern identified skeletal collections (*e.g*., *Hamann−Todd Human Osteological Collection*, *Robert J. Terry Anatomical Skeletal Collection*, and *Coimbra Identified Skeletal Collection*), as they occurred more frequently in individuals reported to have died of TB than in specimens identified to have died of non-tuberculous (NTB) causes (*e.g*., Kelley & Micozzi, 1984; Roberts *et al*., 1994; Winland *et al*., 1997; Rothschild & Rothschild, 1998, 1999; Santos & Roberts, 2001, 2006; Hershkovitz *et al*., 2002; Maczel, 2003; Matos & Santos, 2006; Giacon, 2008; Mariotti *et al*., 2015).

PNBFs on the inner surface of ribs **(Fig. 6)** may very likely result from pulmonary TB that provokes a localised or generalised inflammatory response on the visceral costal surfaces by initiating the development of TB pleurisy with or without collection of pus in the pleural cavity (*i.e*., pleural empyema). PNBFs particularly involve ribs in the middle part of the thoracic cage (4th–8th) – especially at their vertebral ends –, with the pattern and

distribution of lesions resembling that of most often observed in the affected lung tissue during the pathogenesis of pulmonary TB. Localised PNBFs involving one or a few ribs may represent a focal TB pulmonary lesion subjacent to the pleura that leads to transpleural inflammation of ribs without pleural empyema; whereas generalised and multiple level PNBFs affecting many ribs may be indicative of a widespread costal inflammation with pleural empyema. Nevertheless, several pulmonary diseases other than TB, as well as non-pulmonary ones (*e.g.*, acute lobar pneumonia, bronchiectasis, metastatic carcinoma, pyogenic osteomyelitis, syphilis, and actinomycosis), can also stimulate the formation of PNBFs on the inner surface of ribs (Roberts *et al*., 1994; Santos & Roberts, 2001, 2006; Matos & Santos, 2006; Mariotti *et al*., 2015).

Figure 6: PNBFs on the visceral surface of two rib fragments (Tápé – Széntéglaégető, Hungary, 12th–13th century BC, Grave No. 157, *Maturus*, male) (photo by *László Paja*) (Spekker *et al*., 2016).

Diffuse, bilateral, symmetrical PNBFs predominantly affecting the distal and periarticular parts of the shaft of short and long tubular bones **(Fig. 7A−C)** are characteristic features of hypertrophic pulmonary osteopathy (HPO). Although the aetiology of HPO is still unknown, the secondary form of the disease is frequently associated with pulmonary (*e.g.*, pulmonary TB and lung cancer), as well as non-pulmonary (*e.g.*, inflammatory bowel disease and cirrhosis) conditions. Similar to the previously discussed non-endocranial bony changes probably related to TB, signs of HPO were also observed during the palaeopathological examination of ancient human remains (*e.g.*, Spekker *et al*., 2012; Masson *et al*., 2013, 2015; Baker *et al*., 2015; Hershkovitz *et al*., 2015; Anselmo *et al*., 2016) (Kelly *et al*., 1991; Assis *et al*., 2011; Yap *et al*., 2017).

Tuberculous involvement of the central nervous system (such as TB meningitis) may also result in the development of pathological bony changes, affecting the endocranial surface of the skull.

Figure 7: PNBFs on the A) lateral surface of the diaphysis of the right tibia, B) anterior surface of the diaphysis of the right femur, and C) postero-medial surface of the diaphysis of the left radius (Vésztő – Mágori-halom, Hungary, 45th–49th century BC, Grave No. 6, *Maturus*, female) (Spekker *et al*., 2012).

A)

B)

C)

1.4 Palaeopathological diagnosis of tuberculosis – Endocranial bony changes

Nowadays, CNS TB – one of the most devastating clinical manifestations of tuberculosis – occurs in approximately 1% of all active TB cases and accounts for 5 to 15% of extra-pulmonary TB cases. TB may be exclusively confined to the CNS; however, concomitant active extra-neural forms of the disease – such as pulmonary TB, miliary TB or spinal TB – may be present in about one-half of the patients with CNS TB. Furthermore, at autopsy, a large number of individuals died of pulmonary TB without developing neurological symptoms revealed tubercles in the CNS; therefore, indicating that involvement of the central nervous system in pulmonary TB is quite common (Arbeláez *et al*., 2004; Katti, 2004; Gauba & Varma, 2005; Bill, 2006; Rock *et al*., 2008; Vinnard & Macgregor, 2009; Cherian & Thomas, 2011; Christensen *et al*., 2011; Marx & Chan, 2011; Bini & Hernández Pando, 2014; Daniele, 2014).

Usually, tuberculosis of the CNS results from haematogenous dissemination of TB bacteria from a primary location outside the CNS (such as the lungs or the gastrointestinal tract) and is characterised by a slowly progressive granulomatous inflammatory reaction that may affect the meninges, or the brain or spinal cord parenchyma. CNS TB develops in two stages. The initial stage involves the formation of small (0.5–2 mm) tubercles − also known as *Rich* foci − around TB bacteria deposited in the CNS via blood circulation during or shortly after the bacteraemic stage of primary infection or late reactivation of tuberculosis elsewhere in the body. Following their establishment, *Rich* foci may remain dormant for many years. Later, the enlargement or rupture of one or more *Rich* foci results in the development of different types of CNS TB (*e.g*., tuberculous meningitis, tuberculomas, and abscesses) (Rich & McCordock, 1933; Garg, 1999, 2010; Bernaerts *et al*., 2003; Khoo *et al*., 2003; Arbeláez *et al*., 2004; Katti, 2004; Gauba & Varma, 2005; Bill, 2006; Myers, 2007; Rock *et al*., 2008; Be *et al*., 2009; Vinnard & Macgregor, 2009; Bano *et al*., 2012; Brancusi *et al*., 2012; Bini & Hernández Pando, 2014; Daniele, 2014; Chaudhary *et al*., 2017).

The most common form of TB involvement of the CNS is tuberculous meningitis (TBM) of the leptomeninges (*i.e*., the *pia* and *arachnoid mater*), also known as *leptomeningitis tuberculosa*, accounting for about 70 to 80% of all cases with CNS TB. One of the most important risk factors for TBM is age. In low-income and middle-income countries with a high incidence of tuberculosis, children under the age of 5 years represent the most vulnerable group affected by the disease, usually developing TBM within 3 to 6 months of primary infection. However, in high-income countries with a low incidence of

tuberculosis, TBM occurs predominantly in adults, particularly in immigrants from TB-endemic regions of the world and in HIV-positive people, who are five times more likely to develop the disease than HIV-negative individuals. In adults, TBM usually results from the reactivation of dormant *Rich* foci, often many years after the primary infection. Besides age and HIV-infection, other predisposing factors for TBM include malnutrition, alcoholism, *diabetes mellitus*, and recent use of immunosuppressive drugs (such as corticosteroids) (Garg, 1999, 2010; Bernaerts *et al*., 2003; Katti, 2004; Gauba & Varma, 2005; Bill, 2006; Myers, 2007; Rock *et al*., 2008; Thwaites *et al*., 2009; Cherian & Thomas, 2011; Christensen *et al*., 2011; Bano *et al*., 2012; Thwaites, 2013; Bini & Hernández Pando, 2014; Daniele, 2014; Taheri *et al*., 2015; Tyagi *et al*., 2016; Chaudhary *et al*., 2017; Vita *et al*., 2017).

At any age, TBM is one of the most severe extra-pulmonary manifestations of TB, with high short-term mortality and substantial excess morbidity among survivors: approximately one-third of the affected individuals die of the disease and up to one-half of the survivors remain with serious neurological sequels, despite the initiation of anti-tuberculosis therapy. Early, accurate diagnosis and prompt, adequate treatment are crucial in determining the clinical outcome of TBM; nevertheless, these are hampered by several factors: the presenting clinical and radiological features of the disease are often non-specific and may mimic those of other infectious or non-infectious conditions; the conventional laboratory tests may be slow and/or relatively insensitive; and the choice of anti-tuberculosis drugs, dosage regimen, and therapy duration are empiric in TBM and largely based on the experience in treatment of pulmonary tuberculosis. The emergence of MDR-TB further complicates the management of the disease by causing a delay in diagnosis and limiting therapeutic options: drug-susceptibility tests may be time-consuming and some of the second-line drugs have a poor cerebrospinal fluid (CSF) penetration. If left untreated, TBM usually leads to death within 5 to 8 weeks after the onset of its symptoms; although, in some cases (*e.g*., Griffith, 1919; Schmidt, 1941; Green, 1943; Saito, 1956; Traub *et al*., 1986; Kent *et al*., 1993; Newton, 1994), the disease has a protracted course that can last for several months or even years (Thwaites *et al*., 2002; Bernaerts *et al*., 2003; Arbeláez *et al*., 2004; Gauba & Varma, 2005; Thwaites & Tran, 2005; Bill, 2006; Be *et al*., 2009; Garg, 2010; Christensen *et al*., 2011; Marx & Chan, 2011; Brancusi *et al*., 2012; Thwaites, 2013; Bini & Hernández Pando, 2014; Daniele, 2014; Rajashekar *et al*., 2014; van Toorn & Solomons, 2014; Ramirez-Lapausa *et al*., 2015; Taheri *et al*., 2015; Vita *et al*., 2017).

As for its pathogenesis, TBM usually develops subsequent to the rupture of one or more meningeal, subpial, and/or subependymal caseating *Rich* foci into the subarachnoid

space or into the ventricular system, both occupied by the CSF. The release of sufficient numbers of TB bacteria into the CSF triggers the onset of diffuse granulomatous inflammation of the leptomeninges, with a strong predilection for the basal areas of the brain. Nonetheless, not only the *pia* and *arachnoid mater* but additionally, the *dura mater* can be affected by the disease. Besides the small tubercles primarily formed in the leptomeninges and later also in the *dura mater*, characteristic pathological features of TBM include enhancing basal meningeal exudate, progressive hydrocephalus, and vasculitis of blood vessels adjacent to or traversing the exudate (Aschoff, 1936; Garg, 1999, 2010; Bernaerts *et al*., 2003; Arbeláez *et al*., 2004; Katti, 2004; Donald *et al*., 2005; Gauba & Varma, 2005; Bill, 2006; Be *et al*., 2009; Vinnard & Macgregor, 2009; Christensen *et al*., 2011; Bano *et al*., 2012; Brancusi *et al*., 2012; Bini & Hernández Pando, 2014; Rajashekar *et al*., 2014; Taheri *et al*., 2015; Chaudhary *et al*., 2017).

In the initial stage of TBM, the granulomatous inflammatory reaction results in the formation of a thick, gelatinous or slightly nodular exudate between the two layers of the leptomeninges, primarily located in close vicinity to the basal subarachnoid cisterns, along the infero-medial surface of the frontal lobes, the antero-medial surface of the temporal lobes, the floor of the third ventricle, and the superior aspect of the cerebellum. From here, the inflammatory exudate rapidly extends towards the basal subarachnoid cisterns (*i.e*., the interpeduncular and suprasellar cisterns). As the disease progresses, the infection may gradually spread to other subarachnoid cisterns, such as the prepontine, ambient, and *Sylvian* cisterns, and eventually, it can reach the meninges covering the cerebral convexities, the ependymal surface of the ventricles, and the choroid plexuses (Bernaerts *et al*., 2003; Arbeláez *et al*., 2004; Gauba & Varma, 2005; Rock *et al*., 2008; Vinnard & Macgregor, 2009; Bano *et al*., 2012; Raut *et al*., 2013; Taheri *et al*., 2015; Chaudhary *et al*., 2017).

The inflammatory exudate, partially or completely filling the subarachnoid space and the ventricular pathways, may result in the development of persistent and progressive hydrocephalus (*i.e*., disturbance of CSF flow, reabsorption or production, leading to an increase in volume occupied by the cerebrospinal fluid in the CNS) that is one of the most common complications of tuberculous meningitis, occurring in more than two-thirds of the cases. In TBM, either the communicating or the non-communicating form of hydrocephalus can develop, with the former type being more frequent. The communicating type of TB hydrocephalus generally occurs when the inflammatory exudate blocks the flow of the cerebrospinal fluid within the subarachnoid space, resulting in impaired reabsorption of the CSF. In later stages of the disease, inflammation of the ependymal surface of the ventricles

and of the choroid plexuses leads to overproduction of the CSF, also contributing to the progression of communicating TB hydrocephalus. The non-communicating form of TB hydrocephalus develops when the inflammatory exudate obstructs the pathways connecting the ventricles (*i.e*., the foramina of *Monro* and the aqueduct of *Sylvius*) or the passages between the fourth ventricle and the subarachnoid space (*i.e*., the foramina of *Luschka* and the foramen of *Magendie*), resulting in blockage of the CSF flow. Tuberculous hydrocephalus is often associated with elevated intracranial pressure (eICP) (Bernaerts *et al*., 2003; Arbeláez *et al*., 2004; Gauba & Varma, 2005; Rajshekhar, 2009; Vinnard & Macgregor, 2009; Bano *et al*., 2012; Morgado *et al*., 2013; Nielsen & Breedt, 2013; Raut *et al*., 2013; van Toorn & Solomons, 2014; Taheri *et al*., 2015; Tyagi *et al*., 2016).

Since the late 20th century, palaeopathological studies on osteoarchaeological series (*e.g*., Schultz, 1993, 1999, 2001, 2003; Templin & Schultz, 1994; Teschler-Nicola *et al*., 1994, 2015; Jankauskas & Schultz, 1995; Jankauskas, 1999; Maczel, 2003; Schultz & Schmidt-Schultz, 2015) and documented skeletal collections (*e.g*., Hershkovitz *et al*., 2002; Maczel, 2003; Schultz & Schmidt-Schultz, 2015) have revealed a positive correlation between TBM and a number of endocranial bony alterations, namely abnormally pronounced digital impressions (APDIs), periosteal appositions (PAs), abnormal blood vessel impressions (ABVIs), *serpens endorcrania symmetrica* (SES), and granular impressions (GIs).

Digital impressions (DIs), also known as convolutional markings, on the inner surface of the skull (*i.e*., shallow depressions resembling to the imprint of a finger and corresponding to cerebral gyri that are intervened by thicker bony ridges corresponding to cerebral sulci) are probably formed by localised pressure of the pulsating brain underlying the bone. Although very pronounced DIs, generally confined to the base and lower two-thirds of the skull vault, may be normal in childhood (particularly during periods of rapid brain growth), their prominence decreases during adolescence. In adulthood, the presence of **abnormally pronounced digital impressions (Fig. 8)** over the upper portion of the skull vault indicates a prolonged rise in the intracranial pressure: according to estimates, the formation of APDIs secondary to eICP requires at least 10 weeks. Although APDIs can be caused by TB hydrocephalus accompanied by eICP, they are not pathognomonic features of TBM, since other pathological conditions (such as other CNS infections, brain tumours or haemorrhages) can also result in the development of eICP (Schüller, 1940–41; du Boulay, 1956, 1980; Bell, 1978; Schultz, 1993, 2001, 2003; Mahomed *et al*., 2012; Paul *et al*., 2013, 2014; Desai *et al*., 2014; Pemmaiah, 2015).

Figure 8: APDIs on the endocranial surface of the squamous part of the frontal bone (Eperjes – Ifjú Gárda Tsz., Hungary, 10th–11th century AD, Grave No. 4/A, *Infantia II*) (Spekker *et al*., 2014).

Abnormal blood vessel impressions (Fig. 9A−B, 10A−B) and **periosteal appositions (Fig. 9B, 10A−B)** localised on the inner surface of the skull were recognised as vestiges of inflammatory and/or haemorrhagic processes of the meninges (*e.g*., Mensforth *et al*., 1978; Schultz, 1993, 1999, 2001, 2003; Maczel, 2003; Lewis, 2004). These non-specific bony changes may be generated by a number of infectious (*e.g*., non-specific and specific meningitis) and non-infectious (*e.g*., trauma and scurvy) conditions, including TBM. The initial stage of the haemorrhagic process involves the formation of small, patch-like areas of very short, sinuous, branching blood vessel impressions extending into the endocranial lamina of the skull consequent to the development of an epidural haemorrhage. As the meningeal process progresses, ABVIs may be covered by appositions of newly formed bone (PAs) with a fibrous, porous, irregular, scab-like appearance. In more advanced stages, the groups of tongue-like PAs with a very smooth, more mature appearance are separated by an extensive net-like aggregation of ABVIs. Bony changes resulted from haemorrhagic meningeal reactions can only be found external to the original bone surface. The inflammatory meningeal process is expressed by small, flat, plate-like appositions of newly built bone (PAs) that are oriented tangentially to the endocranial surface of the affected bone. Later, isolated plates may be confluent as one or more layers, their contours become indistinct, and their plate-like character will be lost as a consequence of bone remodelling.

In contrast to the haemorrhagic meningeal processes, the inflammatory reactions always affect the original bone surface, frequently also the deeper structures of the original bone material. Both ABVIs and PAs are generally situated in the APDIs; nevertheless, they may spread over larger areas of the skull vault in more advanced stages. Although the bony vestiges of meningeal processes may be confused by macroscopic examinations only, they can be differentiated by microscopic investigations (*e.g.*, polarised light microscopy) into inflammatory, haemorrhagic, and mixed forms (Mensforth *et al*., 1978; Schultz, 1993, 2001, 2003).

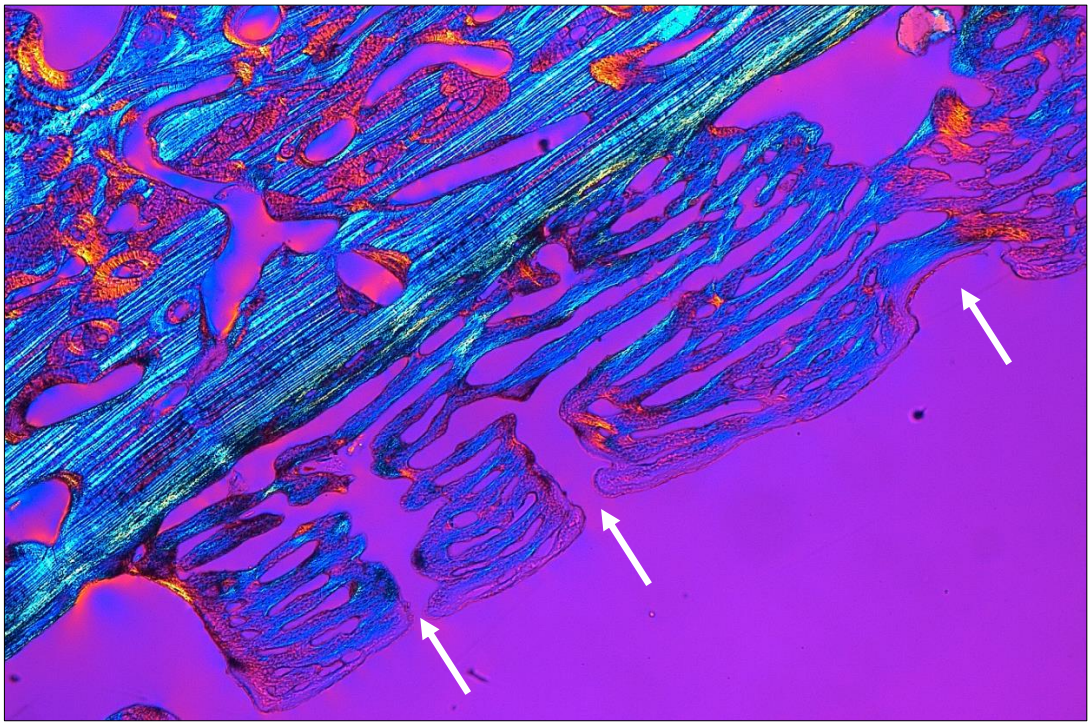
A)

B)

Figure 9: A) ABVIs on the endocranial surface of the squamous part of the frontal bone (Vésztő – Mágori-halom, Hungary, 45th–49th century BC, Grave No. 5, *Infantia II*) (Spekker *et al*., 2012) and B) small ABVIs accompanied by PAs on the inner surface of the frontal bone (Tápé – Széntéglaégető, Hungary, 12th–13th century BC, Grave No. 61, *Infantia I*) (Spekker *et al*., 2016).

Figure 10: Newly built bone formations (PAs) and abnormal blood vessel impressions (white arrows) representing haemorrhagic-inflammatory processes of the meninges probably due to tuberculosis on the endocranial surface of the frontal bone of an adult individual (historic collection of the Department of Pathology, University of Göttingen, Göttingen, Germany; GP-1985616). Thin-ground sections (A): thickness: 50 µm, magnification: 25x and B) thickness: 70 µm, magnification: 25x1.6x) viewed in polarised light using a hilfsobject red 1st order (quartz) as compensator (photos by *Michael Schultz*) (Schultz, 2003).

A)



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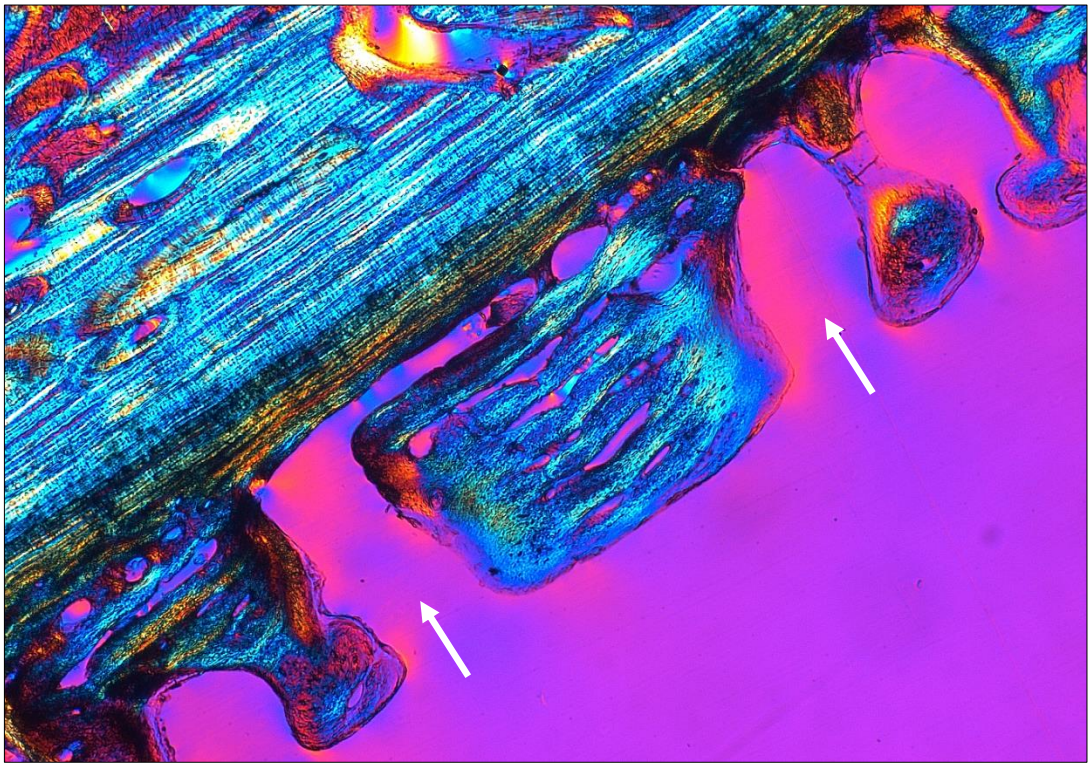


During the examination of skeletons of known cause of death from the *Hamann−Todd Human Osteological Collection*, *Hershkovitz* and his colleagues (2002) observed serpentine branching surface excavations characterised by a maze-like appearance **(Fig. 11)** predominantly in specimens identified to have died of respiratory diseases, particularly of tuberculosis. They termed these lesions, generally located on the endocranial surface of the frontal bone (predominantly around its most protruding parts), parietal bones (particularly around their most protruding part or along the superior sagittal sinus), and occipital bone (mainly along the dominant transverse sinus), as "***serpens endocrania symmetrica***". SES may represent an advanced stage of the haemorrhagic process of the meninges: *Hershkovitz* and his co-workers (2002) attributed it to vascular anomaly, namely to changes in the primary and secondary anastomotic arteries traversing the *dura mater*, subsequent to the development of an epidural haemorrhage. The pathological process leading to the formation of SES affects only the superficial part of the endocranial lamina of the skull with no diploic and/or ectocranial involvement (Hershkovitz *et al*., 2002; Maczel, 2003; Lewis, 2004).

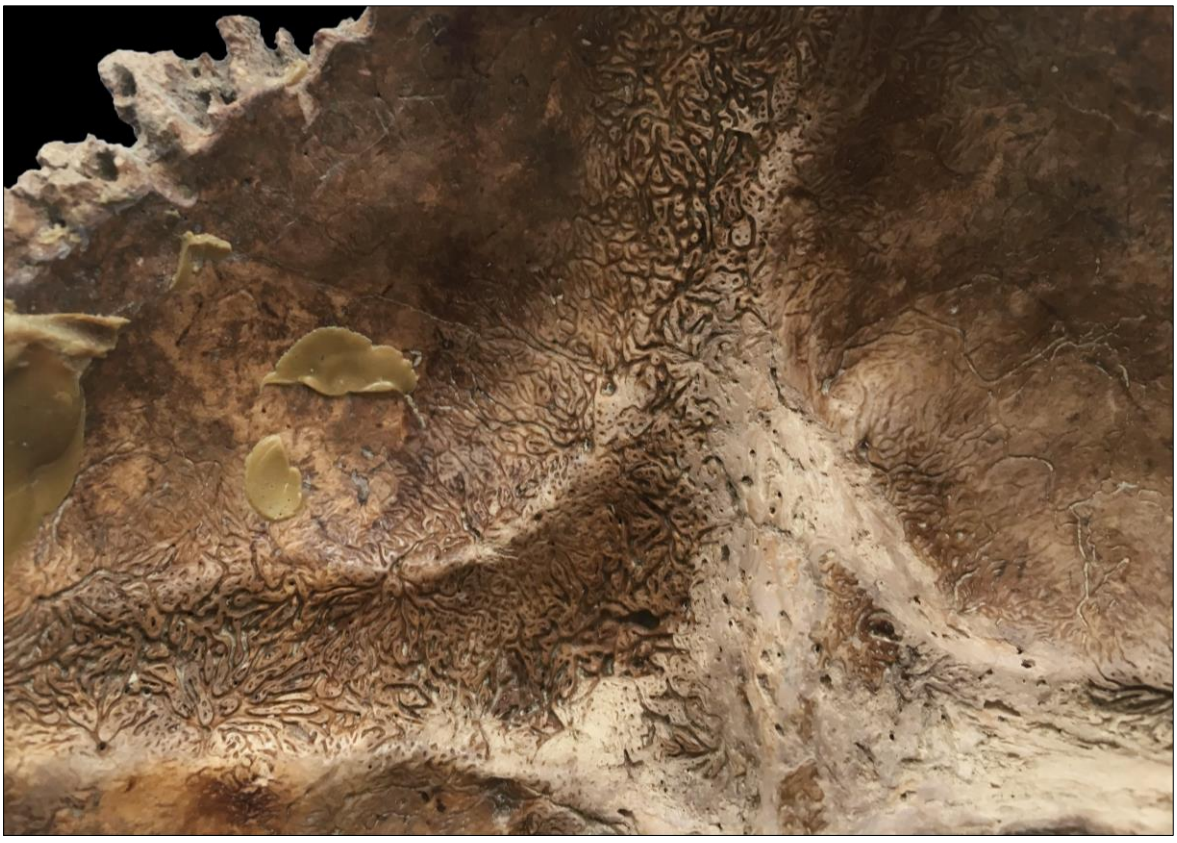


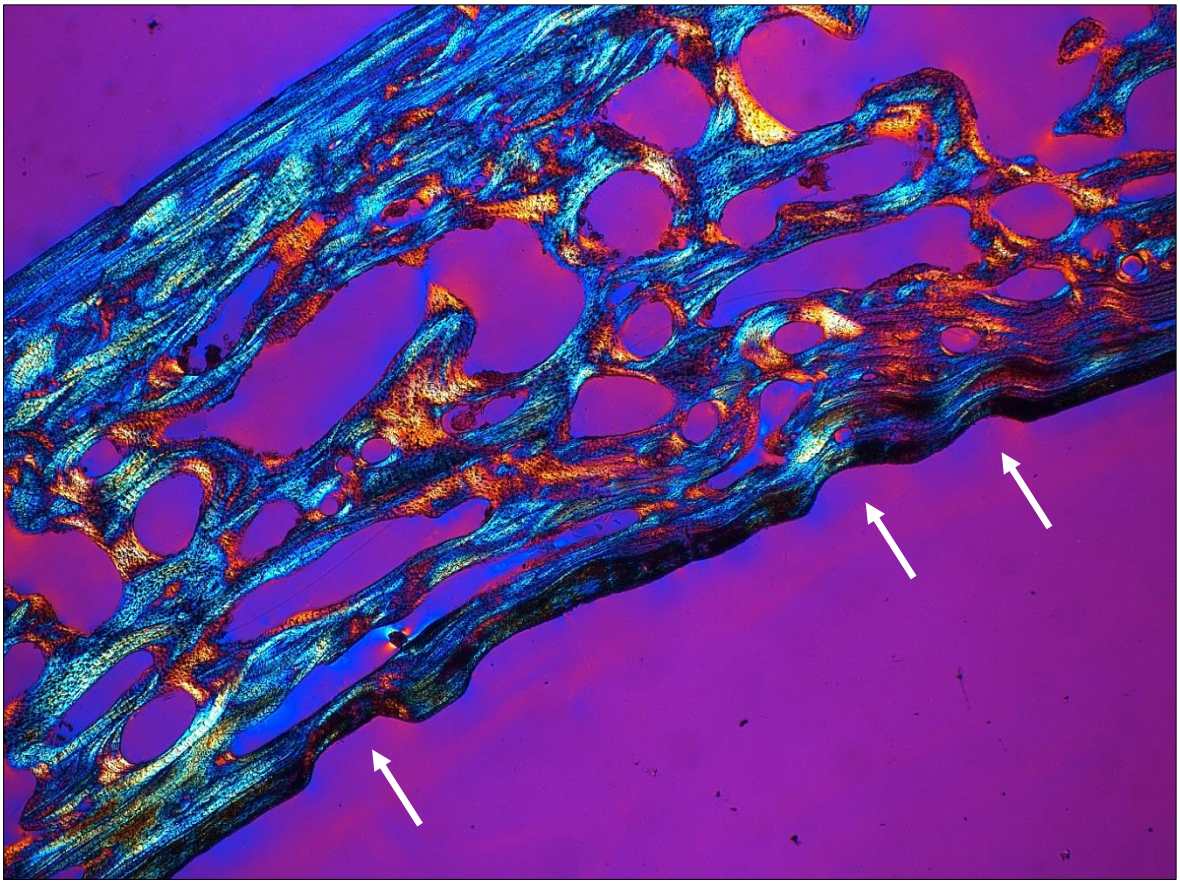
Figure 11: SES along the sagittal and transverse sinuses on the endocranial surface of the squamous part of the occipital bone (Tápé – Széntéglaégető, Hungary, 12th–13th century BC, Grave No. 608, *Juvenis*, male) (Spekker *et al*., 2016).

In contrast to the above-mentioned endocranial alterations, *Schultz* (1999, 2001, 2003) described small (0.5–1.0 mm in diameter), relatively shallow (less than 0.5 mm in depth), roundish impressions with smooth margins and walls **(Fig. 12, 13A−B)**, generally appearing as isolated or confluent lesions grouped in clusters on the inner surface of the skull base or sometimes of the lateral skull vault, as pathognomonic features of TBM. These **granular impressions** – particularly situated in the greater wings of the sphenoid bone, the squamous part of the temporal bones, and the lateral and squamous parts of the occipital bone – may be established by pressure atrophy of the tubercles formed in the *dura mater* during later stages of TBM. Although GIs were named as sharply demarcated erosive defects by *Hershkovitz* and his colleagues (2002), the lesions have an erosive appearance with more irregular shape and sharper walls and margins **(Fig. 13A, C)** only when the pathological process progresses, and the tubercles resulting in the impressions become caseating. Similar to the aforementioned endocranial alteration types, GIs represent a pathological process that affects only the superficial part of the inner lamina of the skull with no diploic and/or ectocranial involvement (Schultz, 1999, 2001, 2003; Hershkovitz *et al*., 2002; Maczel, 2003; Schultz & Schmidt-Schultz, 2015).

Figure 12: GIs accompanied by ABVIs on the endocranial surface of the right parietal bone (Csongrád – Felgyő (Ürmös-tanya), Hungary, 7th–8th century AD, Grave No. 221, *Juvenis*, female?) (Maczel, 2003).

Figure 13: Granular impressions probably caused by pressure atrophy of the tubercles on the endocranial surface of the frontal bone (right side) of a 22-year-old male (individual 59) from the Weisbach Collection (Vienna, Austria; end of the 19th century) who was clinically diagnosed with TB: A) group of three GIs (arrows) (thickness: 70 µm; magnification: 16x), B) a flat, roundish impression with smooth walls (thickness: 70 µm; magnification: 100x), and C) an erosive impression with sharper walls (thickness: 70 µm; magnification: 100x). Thin-ground sections viewed in polarised light using a hilfsobject red 1st order (quartz) as compensator (photos by *Michael Schultz*) (Schultz, 2001, 2003).

A)



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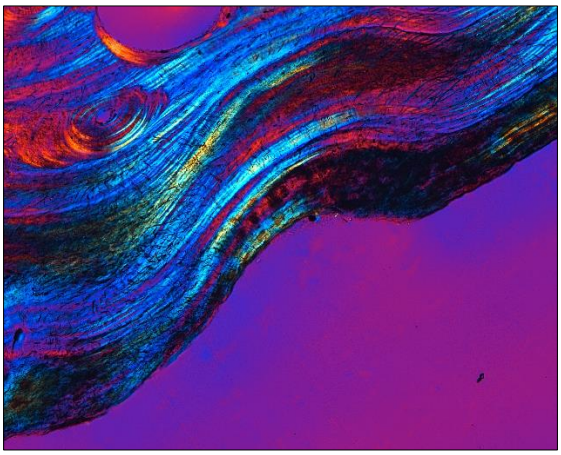

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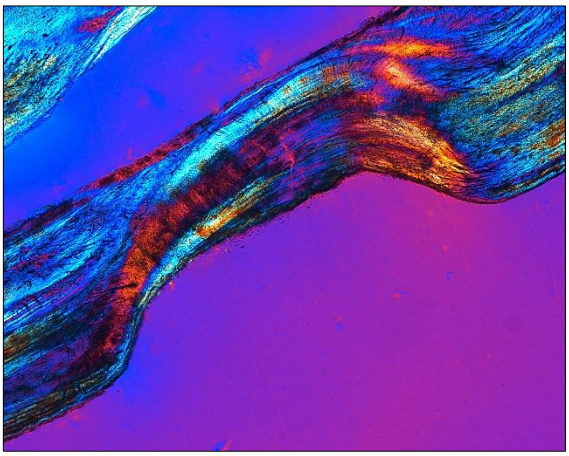


2 AIMS & OBJECTIVES

Using modern medical knowledge, palaeopathologists attempt to establish a retrospective diagnosis of prehistoric and historic TB cases by identifying pathological conditions in bone remains of people lived in the past that may be related to tuberculosis (*e.g.*, vertebral changes, rib lesions, and endocranial alterations). However, on the one hand, probable TB-associated bony changes observed in recent cases may differ from those of detectable in skeletons from archaeological sites, due in part to the introduction of antibiotics in the treatment of tuberculosis. On the other hand, in modern clinical cases, bony lesions cannot be surveyed with macromorphological methods but with medical imaging techniques (*e.g.*, X-ray radiography, computed tomography, and magnetic resonance imaging) only; nevertheless, subtle bony alterations probably related to TB (*e.g.*, PNBFs) may be impossible to be visualised by the latter ones. Therefore, they are not relevant to the diagnosis of tuberculosis in recent cases and are not described as diagnostic criteria for the disease by physicians in the modern medical literature, even if they could be potentially important elements of TB identification for palaeopathologists. Thus, utilisation of modern diagnostic criteria for tuberculosis in the palaeopathological practice may not be appropriate (Santos & Roberts, 2001, 2006; Ortner, 2003; Roberts & Buikstra, 2003; Matos & Santos, 2006).

Nonetheless, detailed analysis of well-documented collections of pre-antibiotic era skeletons of known cause of death can serve as a unique and important basis for the diagnosis of TB in past human populations, since bone remains of specimens identified to have died of tuberculosis and not treated with antibiotics may exhibit similar TB-related bony changes to those of observable in skeletons from archaeological sites; they can be directly surveyed with macromorphological methods; and even subtle bony changes can be recognised in them. Therefore, examination of such collections (*e.g.*, *Hamann−Todd Human Osteological Collection*, *Robert J. Terry Anatomical Skeletal Collection*, and *Coimbra Identified Skeletal Collection*) can contribute to determining the appropriate palaeopathological diagnostic criteria for TB (Santos & Roberts, 2001, 2006; Matos & Santos, 2006; Pálfi *et al.*, 2012; Mariotti *et al.*, 2015).

In the last three decades, the *Terry Collection* has been used to define and refine palaeopathological diagnostic criteria for tuberculosis in several studies (*e.g.*, Roberts *et al.*, 1994; Winland *et al.*, 1997; Rothschild & Rothschild, 1998, 1999; Pálfi *et al.*, 2012); however, probable TB-associated endocranial alterations were beyond the scope of the aforementioned research projects. Although a number of endocranial bony alterations (*e.g.*, APDIs; PAs; ABVIs, including SES; and GIs) have been attributed to TB infection in the palaeopathological literature, their diagnostic value has more recently been questioned (*e.g.*,

Lewis, 2004; Roberts *et al.*, 2009; Janovic *et al*., 2015), as their precise aetiology is still a matter of controversy, and additionally, similar or even the same morphological features can be found in non-TB-related cases, such as in non-specific inflammatory (*e.g*., bacterial meningitis) and haemorrhagic (*e.g*., epidural haematoma) processes.

The main aim of the present PhD dissertation is to expand knowledge and understanding about the development of probable TB-associated endocranial alterations and to improve their palaeopathological interpretation, as well as to contribute to strengthening their diagnostic value in the identification of TB in human osteoarchaeological material. Therefore, review of the modern medical and palaeopathological literature regarding tuberculosis was conducted, with special attention to bony changes likely related to TB. Furthermore, a detailed investigation focusing on the macromorphological characteristics and frequencies of the above-mentioned lesions, as well as of their co-occurrence with each other and with non-endocranial bony changes probably related to TB, was performed on all individuals recorded to have died of different types of tuberculosis in the *Terry Collection*, and on a control group consisting of randomly selected specimens from the remaining skeletons of the *Terry Collection*, identified to have died of causes other than TB.

The objectives of the present PhD dissertation are the following:

1) To macroscopically evaluate skeletons from the *Terry Collection* for the presence of the four types of probable TBM-associated endocranial alterations, as well as for their co-occurrence with each other and with non-endocranial lesions possibly related to TB;
2) To compare the frequencies of the four types of probable TBM-related endocranial alterations, as well as of their co-occurrence with each other and with non-endocranial bony changes possibly associated with tuberculosis, between individuals recorded to have died of TB and specimens identified to have died of causes other than TB, considering sex and age at death of individuals;
3) To macromorphologically characterise the four probable TBM-associated endocranial alteration types detected in skeletons from the *Terry Collection* regarding the prominence (APDIs), as well as the localisation, extent, and number (PAs, ABVIs, and GIs) of lesions on the affected cranial bone(s);
4) To provide example cases showing the most important macromorphological characteristics of the four types of possible TBM-related endocranial alterations; and
5) To evaluate the diagnostic value of the four probable TBM-associated endocranial alteration types examined in skeletons from the *Terry Collection*.

3 MATERIALS & METHODS

3.1 The *Robert J. Terry Anatomical Skeletal Collection*

The *Robert J. Terry Anatomical Skeletal Collection* − currently curated in the Department of Anthropology at the National Museum of Natural History (NMNH) (Smithsonian Institution, Washington, DC, USA) **(Fig. 14A−B)** − consists of 1,728 human skeletons (1,011 males and 717 females) that were accumulated first by *Robert J. Terry*, professor of anatomy and head of the Anatomy Department at Washington University Medical School in St. Louis (Missouri, USA), from the second decade of the 20th century until his retirement in 1941, and later by *Mildred Trotter*, who succeeded *Terry* as anatomy professor, between 1941 and 1967. In the *Terry Collection*, individuals were born between 1828 and 1943 and died between 1905 and 1966, with age at death ranging from 16 to 102 years. Owing to *Terry*'s well-established uniform protocol for the collecting, cataloguing, maceration, and storage of bone remains, almost all of the skeletons in the *Terry Collection* are complete and well-preserved, and for each of them, a series of documentary forms (*e.g.*, morgue record, dental chart, anthropometric and anthroposcopic data form, and bone inventory list) providing various biographical information (*e.g.*, name, sex, age at death, "race", occupation, and cause of death) and basic anthropological data is available at the NMNH. Therefore, the *Terry Collection* serves as an invaluable resource for anthropological and medical research, including developing new criteria for the diagnosis of specific infectious diseases (such as tuberculosis) in osteoarchaeological material from the pre-antibiotic era (Hunt & Albanese, 2005).

A) **B)**

Figure 14: Current locations of skeletons from the *Terry Collection*: A) Natural History Building and B) Museum Support Center (http://2.bp.blogspot.com/-gMOj8xL8pC8/T9-rS_HBYNI/AAAAAAAAAOU/1P-DVfCXlko/s1600/IMG_1616.jpg).

3.2 Materials and methods

As part of a comprehensive research project, a detailed investigation **(Fig. 15A−C)** focusing on the macromorphological characteristics, frequencies, and co-occurrences of different types of pathological bony alterations probably related to tuberculosis (*e.g.*, vertebral changes, rib lesions, and endocranial alterations) was performed on all specimens (N=302) recorded to have died of different types of TB (*e.g.*, pulmonary TB, miliary TB, peritoneal TB, and skeletal TB) in the *Terry Collection* **(Suppl. table 1)**, and on a control group (NTB group) consisting of randomly selected individuals (N=302) from the remaining specimens of the *Terry Collection*, identified to have died of causes other than TB (*e.g.*, other infectious diseases, cardiovascular problems, cancer, and external causes, such as suicide or homicide) **(Suppl. table 2)**. It must be noted that even if the recorded cause of death may not have been tuberculosis, individuals could still have suffered from the disease but their death was attributed to another cause (Roberts *et al.*, 1994; Santos & Roberts, 2001).

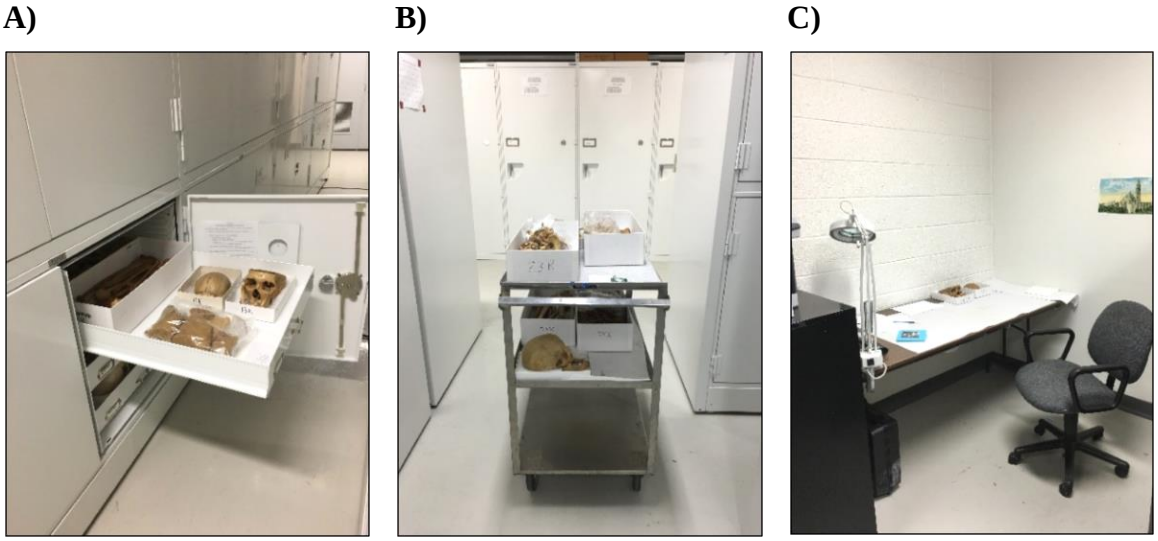


Figure 15: A) Selection, B) moving, and C) evaluation of skeletons in the *Terry Collection*.

From the 604 skeletons surveyed in the *Terry Collection*, 177 were excluded from the examination considering endocranial alterations probably associated with TBM: the skullcap was missing in two cases and the skull was not sectioned in a further 173 cases; therefore, precluding the accurate observation of the inner surface of the skull; whereas the age at death was uncertain in two additional cases; thus, compromising the statistical analysis of data. The remaining 427 late adolescent (16–19 years old; Σ=7; three males and four females) and adult (>20 years old; Σ=420; 272 males and 148 females) individuals with skulls sectioned

in the transverse plane and occasionally also in the mid-sagittal plane were divided into two main groups on the basis of their causes of death:

1) **TB group**, consisting of 234 specimens (169 males and 65 females) identified to have died of TB, with age at death ranging from 16 to 81 years **(Fig. 16, Suppl. table 1)**; and

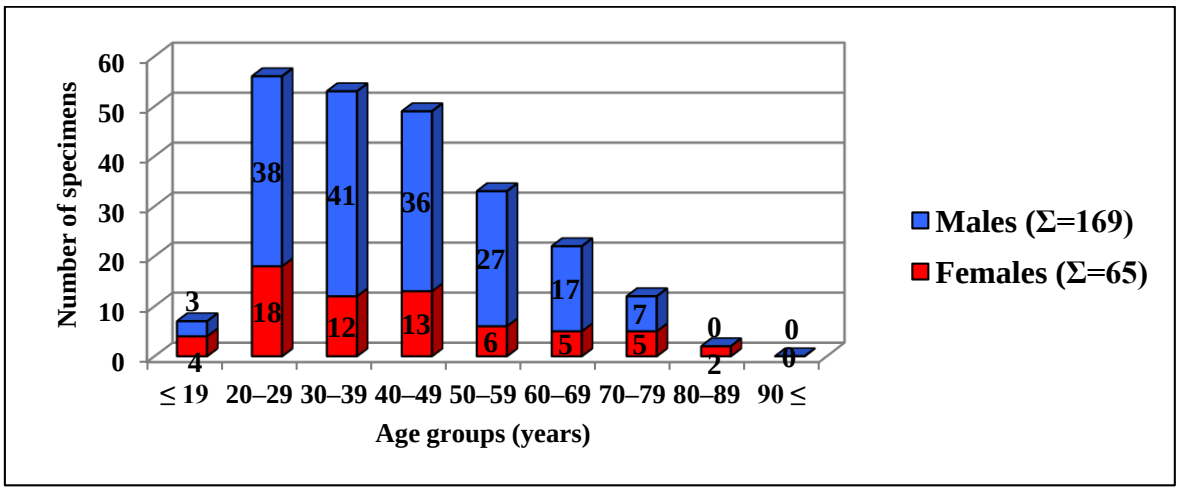


Figure 16: Demographic profile of specimens surveyed in the TB group (Σ=234).

2) **Control (NTB) group**, composed of 193 individuals (106 males and 87 females) recorded to have died of causes other than TB, with age at death ranging from 20 to 90 years **(Fig. 17, Suppl. table 2)**.

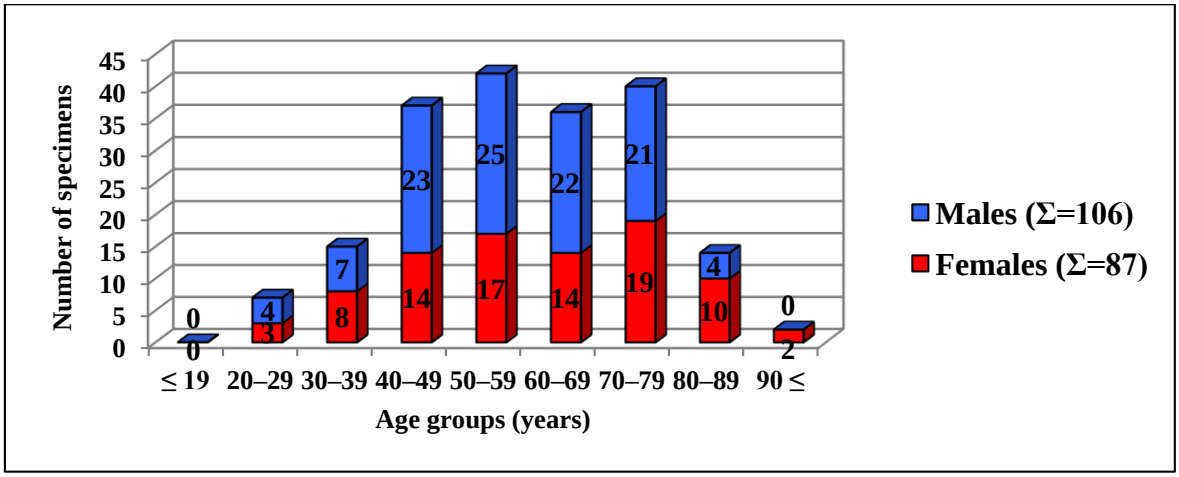


Figure 17: Demographic profile of specimens surveyed in the NTB group (Σ=193).

The endocranial surface of the selected skulls was macroscopically surveyed for the presence of the four types of endocranial alterations probably related to TBM (*i.e.*, periosteal appositions **(Fig. 18A)**; abnormal blood vessel impressions, including SES **(Fig. 18B)**; granular impressions **(Fig. 18C)**; and abnormally pronounced digital impressions **(Fig. 18D)**), without prior knowledge of the cause of death of specimens.

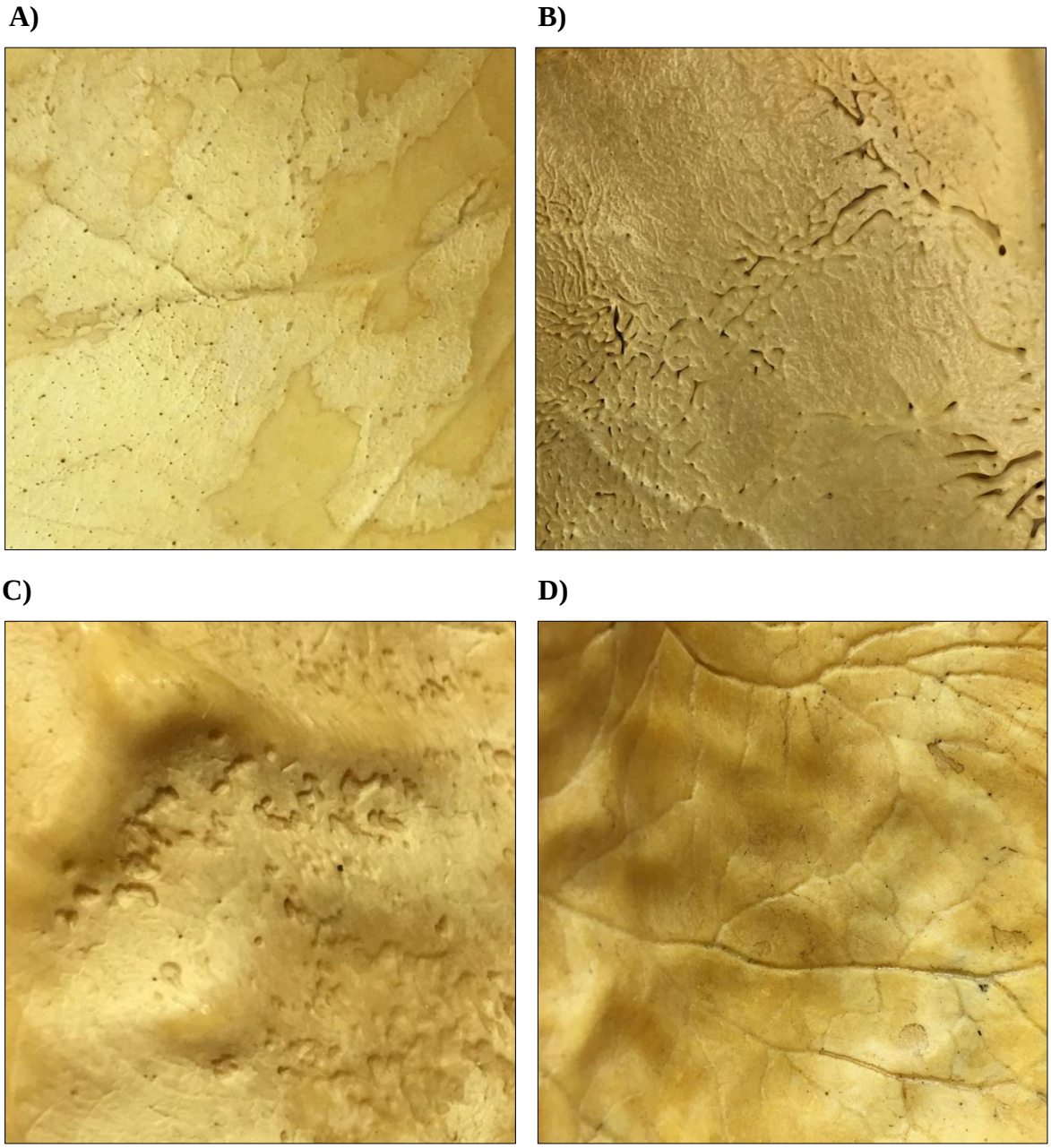


Figure 18: Different types of endocranial alterations probably related to TBM: A) PAs in the left parietal bone (Terry No. 987, 23-year-old, male, pulmonary TB), B) ABVIs on the right side of the squamous part of the frontal bone (Terry No. 329, 18-year-old, male, pulmonary TB), C) GIs on the left side of the orbital part of the frontal bone (Terry No. 1159, 26-year-old, male, pulmonary TB), and D) APDIs in the right parietal bone (Terry No. 89R, c. 32-year-old, male, TB).

During the macromorphological investigation, a lamp was always positioned at a distance of few centimetres from the bone surface, since the examined bony changes can have a very subtle appearance, making their detection difficult. For each selected individual, detailed written and pictorial descriptions of all observed endocranial alterations probably associated with TBM were made on a data collection sheet prepared for the current research project **(Table 1)**.

Terry No. 1159	Frontal bone	Parietal bones		Temporal bones		Sphenoid bone		Occipital bone
		Left	Right	Left	Right	Left	Right	
PAs	M 1	M 1	M 1	M 1	M 1	0	0	M 1
ABVIs	0	0	0	0	0	0	0	0
GIs	M 1	0	0	0	0	0	0	M 1
Abnormally pronounced digital impressions (APDIs)								+

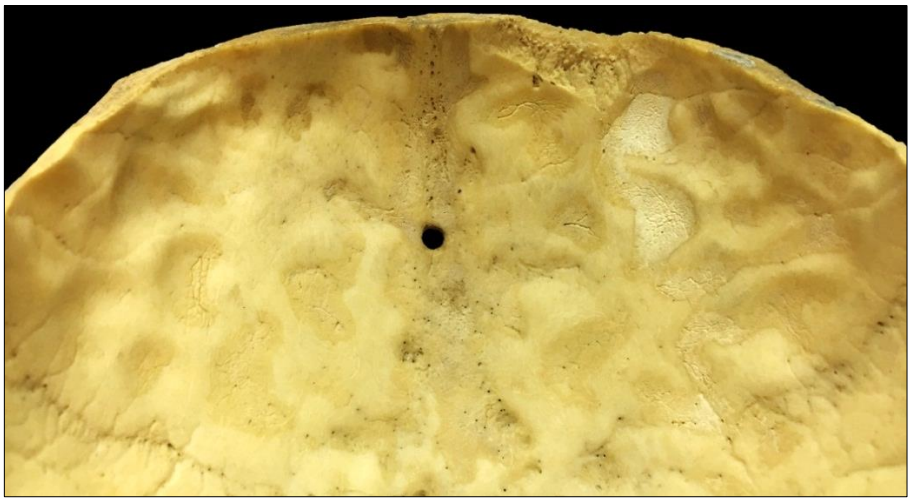
Table 1: Data collection sheet for recording endocranial alteration types probably related to TBM. Example case: Terry No. 1159, 26-year-old, male, pulmonary TB (0 = not present, M = multifocal, 1 = stage 1 (x < 25%), + = very slight).

With respect to the PAs, ABVIs **(Fig. 19A–C)**, and GIs **(Fig. 20A–C)**, the affected cranial bone(s) (considering the left and right greater wings of the sphenoid bone as two separate bones); the number of detected lesions in the affected cranial bone(s) (unifocal or multifocal); and the extent of the endocranial surface area the observed lesion(s) covered (x) in the affected cranial bone(s) (4-level scale: 1) $x < 25\%$, 2) $25\% \leq x < 50\%$, 3) $50\% \leq x < 75\%$, and 4) $75\% \leq x$) were recorded; whereas concerning the APDIs **(Fig. 21A–C)**, their prominence was registered (3-level scale: 1) very slight: shallow DIs (< 2mm in depth) predominantly over the anterior portion of the endocranial surface, 2) slight: deeper DIs (2–4 mm in depth) particularly over the anterior and middle portions of the endocranial surface, and 3) pronounced: deep DIs (4 mm < in depth) all over the endocranial surface) **(Table 1)**. Besides the above-mentioned endocranial alterations, the presence of different types of non-endocranial bony lesions probably related to TB (*e.g.*, vertebral changes, rib lesions, and joint alterations) was also recorded in the 427 selected specimens from the *Terry Collection*.

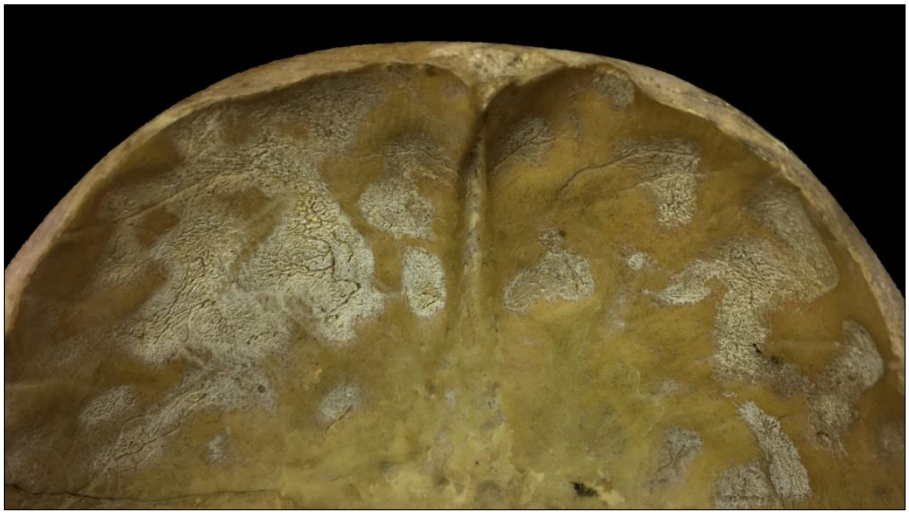
After the detailed macromorphological evaluation of the skeletons, all information collected was entered into a spreadsheet in *Microsoft Office Excel 2010*, and subsequent statistical analysis of data was performed: absolute and percentage frequencies of the four types of endocranial alterations probably associated with TBM, as well as of their co-occurrence with each other and with non-endocranial bony changes possibly related to TB, were calculated in both the TB group and NTB group; and χ^2 testing of data to determine the significance of differences (if any) in frequencies of all examined endocranial alteration types, as well as of their association with each other and with non-endocranial bony lesions probably related to TB between the two groups, was undertaken using the *MedCalc* statistical software package.

Figure 19: Different stages of multifocal PAs and ABVIs on the squamous part of the frontal bone: A) stage 2 (Terry No. 1322, 34-year-old, male, pulmonary TB), B) stage 3 (Terry No. 306, 18-year-old, female, pulmonary TB), and C) stage 4 (Terry No. 254, 21-year-old, male, pulmonary TB).

A)



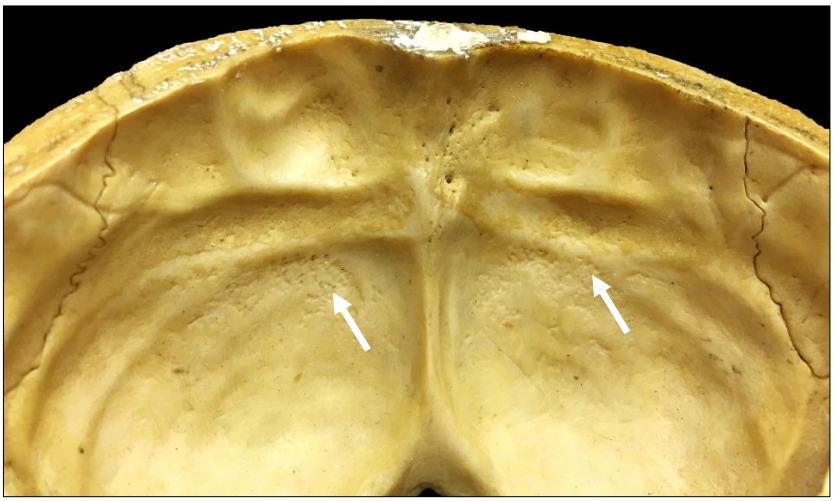
B)



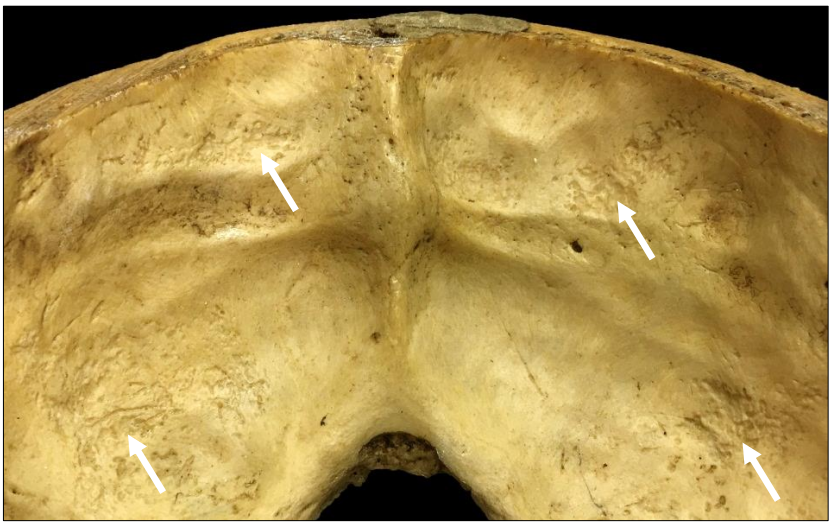
C)

Figure 20: Different stages of multifocal GIs on the squamous part of the occipital bone: A) stage 1 (Terry No. 1106, 28-year-old, male, skeletal TB), B) stage 2 (Terry No. 933R, 40-year-old, male, peritoneal TB), and C) stage 3 (Terry No. 562, 17-year-old, female, pulmonary TB).

A)



B)



C)

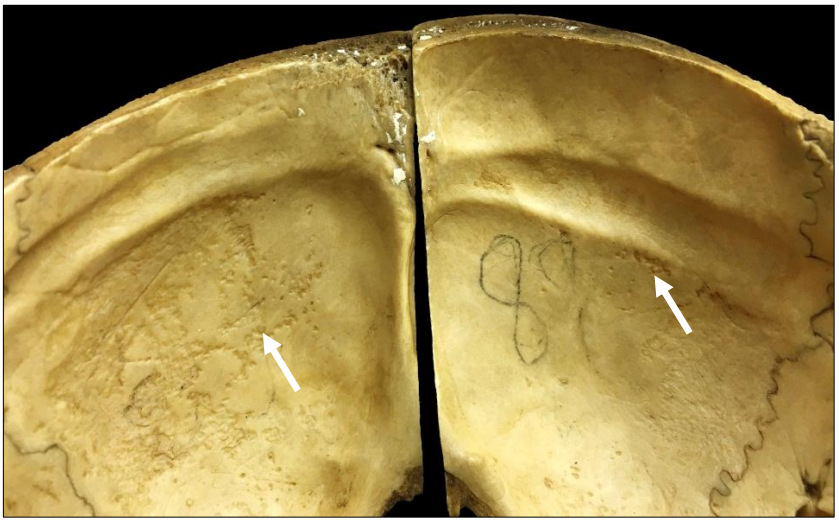
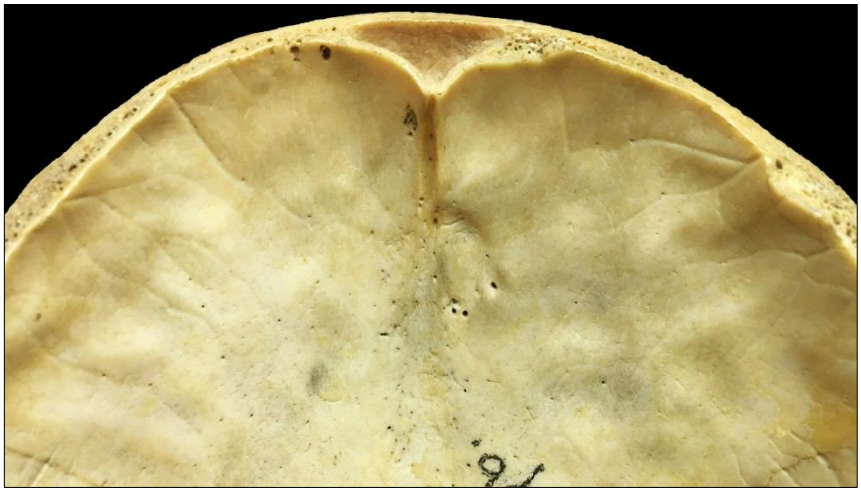


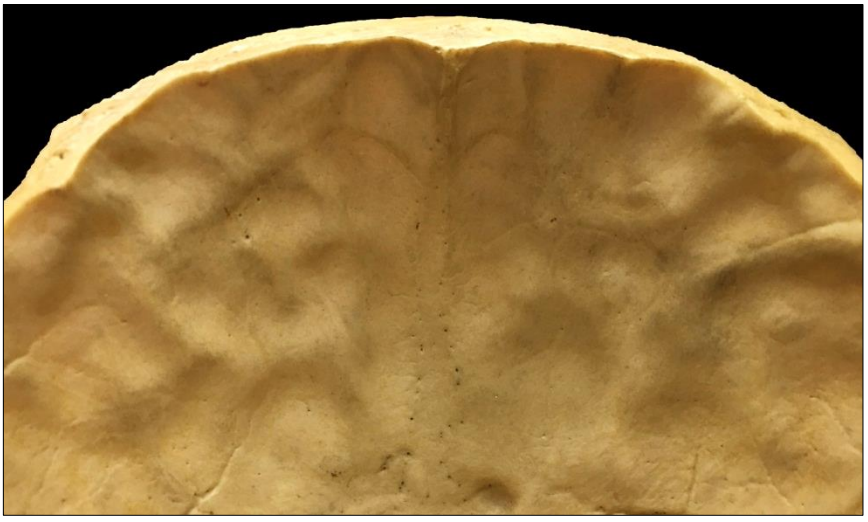
Figure 21: Different stages of the prominence of APDIs on the squamous part of the frontal bone: A) very slight (Terry No. 1036, 38-year-old, male, pulmonary TB), B) slight (Terry No. 265, 32-year-old, male, TB), and C) pronounced (Terry No. 251, 34-year-old, male, pulmonary TB).

A)

B)



C)



4 RESULTS & CASE STUDIES

4.1 Endocranial alteration types probably related to tuberculosis

4.1.1 Abnormally pronounced digital impressions

Σ=427		TB group		NTB group	
Number of specimens affected by APDIs		154/234 (65.81%)		62/193 (32.12%)	
Females	Males	34/65 (52.31%)	120/169 (71.01%)	19/87 (21.84%)	43/106 (40.57%)

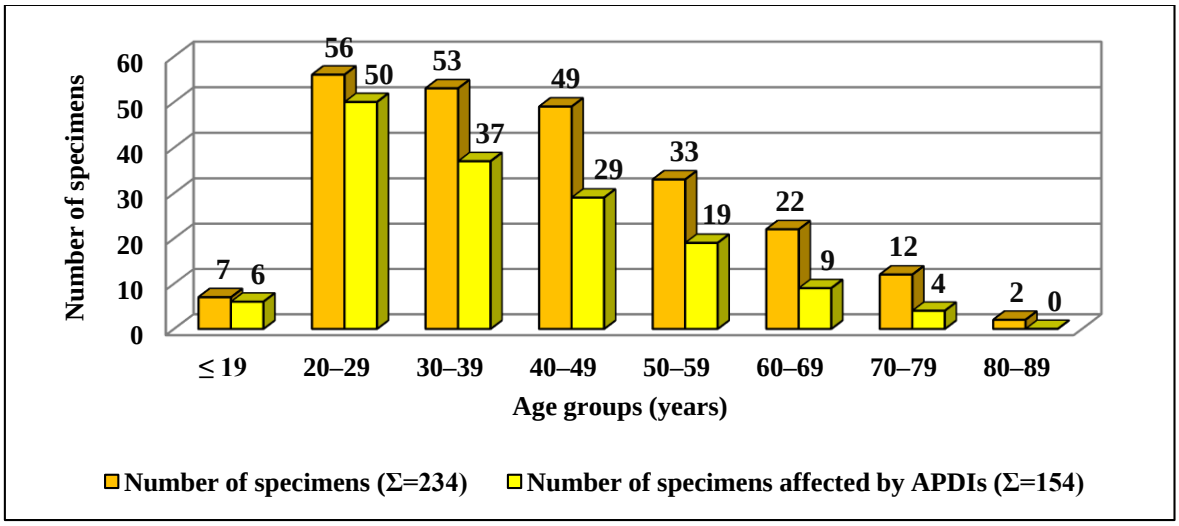
Table 2: Number of specimens exhibiting APDIs in the TB group and NTB group by sex.

From a total of 427 skeletons evaluated, 216 (50.59%) exhibited APDIs on the inner surface of the skull: 154 (65.81%) of 234 individuals recorded to have died of TB and 62 (32.12%) of 193 specimens identified to have died of causes other than TB **(Table 2)**; thus, there was a statistically extremely significant difference in the frequencies of APDIs between the TB group and NTB group (χ^2=46.680, df=1, P<0.0001). When the two groups were compared considering the sex **(Table 2)**, the difference in the frequencies of APDIs remained significant for both females (χ^2=13.896, df=1, P=0.0002) and males (χ^2=23.759, df=1, P<0.0001). Furthermore, an approximately 20 percentage point difference in the frequencies of APDIs between females and males was found in both groups: 52.31% versus 71.01% in the TB group and 21.84% versus 40.57% in the NTB group, respectively **(Table 2)**. The χ^2 comparison of the frequencies of APDIs between the two sexes **(Table 2)** revealed a statistically significant difference in both individuals with TB as the cause of death (χ^2=6.487, df=1, P=0.0109) and specimens with NTB causes of death (χ^2=6.850, df=1, P=0.0089).

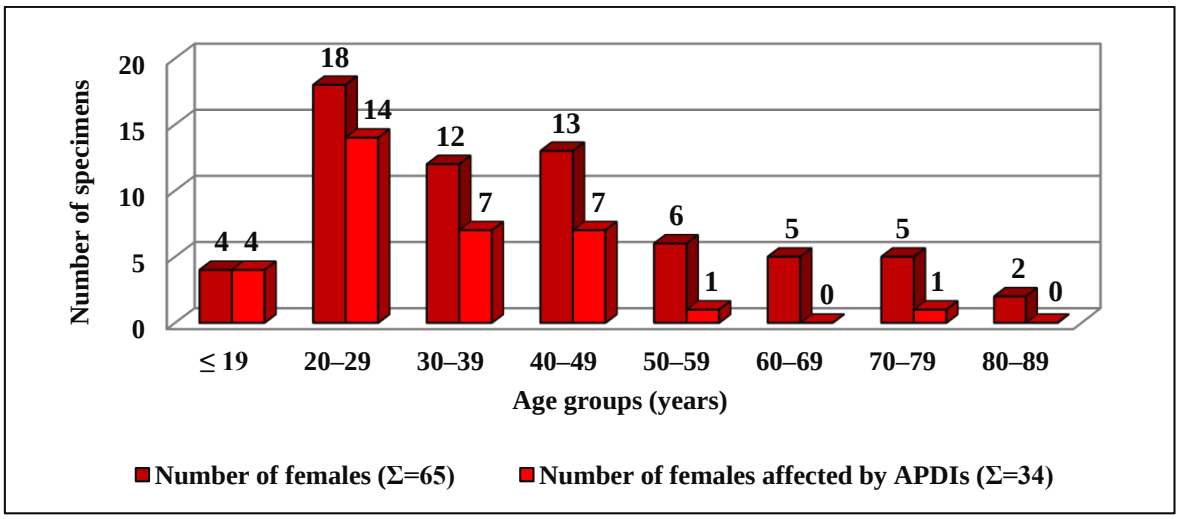
Concerning the distribution of affected individuals by age at death, APDIs occurred with the highest frequency among specimens under the age of 30 years (61/70, 87.14%): with 88.89% (56/63) in the TB group **(Fig. 22A)** and with 71.43% (5/7) in the NTB group **(Fig. 23A)**. Of females and males under the age of 30 years and identified to have died of TB, 81.82% (18/22) **(Fig. 22B)** and 92.68% (38/41) **(Fig. 22C)** showed APDIs, respectively. Nevertheless, more than one-half of females between 30 and 49 years of age (14/25, 56.00%) **(Fig. 22B)** and more than two-thirds of males between 30 and 59 years of age (70/104, 67.31%) **(Fig. 22C)** also exhibited APDIs in the TB group. Moreover, among individuals recorded to have died of causes other than TB, besides females (2/3, 66.67%) **(Fig. 23B)** and males (3/4, 75.00%) **(Fig. 23C)** under the age of 30 years, males between 60 and 69 years of age (12/22, 54.55%) **(Fig. 23C)** were most frequently affected by APDIs. The χ^2 testing of the frequencies of APDIs between various age groups was not assessed because of the low number of specimens in certain age groups.

Figure 22: Demographic profile of specimens exhibiting APDIs in the TB group: A) total sample (154/234, 65.81%), B) females (34/65, 52.31%), and C) males (120/169, 71.01%).

A)



B)



C)

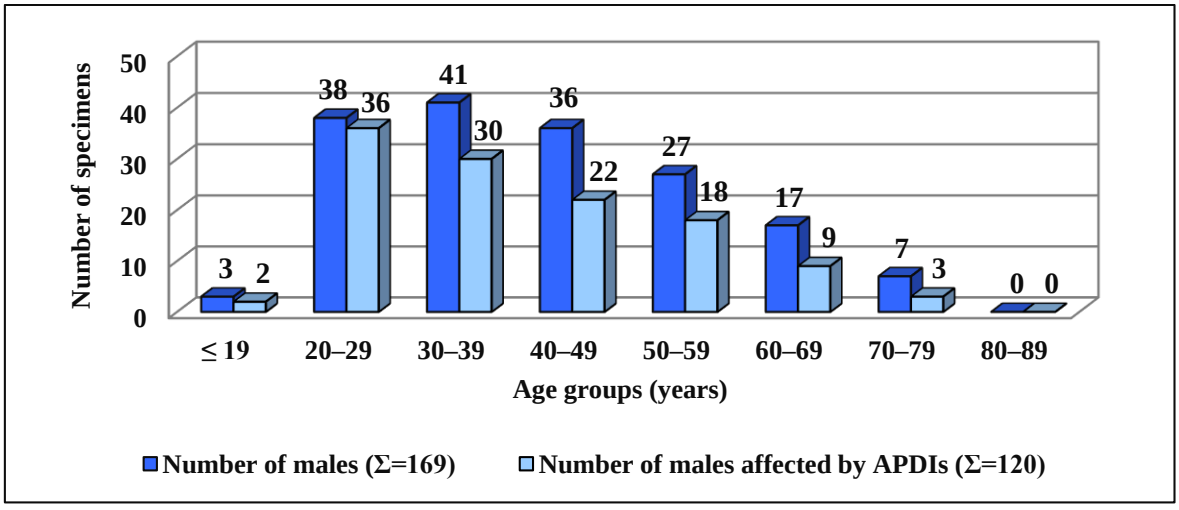
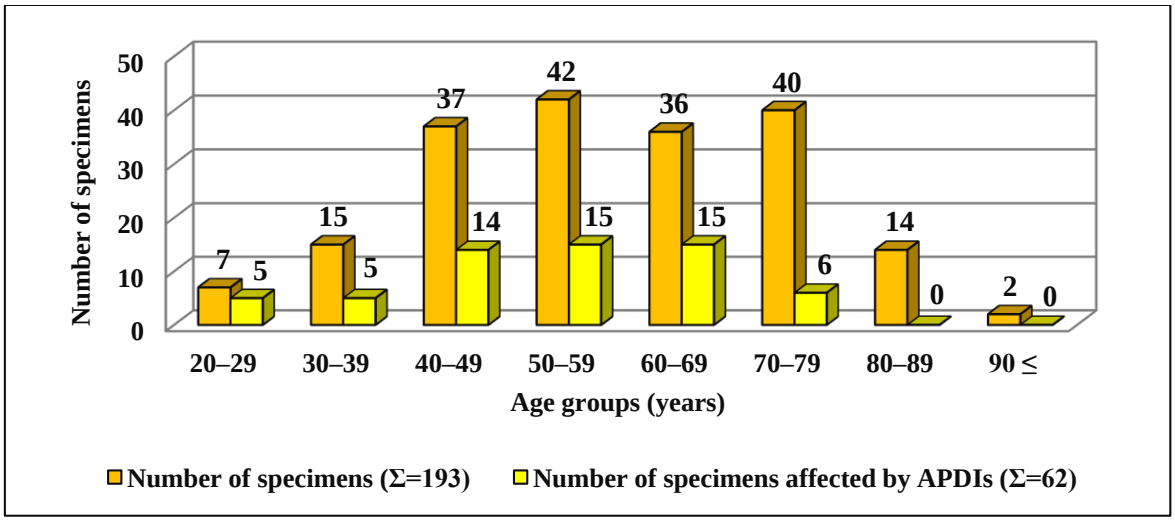
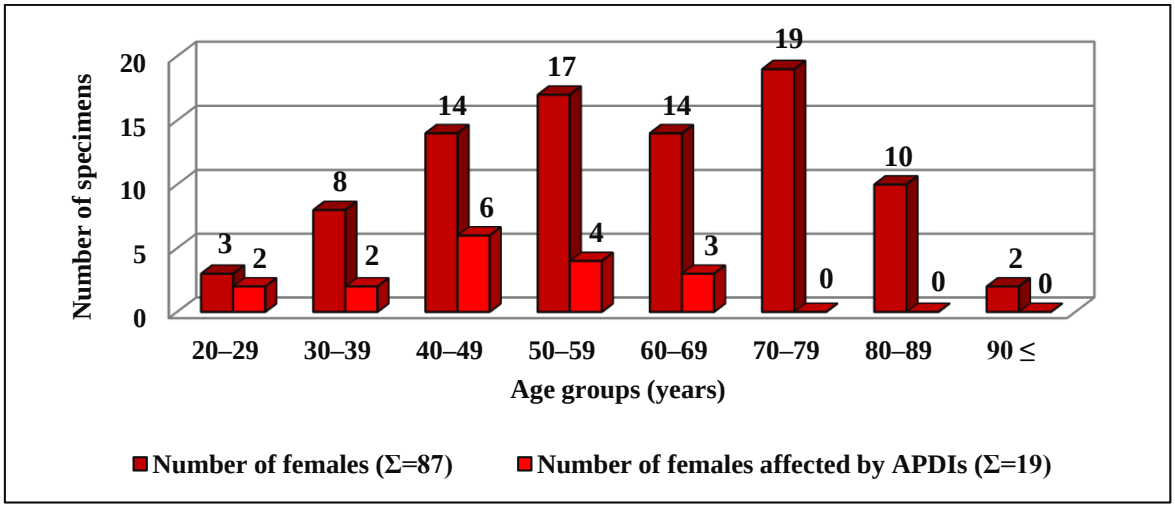


Figure 23: Demographic profile of specimens exhibiting APDIs in the NTB group: A) total sample (62/193, 32.12%), B) females (19/87, 21.84%), and C) males (43/106, 40.57%).

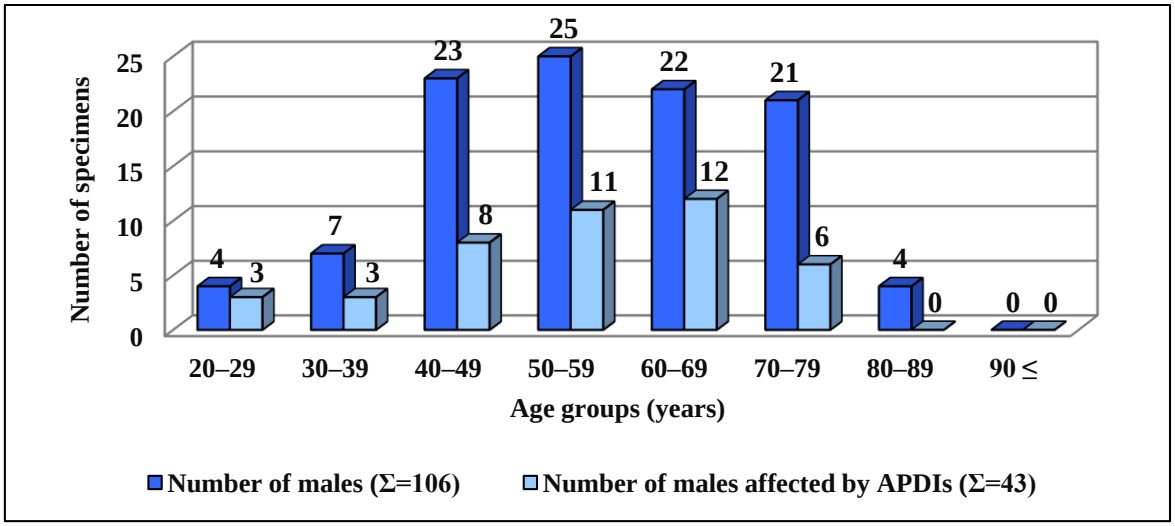
A)



B)



C)



As for the prominence of APDIs, from the 216 skulls affected, 148 (68.52%), 51 (23.61%), and 17 (7.87%) had very slight **(Fig. 24A, 25A–B)**, slight **(Fig. 24B, 25A–B)**, and pronounced APDIs **(Fig. 24C–D, 25A–B)**, respectively.

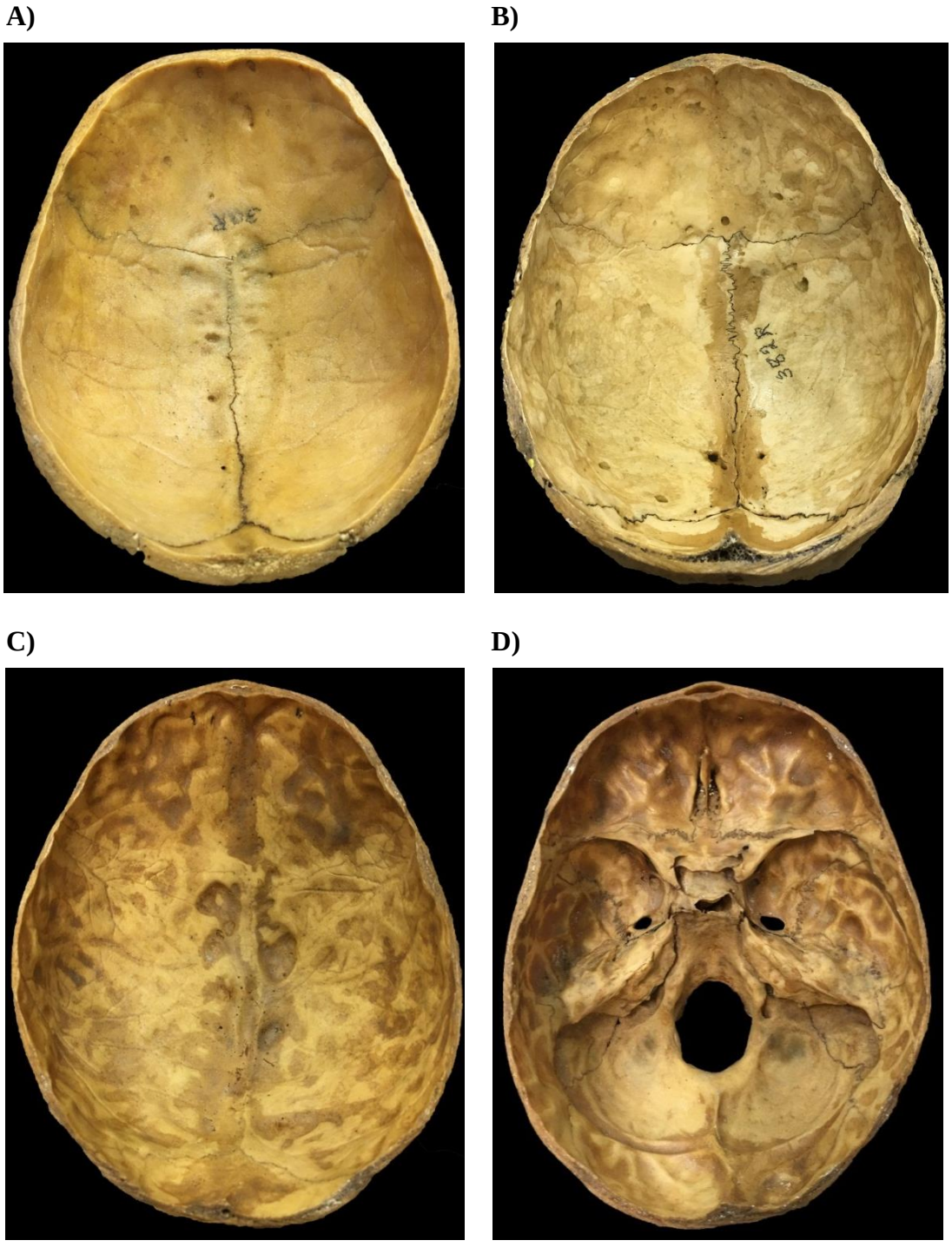


Figure 24: Different stages of the prominence of APDIs on the inner surface of the skull: A) very slight (skullcap, Terry No. 30R, 26-year-old, male, TB meningitis), B) slight (skullcap, Terry No. 382R, 26-year-old, male, pulmonary TB), C) pronounced (skullcap, Terry No. 1033, 26-year-old, male, pulmonary TB), and D) pronounced (skull base, Terry No. 1033, 26-year-old, male, pulmonary TB).

Although the very slight stage of the prominence of APDIs was more common among specimens with NTB causes of death **(Fig. 24A, 25A−B)** and the more pronounced (*i.e.*, slight and pronounced) stages of the prominence of APDIs occurred more frequently among individuals with TB as the cause of death **(Fig. 24B−D, 25A−B)**, statistically significant difference between the two groups was found only in the frequencies of the very slight stage of the prominence of APDIs (very slight: χ^2=8.530, df=1, P=0.0035; slight: χ^2=3.312, df=1, P=0.0688; and pronounced: χ^2=3.564, df=1, P=0.0591).

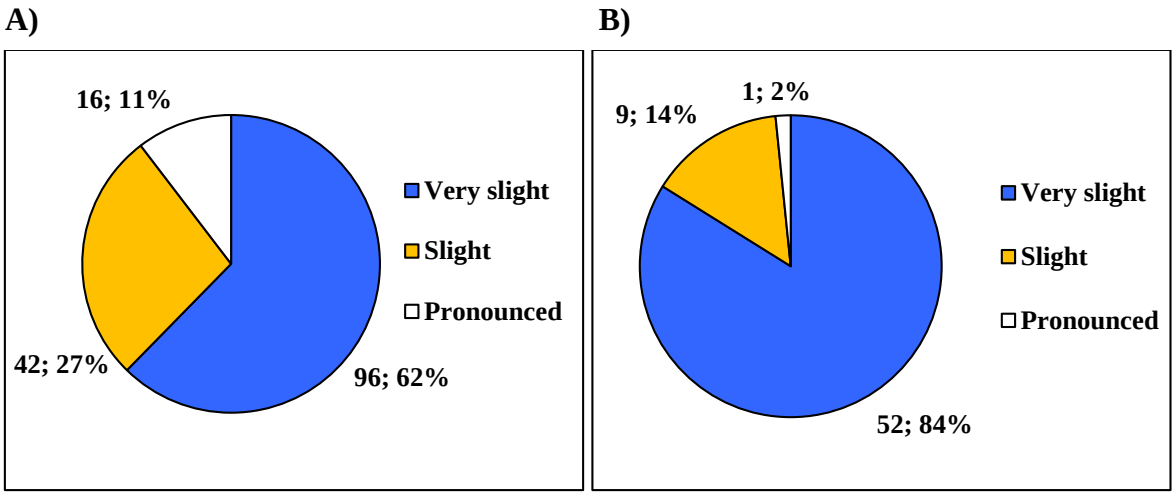


Figure 25: Distribution of specimens affected by APDIs in the A) TB group (Σ=154) and B) NTB group (Σ=62) by stages of the prominence of APDIs.

Of the 154 specimens with APDIs in the TB group, 124 were identified to have died of pulmonary TB **(Suppl. table 1, 3)**. Nine additional individuals died of other types of tuberculosis, such as skeletal TB (four cases), peritoneal TB (two cases), TB meningitis (two cases), and miliary TB (one case); whereas in the remaining 21 cases, the type of tuberculosis as the cause of death was not specified on the morgue record and/or death certificate **(Suppl. table 1, 3)**. In the NTB group, the most frequently registered NTB causes of death were cardiovascular problems, followed by respiratory diseases, infectious diseases other than TB, and different types of cancer among specimens exhibiting APDIs on the inner surface of the skull **(Suppl. table 2, 4)**.

In the skeleton of **Terry No. 30R** – a 26-year-old male recorded to have died of TBM **(Suppl. table 1)** –, pathological bony changes that may be attributed to tuberculosis were registered both in the cranial and postcranial elements. Regarding the skull, shallow APDIs (very slight stage) were noted on the squamous part of the frontal bone **(Fig. 24A, 26)**, probably referring to eICP secondary to TBM (*e.g.*, Schultz, 1993, 2001, 2003). Furthermore, GIs − described by *Schultz* (*e.g.*, 1999, 2001, 2003) and *Schultz* & *Schmidt*-

Schultz (2015) as pathognomonic vestiges of TBM, since representing pressure atrophy of the tubercles that affect the *dura mater* − were detected on the orbital part of the frontal bone and on the squamous part of the occipital bone, covering less than one-fourth (stage 1) of the inner surfaces.

Figure 26: Shallow APDIs (very slight stage) on both sides of the squamous part of the frontal bone (Terry No. 30R, 26-year-old, male, TB meningitis).

Besides the endocranial alterations very likely associated with TBM, in the vertebral column, signs of hypervascularisation were noted in the form of circumferential pitting on the lateral and anterior aspects of the lower thoracic (T10–12), as well as on the lateral aspects of the lumbar (L1–5) vertebral bodies. Although vertebral hypervascularisation is not a specific feature of tuberculosis, it has been described in relation to early-stage skeletal TB in a number of studies (*e.g.*, Ménard, 1888; Baker, 1999; Maczel, 2003; Giacon, 2008; Mariotti *et al.*, 2015). The recorded cause of death of Terry No. 30R supports the tuberculous origin of the observed endocranial and vertebral changes.

The skeletal remains of **Terry No. 382R** – a 26-year-old male whose morgue record states pulmonary TB as the cause of death **(Suppl. table 1)** – exhibited numerous pathological bony changes that probably resulted from tuberculosis. In the skull, APDIs (slight stage) affecting the squamous part of the frontal bone **(Fig. 24B, 27)** and the left and right parietal bones **(Fig. 24B)** were registered, indicating eICP possibly due to hydrocephalus that may be associated with TBM (*e.g.*, Schultz, 1993, 2001, 2003).

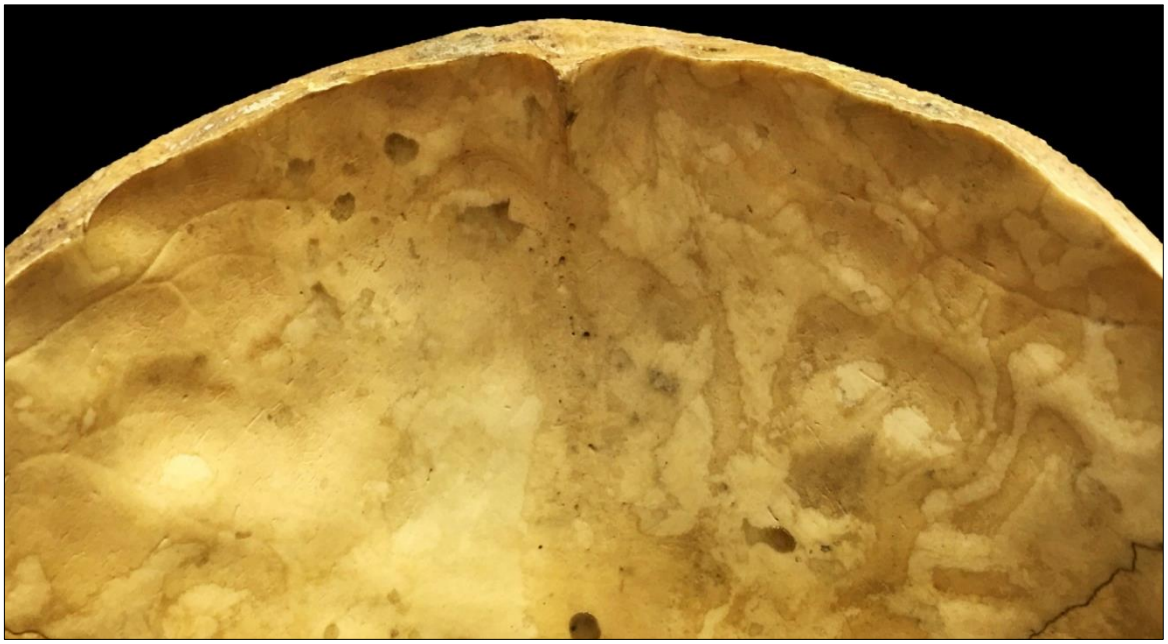


Figure 27: APDIs (slight stage) on both sides of the squamous part of the frontal bone (Terry No. 382R, 26-year-old, male, pulmonary TB).

As for the postcranial skeleton, all left side ribs showed slight PNBFs on the visceral surface of the vertebral end (2^{nd}–12^{th}), body (10^{th}–12^{th}), and/or sternal end (1^{st}, 5^{th}–8^{th}, and 10^{th}). Moreover, slight PNBFs occurred on the vertebral end (2^{nd}–11^{th}) and occasionally on the sternal end (3^{rd}–7^{th}) of ten right side ribs (2^{nd}–11^{th}), exclusively affecting the visceral surfaces. Besides the ribs, the visceral surface of the middle and lower parts of the manubrium and the upper and middle parts of the body of the sternum, as well as the upper part of the costal surface of both scapulae, also revealed slight PNBFs. PNBFs affecting bones of the thoracic region (ribs, sternum, and scapulae) may represent vestiges of an inflammatory response secondary to pulmonary TB and/or TB pleurisy (*e.g.*, Kelley & Micozzi, 1984; Roberts *et al.*, 1994; Santos & Roberts, 2001, 2006; Maczel, 2003; Matos & Santos, 2006; Giacon, 2008; Mariotti *et al.*, 2015). In the vertebral column, signs of hypervascularisation possibly referring to early-stage skeletal TB (*e.g.*, Ménard, 1888; Baker, 1999; Maczel, 2003; Giacon, 2008; Mariotti *et al.*, 2015) were detected on the lateral and anterior aspects of the cervical (C2–7), thoracic (T1–12), and lumbar (L1–5) vertebral bodies, as well as on the ventral surface of the lower part of the sacrum (S3–5). Based on the recorded cause of death of Terry No. 382R, the most likely aetiology of the observed endocranial and postcranial bony changes is tuberculosis.

Similar to the previous cases, both the cranial and postcranial remains of **Terry No. 1033** – a 26-year-old male who had died of pulmonary TB **(Suppl. table 1)** – showed different types of pathological bony changes that may be ascribed to tuberculosis.

Regarding the cranium, deep APDIs (pronounced stage) were registered all over the inner surface of the skullcap **(Fig. 24C, 28)** and skull base **(Fig. 24D)**, indicating eICP possibly due to tuberculous involvement of the CNS (*e.g.*, Schultz, 1993, 2001, 2003). Furthermore, non-specific vestiges of haemorrhagic and/or inflammatory meningeal reactions − namely multifocal, small, serpentine branching ABVIs accompanied by slight PAs (*e.g.*, Schultz, 1993, 1999, 2001, 2003) − were noted in the deep DIs located in the frontal **(Fig. 28)** and the left and right parietal bones, covering less than one-fourth (stage 1) of the inner surfaces.

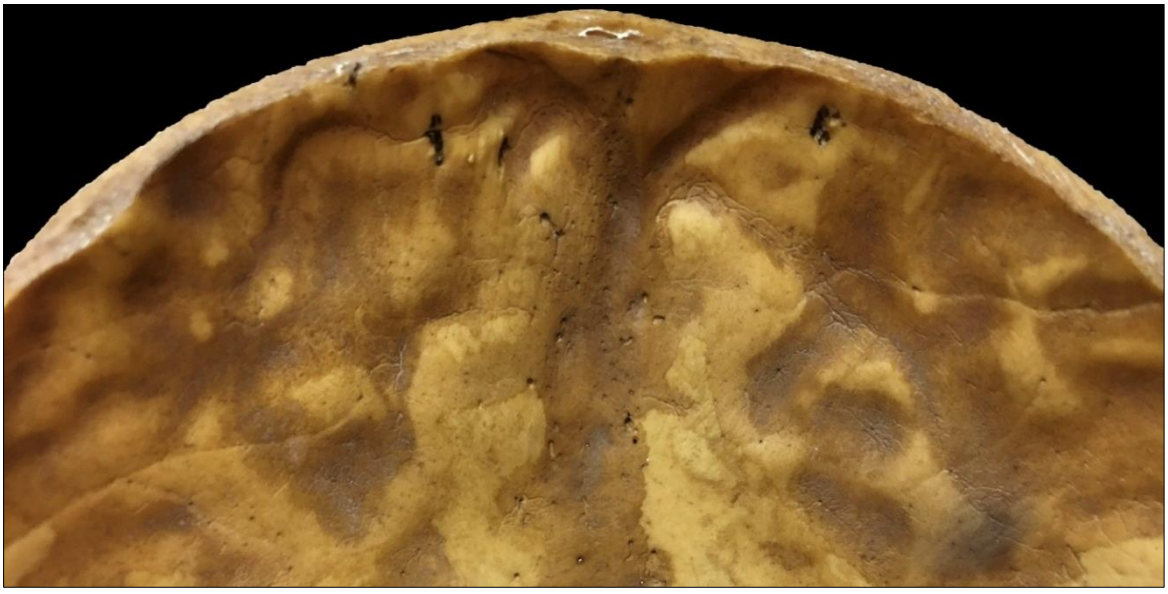


Figure 28: Multifocal PAs and ABVIs localised in the deep APDIs (pronounced stage) on both sides of the squamous part of the frontal bone (Terry No. 1033, 26-year-old, male, pulmonary TB).

With respect to the postcranial elements, slight PNBFs − frequently described as not specific but probable signs of pulmonary TB and/or TB pleurisy (*e.g.*, Kelley & Micozzi, 1984; Roberts *et al.*, 1994; Santos & Roberts, 2001, 2006; Maczel, 2003; Matos & Santos, 2006; Giacon, 2008; Mariotti *et al.*, 2015) − occurred on the vertebral end (2^{nd}–4^{th} and 7^{th}–8^{th}), and occasionally on the body (2^{nd}–4^{th}) and/or sternal end (3^{rd}–4^{th}) of five left side ribs (2^{nd}–4^{th} and 7^{th}–8^{th}), as well as on the vertebral end of two right side ribs (7^{th}–8^{th}), exclusively affecting the visceral surfaces. In the vertebral column, multiple, smooth-walled resorptive pits often connected by horizontal, superficial vascular channels were recognised on the lateral aspects of the thoracic (T3–12) and lumbar (L1–5) vertebral bodies, possibly referring to early-stage skeletal TB (*e.g.*, Ménard, 1888; Baker, 1999; Maczel, 2003; Giacon, 2008; Mariotti *et al.*, 2015). Although the observed endocranial and postcranial bony changes are not pathognomonic features of TB, the cause of death of Terry No. 1033 supports their tuberculous origin.

4.1.2 Periosteal appositions

Σ=427		TB group		NTB group	
Number of specimens affected by PAs		47/234 (20.09%)		20/193 (10.36%)	
Females	Males	15/65 (23.08%)	32/169 (18.93%)	9/87 (10.34%)	11/106 (10.38%)

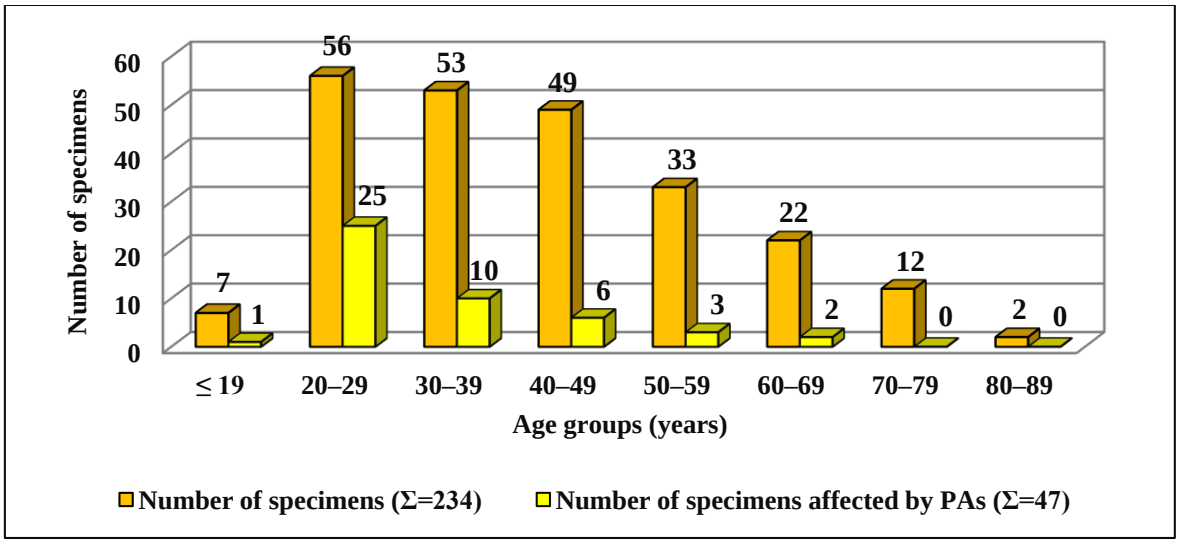
Table 3: Number of specimens exhibiting PAs in the TB group and NTB group by sex.

Periosteal appositions were observed in 67 of 427 (15.69%) skeletons evaluated: of specimens identified to have died of TB, 20.09% (47/234) showed PAs on the endocranial surface of the skull; whereas of individuals recorded to have died of causes other than TB, 10.36% (20/193) exhibited these lesions **(Table 3)**. The χ^2 comparison of the frequencies of PAs revealed a statistically significant difference between the two groups (χ^2=6.841, df=1, P=0.0089). Nevertheless, when the two groups were compared considering the sex **(Table 3)**, there was no statistically significant difference between specimens with TB as the cause of death and individuals with NTB causes of death (females: χ^2=3.629, df=1, P=0.0568; males: χ^2=2.997, df=1, P=0.0834). The frequencies of PAs in females and males were very similar in both the TB group and NTB group **(Table 3)**, and the χ^2 testing of data revealed no statistically significant difference between the two sexes (TB group: χ^2=0.277, df=1, P=0.5987; NTB group: χ^2=0.0529, df=1, P=0.8181).

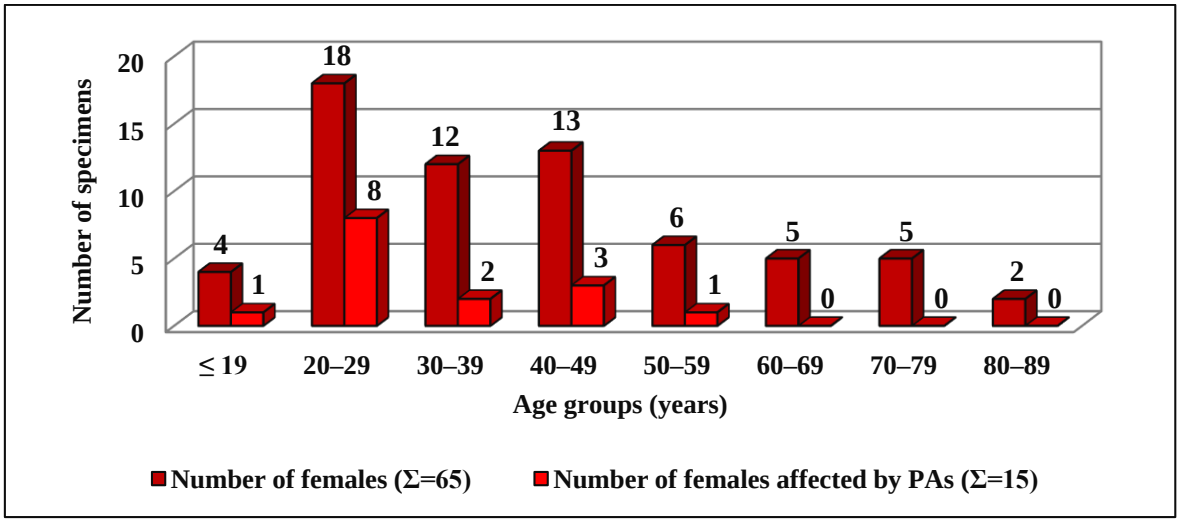
As for the distribution of affected specimens by age at death in the TB group, periosteal appositions occurred with the highest frequency among individuals between 20 and 29 years of age (25/56, 44.64%) **(Fig 29A)**: with 44.44% (8/18) among females **(Fig. 29B)** and with 44.74% (17/38) among males **(Fig. 29C)**. Among specimens under the age of 20 years, only an 18-year-old female revealed PAs on the inner surface of the skull **(Fig. 29B)**; whereas among individuals above the age of 29 years − except for males between 30 and 39 years of age (8/41, 19.51%) **(Fig. 29C)** − PAs were registered only in a few cases both among females **(Fig. 29B)** and males **(Fig. 29C)**. In contrast to the TB group, there was no specimen under the age of 30 years and exhibiting PAs on the inner surface of the skull in the NTB group **(Fig. 30A–C)**. With the exception of a 37-year-old male and a 39-year-old female, individuals with NTB causes of death and PAs (18/20, 90.00%) were above the age of 40 years **(Fig. 30A–C)**. The χ^2 testing of the frequencies of PAs between various age groups was not assessed because of the low number of specimens in certain age groups.

Figure 29: Demographic profile of specimens exhibiting PAs in the TB group: A) total sample (47/234, 20.09%), B) females (15/65, 23.08%), and C) males (32/169, 18.93%).

A)



B)



C)

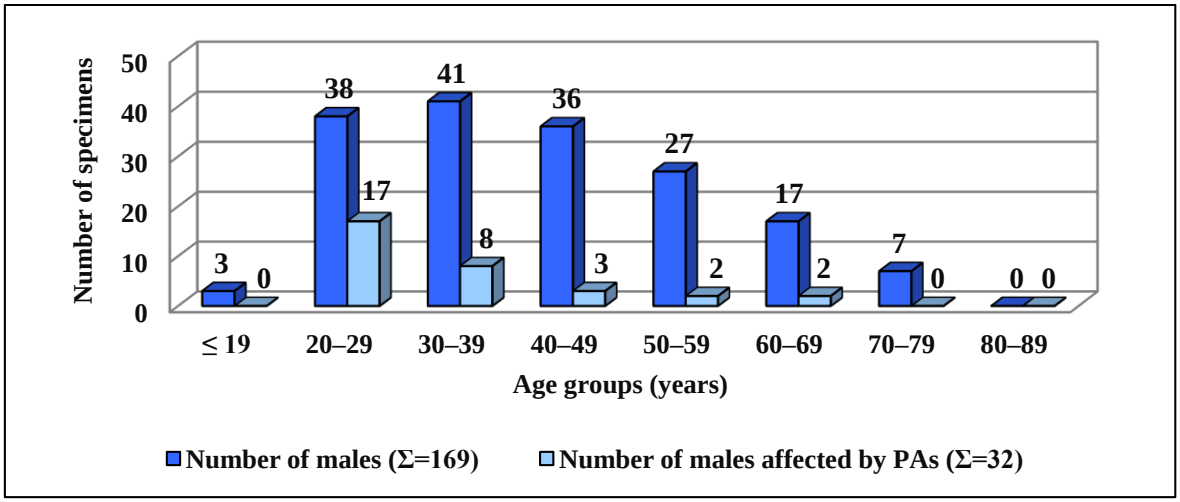
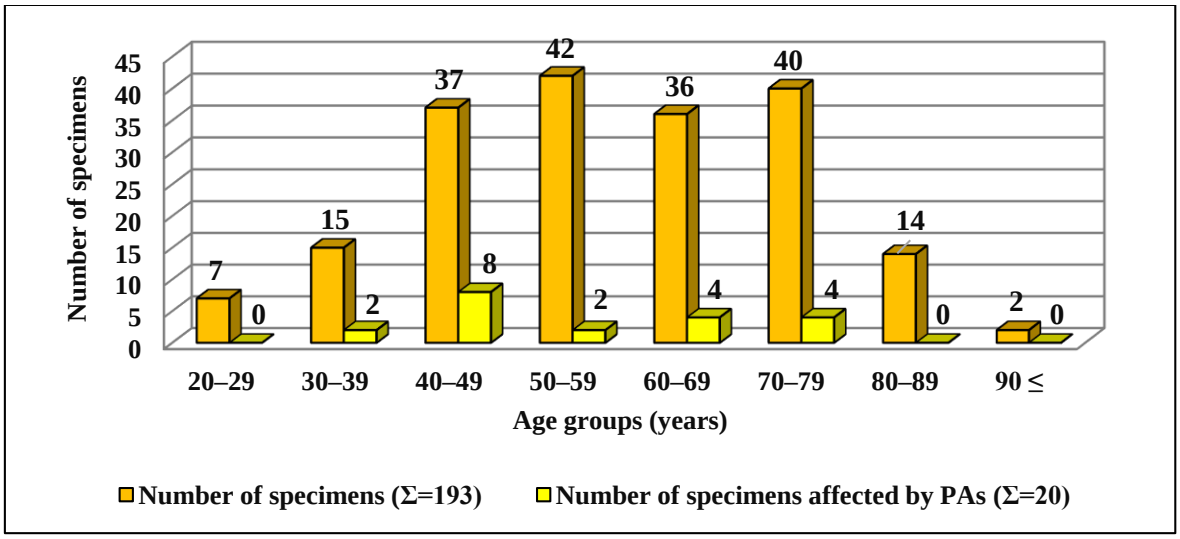
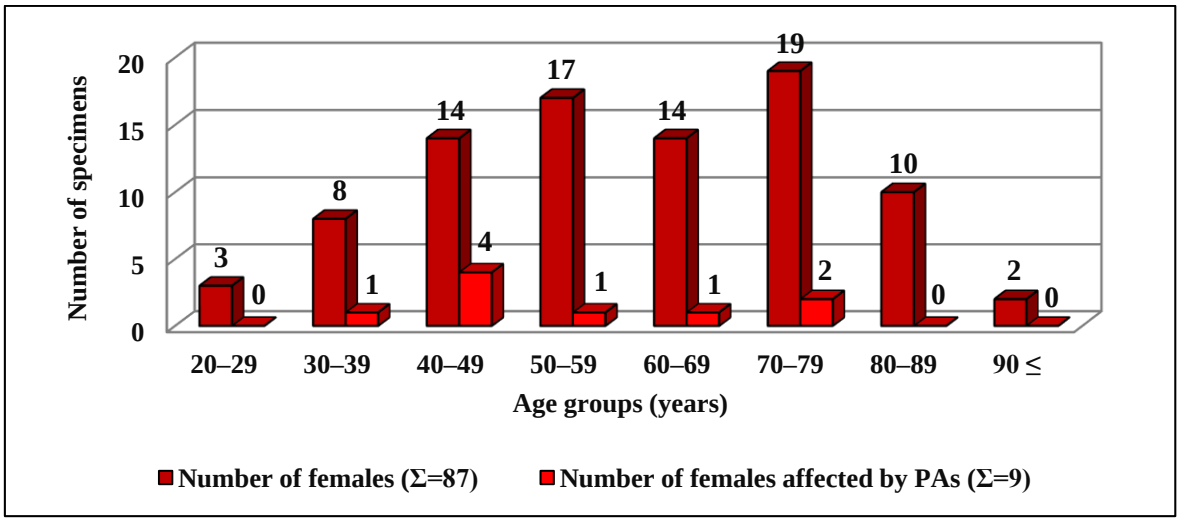


Figure 30: Demographic profile of specimens exhibiting PAs in the NTB group: A) total sample (20/193, 10.36%), B) females (9/87, 10.34%), and C) males (11/106, 10.38%).

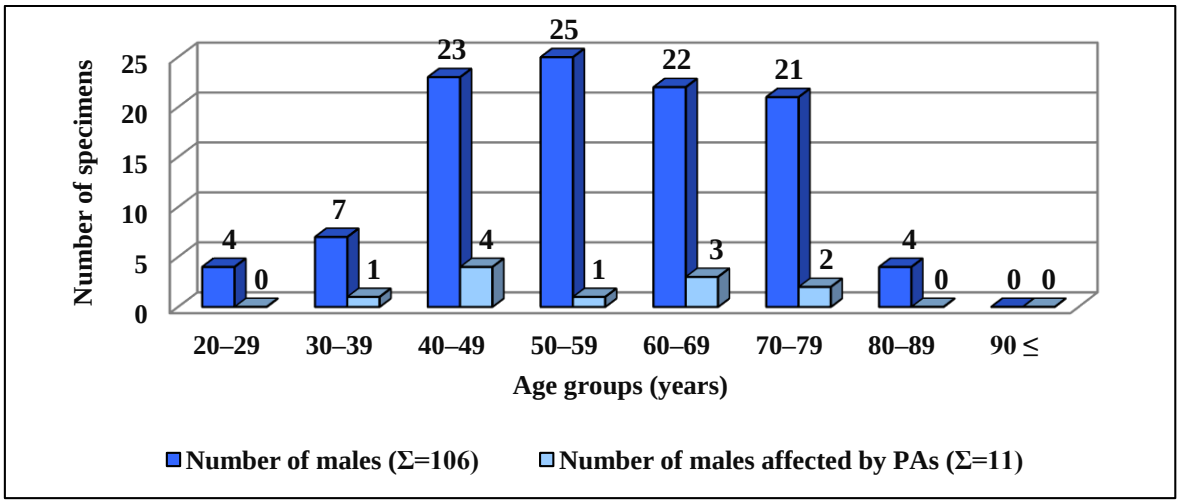
A)



B)



C)



Regarding the localisation of PAs on the inner surface of the skull, the frontal bone (predominantly its most protruding portions **(Fig. 31A – blue)** and/or orbital part **(Fig. 31B – blue)**) and the left and right parietal bones (particularly their most protruding portions and/or their parts along the superior sagittal sinus **(Fig. 31A – blue)**) represented the most common sites of involvement in both the TB group and NTB group **(Table 4A−B)**. Nonetheless, less often the occipital bone (generally its squamous part **(Fig. 31B – orange)**), the left and right temporal bones (predominantly their squamous parts **(Fig. 31B – orange)**), and more rarely the left and right greater wings of the sphenoid bone **(Fig. 31B – yellow)** were also affected **(Table 4A−B)**.

A) **B)**

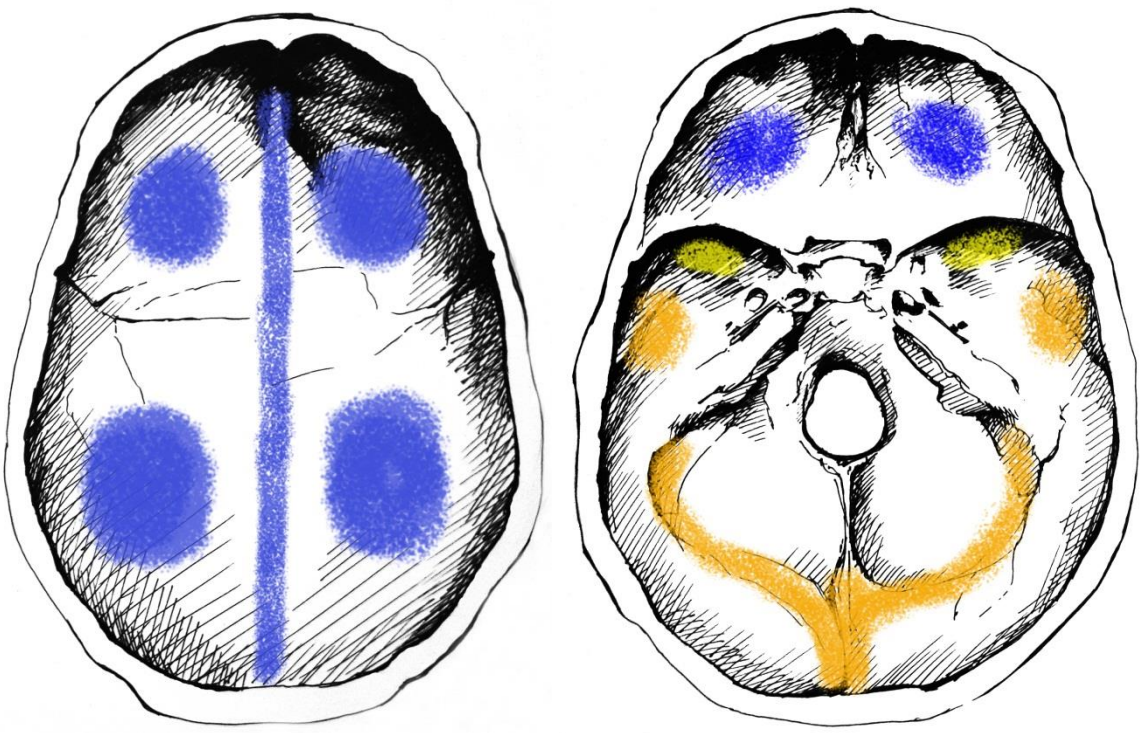


Figure 31: Typical localisations of PAs on the inner surface of the A) skullcap and B) skull base (blue: most commonly affected areas, orange: commonly affected areas, and yellow: less commonly affected areas) (drawings by *Luca Kis*).

Although the number of cranial bones concurrently involved by PAs (considering the left and right greater wings of the sphenoid bone as two separate bones) varied from one to eight in both groups, in 53.19% (25/47) of individuals with TB as the cause of death and PAs, at least four cranial bones were simultaneously affected **(Fig. 32A)**; whereas in nearly two-thirds (13/20, 65.00%) of specimens with NTB causes of death and PAs, less than four cranial bones were concomitantly involved **(Fig. 32B)**.

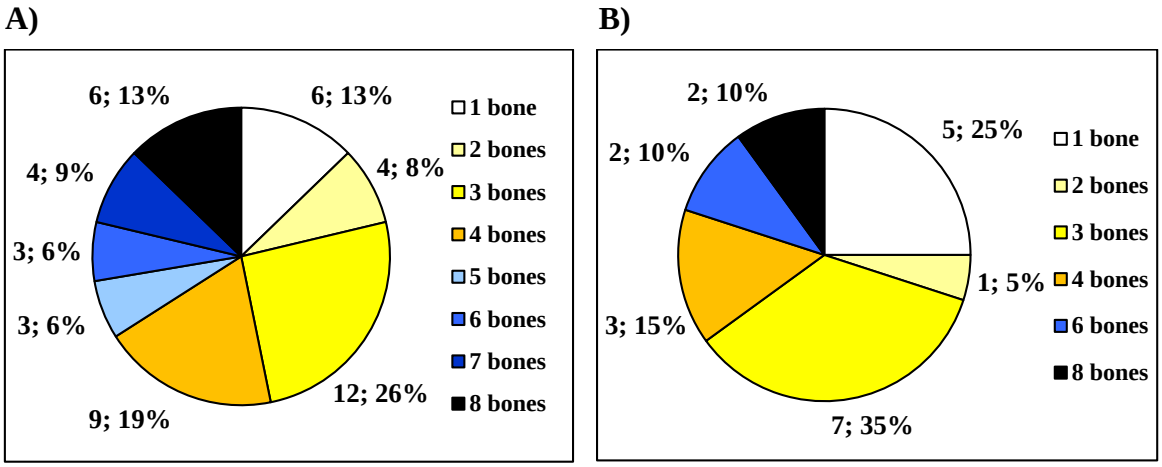


Figure 32: Distribution of specimens affected by PAs in the A) TB group (Σ=47) and B) NTB group (Σ=20) by number of simultaneously involved cranial bones (considering the left and right greater wings of the sphenoid bone as two separate bones).

With respect to the number of presented lesions in the TB group, the vast majority of PAs occurred as multifocal alterations on the inner surface of the skull in all cranial bones examined, except for the left and right greater wings of the sphenoid bone, where the ratio of multifocal and unifocal PAs was about 3:2 **(Table 4A)**. Among individuals recorded to have died of causes other than TB, almost exclusively multifocal PAs were registered in all cranial bones evaluated **(Table 4B)**. Concerning the extent of detected lesions, the majority of PAs observed in the TB group covered less than one-half of the endocranial surfaces in all cranial bones examined **(Table 4A)**. However, the extent of PAs noted around the most protruding parts of the frontal and the left and right parietal bones, as well as in the squamous part of the left temporal bone, exceeded one-half of the inner surfaces quite often: in 20.59% (7/34), 23.68% (9/38), 20.00% (7/35), and 22.22% (4/18) of cases, respectively **(Table 4A)**. Among specimens with NTB causes of death, only four PAs detected around the most protruding portions of the frontal and the left and right parietal bones covered more than one-half of the endocranial surfaces **(Table 4B)**.

Among individuals with PAs in the TB group, the type of tuberculosis as the cause of death was not specified on the morgue record and/or death certificate in six cases **(Suppl. table 1, 3)**. In the remaining 41 cases – with the exception of two specimens identified to have died of TB meningitis and an individual recorded to have died of skeletal TB – pulmonary TB (38 cases) was registered as the cause of death **(Suppl. table 1, 3)**. Among specimens with PAs in the NTB group, cardiovascular problems (14 cases), pneumonia (three cases), cancer (one case), syphilis (one case), and appendicitis (one case) were recorded as NTB causes of death **(Suppl. table 2, 4)**.

Table 4: Distribution of specimens exhibiting PAs in the A) TB group and B) NTB group by affected cranial bones (considering the left and right greater wings of the sphenoid bone as two separate bones), extent, and number of lesions (L = left, R = right).

A) TB group (Σ=234)		Frontal bone	Parietal bone (L)	Parietal bone (R)	Temporal bone (L)	Temporal bone (R)	Sphenoid bone (L)	Sphenoid bone (R)	Occipital bone
		34/47 (72.34%)	38/47 (80.85%)	35/47 (74.47%)	18/47 (38.30%)	20/47 (42.55%)	10/47 (21.28%)	13/47 (27.66%)	27/47 (57.45%)
Extent (x) of lesions	x < 25%	18/34 (52.94%)	23/38 (60.53%)	21/35 (60.00%)	10/18 (55.56%)	14/20 (70.00%)	7/10 (70.00%)	9/13 (69.23%)	24/27 (88.89%)
	25% ≤ x < 50%	9/34 (26.47%)	6/38 (15.79%)	7/35 (20.00%)	4/18 (22.22%)	3/20 (15.00%)	1/10 (10.00%)	3/13 (23.08%)	1/27 (3.70%)
	50% ≤ x < 75%	2/34 (5.88%)	4/38 (10.53%)	4/35 (11.43%)	3/18 (16.67%)	3/20 (15.00%)	–	1/13 (7.69%)	1/27 (3.70%)
	75% ≤ x	5/34 (14.71%)	5/38 (13.16%)	3/35 (8.57%)	1/18 (5.56%)	–	2/10 (20.00%)	–	1/27 (3.70%)
Number of lesions	Unifocal	1/34 (2.94%)	3/38 (7.89%)	4/35 (11.43%)	1/18 (5.56%)	2/20 (10.00%)	4/10 (40.00%)	5/13 (38.46%)	4/27 (14.81%)
	Multifocal	33/34 (97.06%)	35/38 (92.11%)	31/35 (88.57%)	17/18 (94.44%)	18/20 (90.00%)	6/10 (60.00%)	8/13 (61.54%)	23/27 (85.19%)

B) NTB group (Σ=193)		Frontal bone	Parietal bone (L)	Parietal bone (R)	Temporal bone (L)	Temporal bone (R)	Sphenoid bone (L)	Sphenoid bone (R)	Occipital bone
		14/20 (70.00%)	15/20 (75.00%)	15/20 (75.00%)	4/20 (20.00%)	4/20 (20.00%)	2/20 (10.00%)	2/20 (10.00%)	12/20 (60.00%)
Extent (x) of lesions	x < 25%	8/14 (57.14%)	14/15 (93.33%)	12/15 (80.00%)	3/4 (75.00%)	2/4 (50.00%)	1/2 (50.00%)	1/2 (50.00%)	10/12 (83.33%)
	25% ≤ x < 50%	5/14 (35.71%)	–	1/15 (6.67%)	1/4 (25.00%)	2/4 (50.00%)	1/2 (50.00%)	1/2 (50.00%)	2/12 (16.67%)
	50% ≤ x < 75%	1/14 (7.14%)	–	1/15 (6.67%)	–	–	–	–	–
	75% ≤ x	–	1/15 (6.67%)	1/15 (6.67%)	–	–	–	–	–
Number of lesions	Unifocal	2/14 (14.29%)	1/15 (6.67%)	1/15 (6.67%)	1/4 (25.00%)	1/4 (25.00%)	–	–	3/12 (25.00%)
	Multifocal	12/14 (85.71%)	14/15 (93.33%)	14/15 (93.33%)	3/4 (75.00%)	3/4 (75.00%)	2/2 (100.00%)	2/2 (100.00%)	9/12 (75.00%)

The skeletal remains of **Terry No. 987** – a 23-year-old male whose recorded cause of death was pulmonary TB **(Suppl. table 1)** – exhibited numerous pathological bony changes probably resulted from tuberculosis. In the skull, unifocal GIs – described by *Schultz* (*e.g.*, 1999, 2001, 2003) and *Schultz* & *Schmidt-Schultz* (2015) as pathognomonic vestiges of TBM, since representing pressure atrophy of the tubercles that affect the *dura mater* – were observed on the squamous part of the occipital bone. Furthermore, not specific but probable signs of TBM, namely multifocal, small, serpentine branching ABVIs accompanied by PAs (*e.g.*, Schultz, 1993, 1999, 2001, 2003), were recognised on the squamous part of the frontal and occipital **(Fig. 33)** bones.

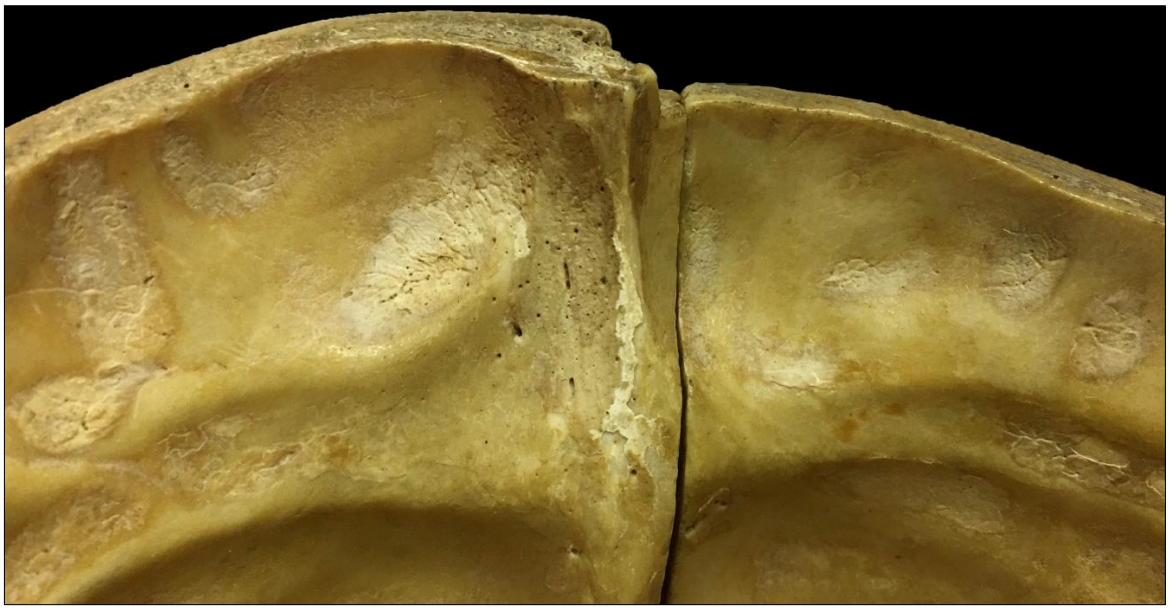


Figure 33: Multifocal ABVIs accompanied by PAs on the squamous part of the occipital bone (Terry No. 987, 23-year-old, male, pulmonary TB).

The left **(Fig. 18A** (p. 42)**)** and right parietal bones, the squamous part of the left and right temporal bones, and the left and right greater wings of the sphenoid bone also revealed patches of PAs. Moreover, APDIs (very slight stage) affecting the squamous part of the frontal bone and the left and right parietal bones were recorded, indicating eICP possibly due to hydrocephalus that may be associated with TBM (*e.g.*, Schultz, 1993, 2001, 2003).

In the postcranial skeleton, nine left side ribs (3^{rd}–11^{th}) showed slight PNBFs on the visceral surface of the sternal end (4^{th}–11^{th}), and occasionally on the body (4^{th}–6^{th} and 9^{th}–11^{th}) and/or vertebral end (3^{rd}–7^{th}) that may represent signs of an inflammatory response secondary to pulmonary TB and/or TB pleurisy (*e.g.*, Kelley & Micozzi, 1984; Roberts *et al.*, 1994; Santos & Roberts, 2001, 2006; Maczel, 2003; Matos & Santos, 2006; Giacon, 2008; Mariotti *et al.*, 2015). Besides the ribs, the anterior and posterior surfaces of both

humeri (predominantly the distal portion of the shaft), the anterior surface of both radii (particularly the distal portion of the shaft), the lateral surface of the right ulna (all along the shaft), the posterior, medial or lateral surfaces of three left side (2^{nd}–4^{th}) and four right side (2^{nd}–5^{th}) metacarpals (mainly the middle and distal portions of the shaft), the lateral surface of both femora (particularly the proximal portion of the shaft), the lateral surface of both tibiae (all along the shaft), the medial surface of both fibulae (predominantly the middle and distal portions of the shaft), and the plantar surface of both 5^{th} metatarsals (mainly the distal portion of the shaft) also exhibited slight PNBFs, probably referring to HPO associated with pulmonary TB (*e.g.*, Mensforth *et al.*, 1978; Kelly *et al.*, 1991; Winland *et al.*, 1997; Rothschild & Rothschild, 1998, 1999; Santos & Roberts, 2001; Hershkovitz *et al.*, 2002; Assis *et al.*, 2011). Based on the recorded cause of death of Terry No. 987, the most likely aetiology of the observed endocranial and postcranial bony changes is tuberculosis.

Similar to the previous case, the skeletal remains of **Terry No. 1027** − a c. 41-year-old female whose morgue record states pulmonary TB as the cause of death **(Suppl. table 1)** − revealed endocranial bony changes probably resulted from TBM. The orbital part of the frontal bone, the left and right parietal bones along the squamous suture, the squamous part of the occipital and the left and right **(Fig. 34)** temporal bones, and the right greater wing of the sphenoid bone exhibited GIs that were described by *Schultz* (*e.g.*, 1999, 2001, 2003) and *Schultz* & *Schmidt-Schultz* (2015) as pathognomonic vestiges of TBM.

Figure 34: Multifocal GIs accompanied by PAs on the squamous part of the right temporal bone (Terry No. 1027, c. 41-year-old, female, pulmonary TB).

Furthermore, non-specific signs of inflammatory-haemorrhagic processes of the meninges – namely multifocal, serpentine branching ABVIs and patches of PAs (*e.g.*, Schultz, 1993, 1999, 2001, 2003) –, occurred on the squamous part of the frontal bone **(Fig. 35)**, in the left and right parietal bones **(Fig. 35)**, on the squamous part of the right temporal bone **(Fig. 34)**, and on the right greater wing of the sphenoid bone. There were no other bony changes probably associated with TB in the skeleton. Based on the recorded cause of death of Terry No. 1027, the tuberculous origin of the observed lesions cannot be excluded.

Figure 35: Multifocal ABVIs and PAs covering the endocranial surface of the frontal, as well as the left and right parietal bones (Terry No. 1027, c. 41-year-old, female, pulmonary TB).

Both the cranial and postcranial remains of **Terry No. 1300** – a 28-year-old male who had died of TB **(Suppl. table 1) –** showed different types of pathological bony changes that may be ascribed to tuberculosis. Concerning the skull, shallow APDIs (very slight stage)

were recorded on the squamous part of the frontal bone, indicating eICP possibly due to tuberculous involvement of the CNS (*e.g.*, Schultz, 1993, 2001, 2003). Moreover, non-specific vestiges of inflammatory-haemorrhagic processes of the meninges − namely multifocal, small patches of PAs (*e.g.*, Schultz, 1993, 1999, 2001, 2003) − were detected on the squamous and orbital **(Fig. 36)** parts of the frontal bone, along the sagittal suture in the left and right parietal bones, and on the squamous part of the left and right temporal bones.

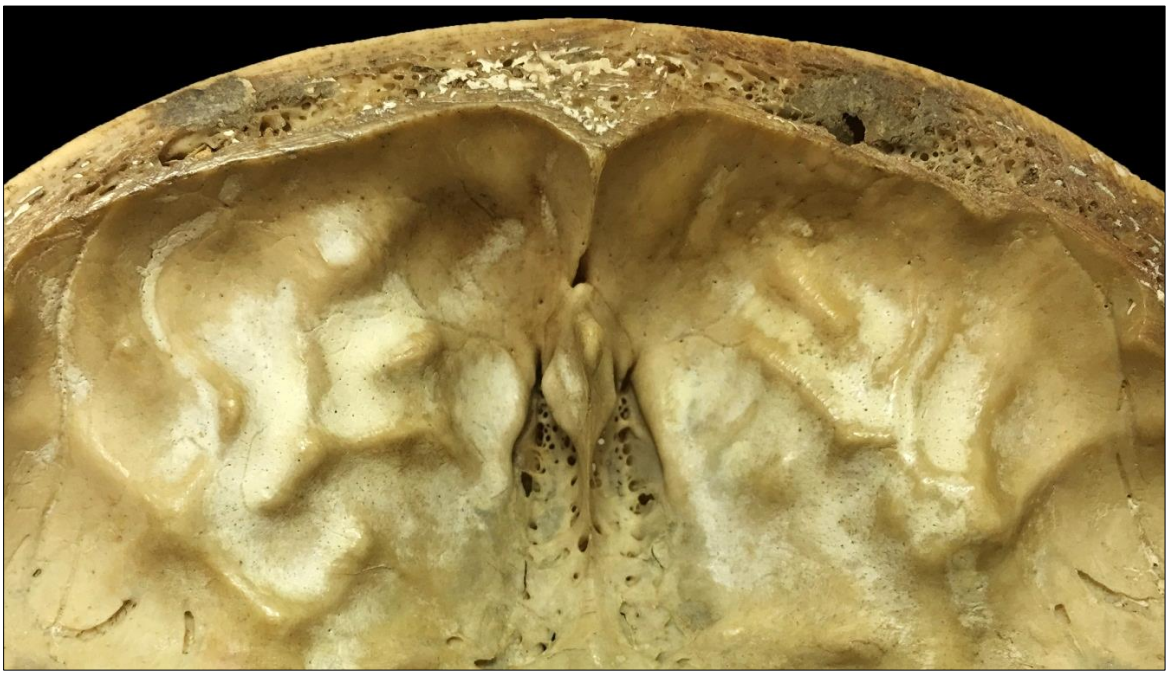


Figure 36: Multifocal PAs on the orbital part of the frontal bone (Terry No. 1300, 28-year-old, male, TB).

Besides the endocranial alterations probably associated with TBM, slight PNBFs − frequently described as not specific but probable signs of pulmonary TB and/or TB pleurisy (*e.g.*, Kelley & Micozzi, 1984; Roberts *et al.*, 1994; Santos & Roberts, 2001, 2006; Maczel, 2003; Matos & Santos, 2006; Giacon, 2008; Mariotti *et al.*, 2015) − were observed on the visceral surface of the sternal (4^{th}–5^{th}) and/or vertebral (5^{th}) end of two right side ribs (4^{th}–5^{th}). In the vertebral column, signs of hypervascularisation were recognised on the lateral aspects of the lower thoracic (T7–12) and lumbar (L1–5) vertebral bodies, possibly referring to early-stage skeletal TB (*e.g.*, Ménard, 1888; Baker, 1999; Maczel, 2003; Giacon, 2008; Mariotti *et al.*, 2015). Although the registered endocranial and postcranial bony changes are not pathognomonic features of TB, the cause of death of Terry No. 1300 supports their tuberculous origin.

4.1.3 Abnormal blood vessel impressions

Σ=427		TB group		NTB group	
Number of specimens affected by ABVIs		50/234 (21.37%)		12/193 (6.22%)	
Females	Males	20/65 (30.77%)	30/169 (17.75%)	6/87 (6.90%)	6/106 (5.66%)

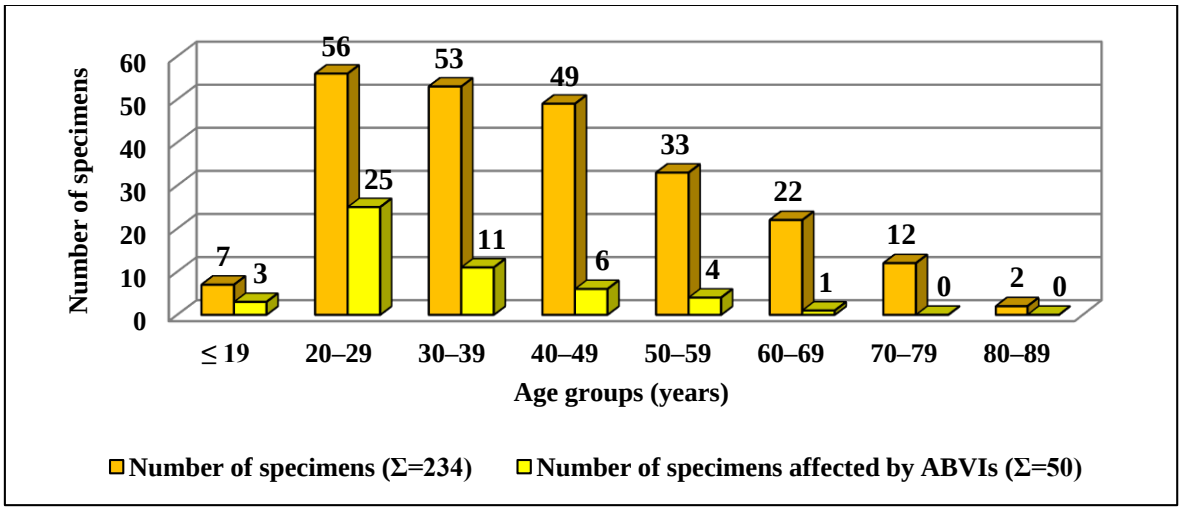
Table 5: Number of specimens exhibiting ABVIs in the TB group and NTB group by sex.

From a total of 427 skeletons evaluated, 62 (14.52%) exhibited ABVIs on the inner surface of the skull: 50 (21.37%) of 234 individuals recorded to have died of TB and 12 (6.22%) of 193 specimens identified to have died of causes other than TB **(Table 5)**; thus, there was a statistically extremely significant difference in the frequencies of ABVIs between the TB group and NTB group (χ^2=18.357, df=1, P<0.0001). When the two groups were compared considering the sex **(Table 5)**, the difference in the frequencies of ABVIs remained significant for both females (χ^2=13.317, df=1, P=0.0003) and males (χ^2=7.342, df=1, P=0.0067). Furthermore, an approximately 13 percentage point difference in the frequencies of ABVIs between females and males was found in the TB group: 30.77% versus 17.75%, respectively **(Table 5)**. The χ^2 comparison of the frequencies of ABVIs between the two sexes in the TB group **(Table 5)** revealed a statistically significant difference (χ^2=3.992, df=1, P=0.0457). Nevertheless, the frequencies of ABVIs among females and males were very similar in the NTB group **(Table 5)**; thus, there was no statistically significant difference between the two sexes (χ^2=0.00295, df=1, P=0.9567).

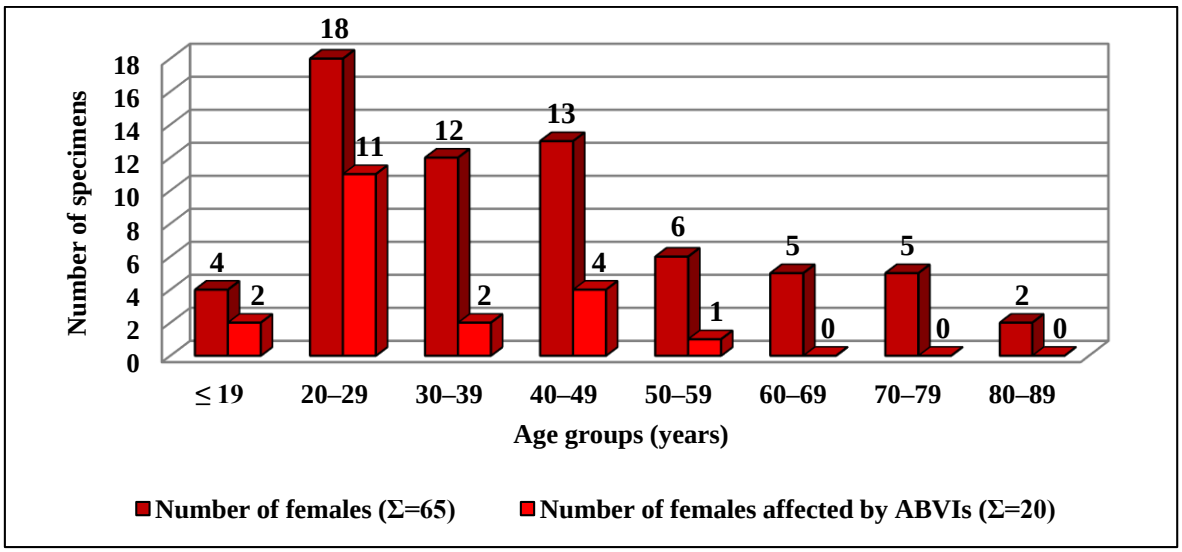
As for the distribution of affected individuals by age at death, abnormal blood vessel impressions occurred with the highest frequency among specimens under the age of 30 years (28/63, 44.44%) in the TB group **(Fig. 37A)**: with 59.09% (13/22) among females **(Fig. 37B)** and with 36.59% (15/41) among males **(Fig. 37C)**. With the exception of females between 40 and 49 years of age (4/13, 30.77%) **(Fig. 37B)** and males between 30 and 39 years of age (9/41, 21.95%) **(Fig. 37C)**, ABVIs were observed only in a few cases among individuals above the age of 29 years **(Fig. 37A)**. In contrast to the TB group, only a 22-year-old male exhibited ABVIs on the inner surface of the skull among specimens under the age of 30 years in the NTB group **(Fig. 38A–C)**. The rest of the individuals with NTB causes of death and ABVIs (11/12, 91.67%) were above the age of 40 years **(Fig. 38A–C)**. The χ^2 testing of the frequencies of ABVIs between various age groups was not assessed because of the low number of specimens in certain age groups.

Figure 37: Demographic profile of specimens exhibiting ABVIs in the TB group: A) total sample (50/234, 21.37%), B) females (20/65, 30.77%), and C) males (30/169, 17.75%).

A)



B)



C)

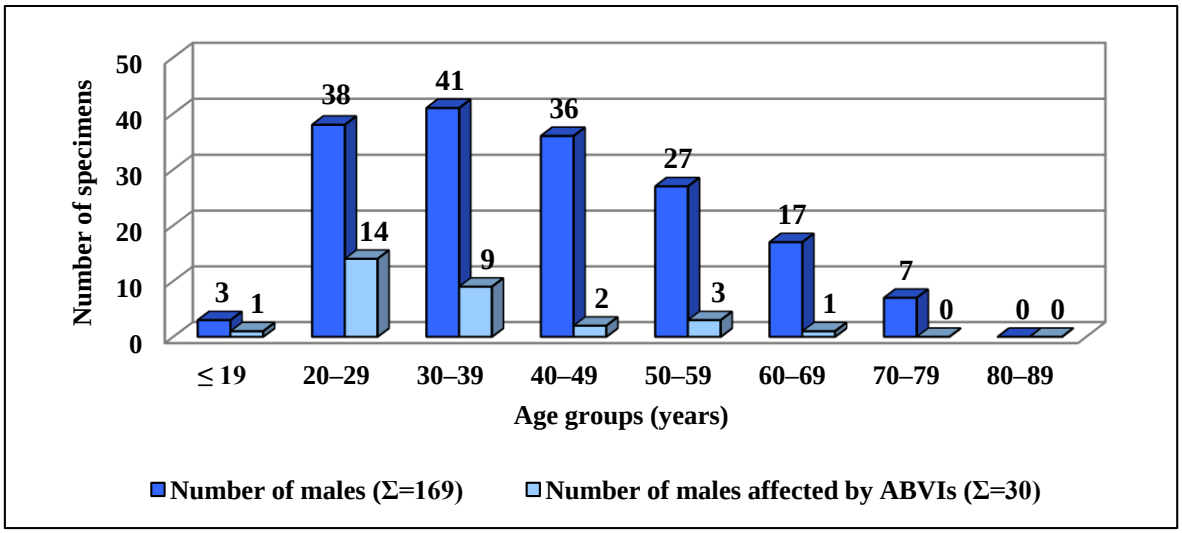
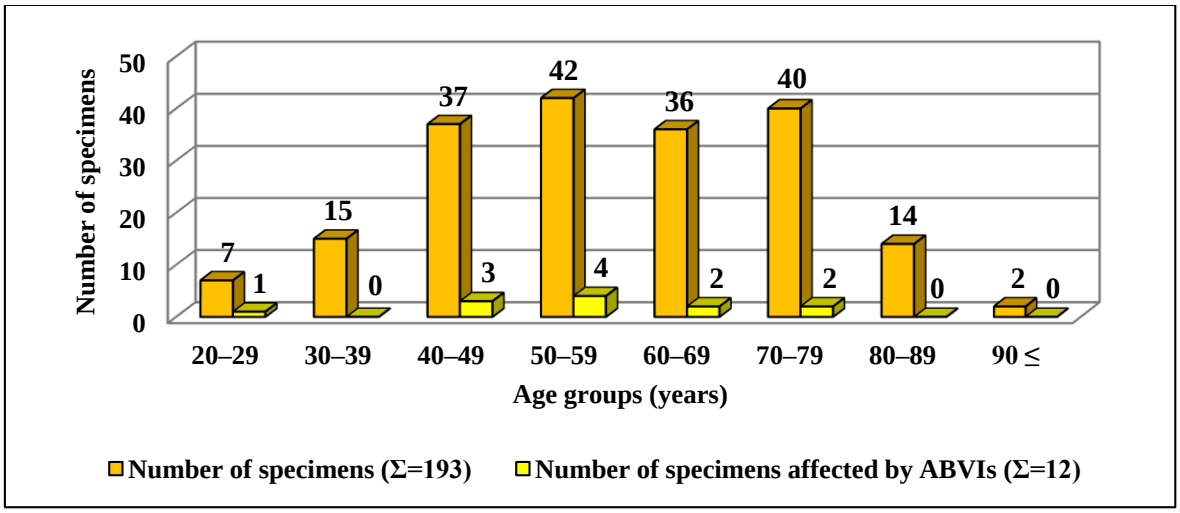
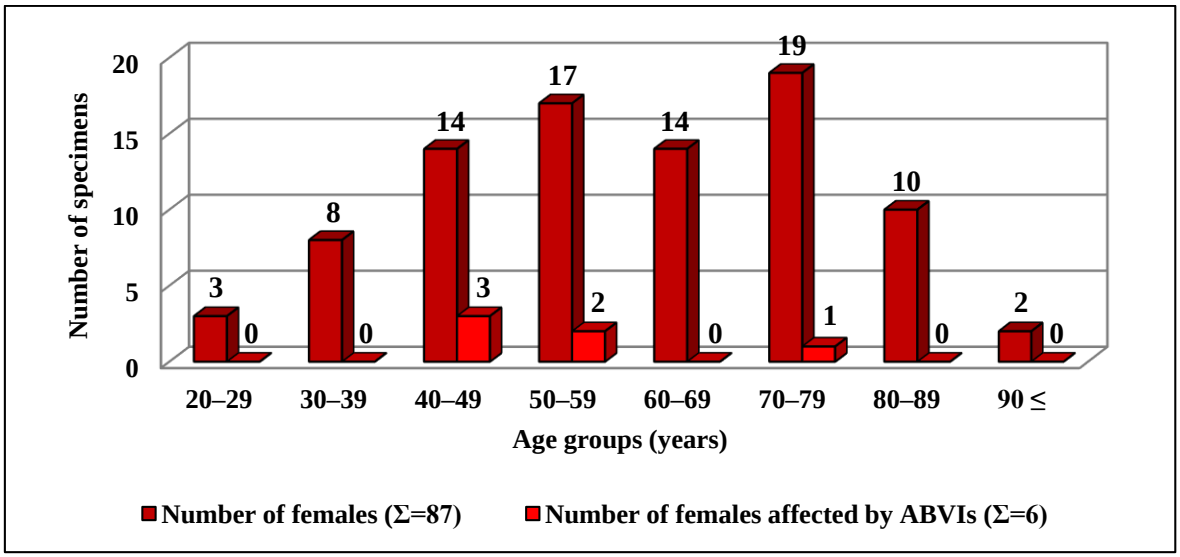


Figure 38: Demographic profile of specimens exhibiting ABVIs in the NTB group: A) total sample (12/193, 6.22%), B) females (6/87, 6.90%), and C) males (6/106, 5.66%).

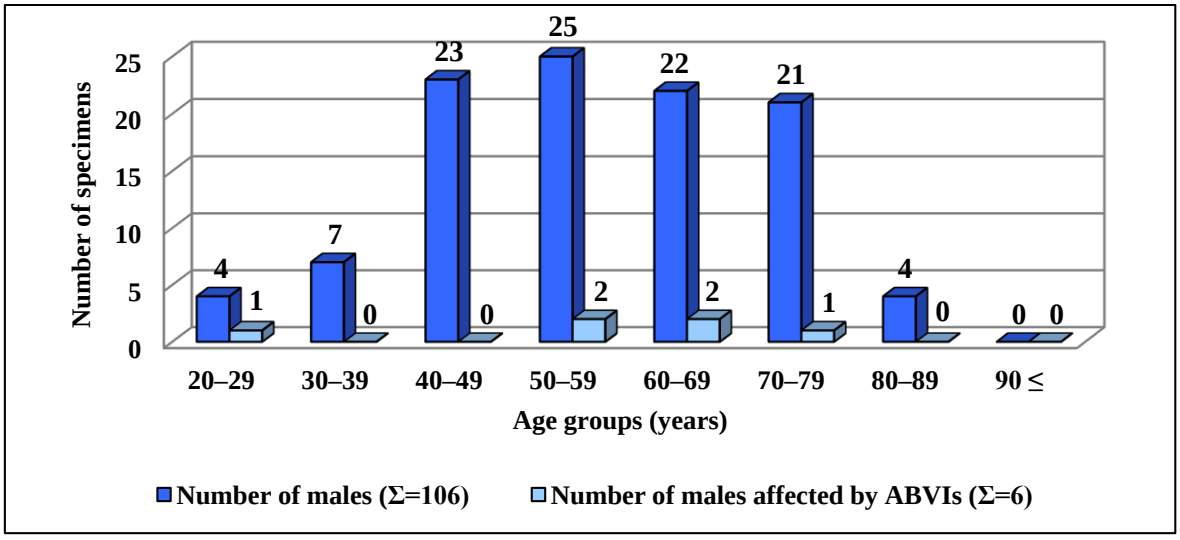
A)



B)



C)



Concerning the localisation of ABVIs, the frontal and the left and right parietal bones (particularly their most protruding portions and/or their parts along the superior sagittal sinus **(Fig. 39A – blue)**) represented the most common sites of involvement in both the TB group and NTB group **(Table 6A−B)**. Occasionally, the involvement of the occipital bone (generally along the superior sagittal and/or transverse sinuses **(Fig. 39B – orange)**) was also registered among individuals with TB as the cause of death **(Table 6A)**. With the exception of two cases showing ABVIs on the squamous part of the right temporal bone, and two further cases on the left and right greater wings of the sphenoid bone in the TB group **(Fig. 39B – yellow)**, the left and right temporal bones, and the left and right greater wings of the sphenoid bone were not affected by these lesions both among specimens identified to have died of TB and individuals recorded to have died of causes other than TB **(Table 6A–B)**.

A) **B)**

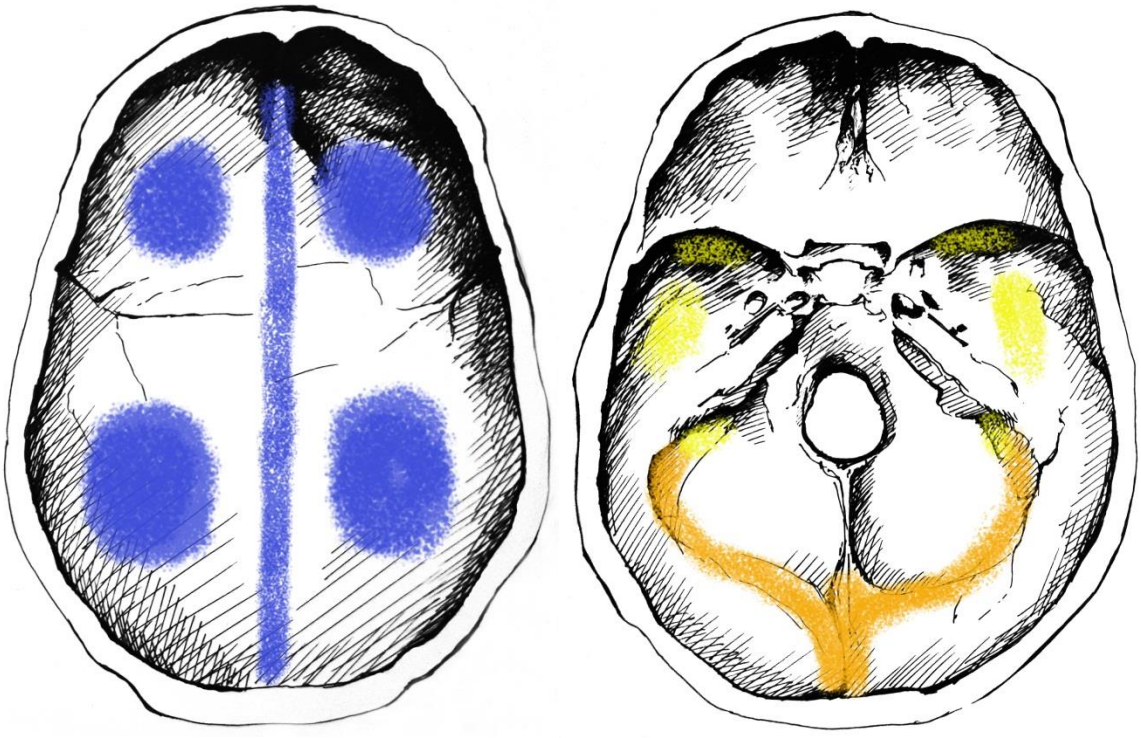


Figure 39: Typical localisations of ABVIs on the inner surface of the A) skullcap and B) skull base (blue: most commonly affected areas, orange: commonly affected areas, and yellow: less commonly affected areas) (drawings by *Luca Kis*).

The number of cranial bones concurrently involved by ABVIs (considering the left and right greater wings of the sphenoid bone as two separate bones) varied from one to six in the TB group and from one to four in the NTB group. In nearly two-thirds (32/50, 64.00%) of specimens with TB as the cause of death and ABVIs, at least three cranial bones were

simultaneously affected **(Fig. 40A)**; whereas in three-fourths (9/12, 75.00%) of individuals with NTB causes of death and ABVIs, less than three cranial bones were concomitantly involved **(Fig. 40B)**.

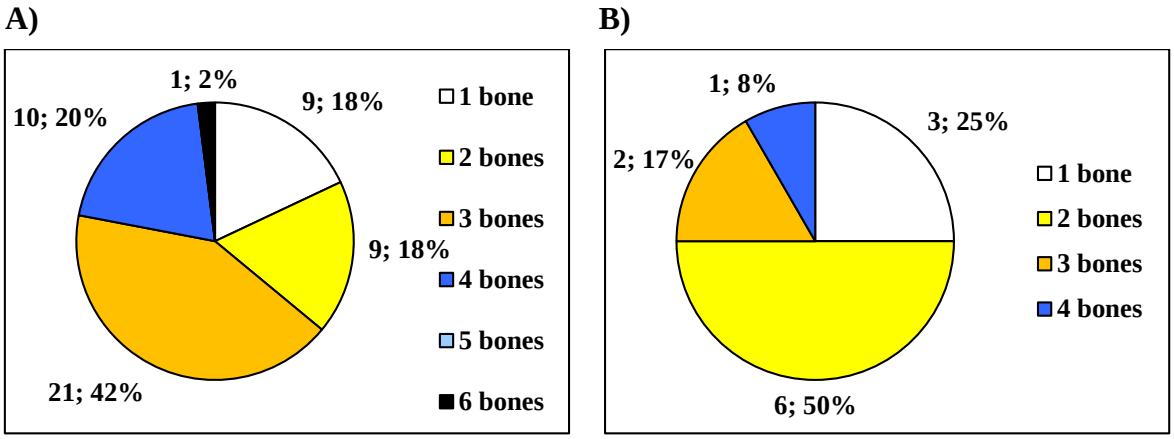


Figure 40: Distribution of specimens affected by ABVIs in the A) TB group (Σ=50) and B) NTB group (Σ=12) by number of simultaneously involved cranial bones (considering the left and right greater wings of the sphenoid bone as two separate bones).

Regarding the number of presented lesions, ABVIs were almost exclusively detected as multifocal bony changes on the inner surface of the frontal, parietal, and occipital bones in both the TB group and NTB group **(Table 6A–B)**. Nonetheless, unifocal ABVIs occurred in the left and right parietal, right temporal, and/or occipital bones in a few cases among both specimens identified to have died of TB and individuals recorded to have died of causes other than TB **(Table 6A–B)**. With respect to the extent of registered lesions, the majority of observed ABVIs covered less than one-half of the endocranial surfaces in all cranial bones examined in both the TB group and NTB group **(Table 6A–B)**. However, in the TB group, the extent of ABVIs noted in the frontal and the left and right parietal bones exceeded one-half of the inner surfaces quite often: in 30.95% (13/42), 18.42% (7/38), and 19.44% (7/36) of cases, respectively **(Table 6A)**.

Of 50 specimens with ABVIs in the TB group, 42 were identified to have died of pulmonary TB **(Suppl. table 1, 3)**. Five additional individuals died of other types of tuberculosis, such as peritoneal TB (three cases), TB meningitis (one case), and miliary TB (one case); whereas in the remaining three cases, the type of tuberculosis as the cause of death was not specified on the morgue record and/or death certificate **(Suppl. table 1, 3)**. In the NTB group, the most frequently registered NTB causes of death were cardiovascular problems, followed by respiratory diseases, syphilis, and different types of cancer among specimens exhibiting ABVIs on the inner surface of the skull **(Suppl. table 2, 4)**.

Table 6: Distribution of specimens exhibiting ABVIs in the A) TB group and B) NTB group by affected cranial bones (considering the left and right greater wings of the sphenoid bone as two separate bones), extent, and number of lesions (L = left, R = right).

A) TB group (Σ=234)		Frontal bone	Parietal bone (L)	Parietal bone (R)	Temporal bone (L)	Temporal bone (R)	Sphenoid bone (L)	Sphenoid bone (R)	Occipital bone
		42/50 (84.00%)	38/50 (76.00%)	36/50 (72.00%)	0/50 (0.00%)	2/50 (4.00%)	1/50 (2.00%)	1/50 (2.00%)	16/50 (32.00%)
Extent (x) of lesions	x < 25%	13/42 (30.95%)	27/38 (71.05%)	23/36 (63.89%)	–	1/2 (50.00%)	–	–	15/16 (93.75%)
	25% ≤ x < 50%	16/42 (38.10%)	4/38 (10.53%)	6/36 (16.67%)	–	–	–	–	1/16 (6.25%)
	50% ≤ x < 75%	7/42 (16.67%)	5/38 (13.16%)	5/36 (13.89%)	–	1/2 (50.00%)	1/1 (100.00%)	–	–
	75% ≤ x	6/42 (14.29%)	2/38 (5.26%)	2/36 (5.56%)	–	–	–	1/1 (100.00%)	–
Number of lesions	Unifocal	–	2/38 (5.26%)	2/36 (5.56%)	–	2/2 (100.00%)	1/1 (100.00%)	1/1 (100.00%)	3/16 (18.75%)
	Multifocal	42/42 (100.00%)	36/38 (94.74%)	34/36 (94.44%)	–	–	–	–	13/16 (81.25%)

B) NTB group (Σ=193)		Frontal bone	Parietal bone (L)	Parietal bone (R)	Temporal bone (L)	Temporal bone (R)	Sphenoid bone (L)	Sphenoid bone (R)	Occipital bone
		5/12 (41.67%)	9/12 (75.00%)	10/12 (83.33%)	0/12 (0.00%)	0/12 (0.00%)	0/12 (0.00%)	0/12 (0.00%)	1/12 (8.33%)
Extent (x) of lesions	x < 25%	2/5 (40.00%)	6/9 (66.67%)	7/10 (70.00%)	–	–	–	–	1/1 (100.00%)
	25% ≤ x < 50%	2/5 (40.00%)	2/9 (22.22%)	2/10 (20.00%)	–	–	–	–	–
	50% ≤ x < 75%	1/5 (20.00%)	1/9 (11.11%)	1/10 (10.00%)	–	–	–	–	–
	75% ≤ x	–	–	–	–	–	–	–	–
Number of lesions	Unifocal	–	1/9 (11.11%)	1/10 (10.00%)	–	–	–	–	–
	Multifocal	5/5 (100.00%)	8/9 (88.89%)	9/10 (90.00%)	–	–	–	–	1/1 (100.00%)

In the skeleton of **Terry No. 254** − a 21-year-old male recorded to have died of pulmonary TB **(Suppl. table 1)** −, pathological bony changes that may be attributed to tuberculosis were registered both in the cranial and postcranial elements. Concerning the skull, deep APDIs (pronounced stage) were noted all over the inner surface of the skullcap and skull base, referring to eICP possibly due to tuberculous involvement of the CNS (*e.g.*, Schultz, 1993, 2001, 2003). Furthermore, non-specific vestiges of haemorrhagic and/or inflammatory meningeal reactions − namely multifocal, small, serpentine branching ABVIs accompanied by slight PAs (*e.g.*, Schultz, 1993, 1999, 2001, 2003) − were detected in the deep DIs located in the frontal **(Fig. 19C** (p. 44)**)** and parietal **(Fig. 41)** bones, covering about three-fourths (stage 4) of the inner surfaces. Moreover, the endocranial surface of the squamous part of the temporal bones and the right greater wing of the sphenoid bone also exhibited small patches of PAs.

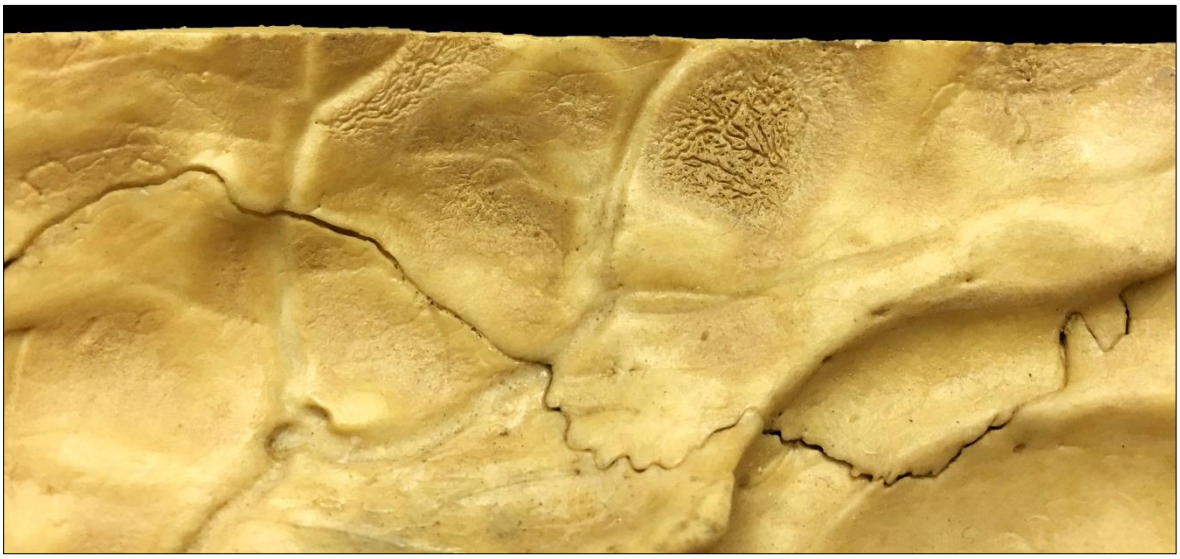


Figure 41: Multifocal ABVIs accompanied by PAs along the squamous suture in the right parietal bone (Terry No. 254, 21-year-old, male, pulmonary TB).

Besides the endocranial alterations probably associated with TBM, very slight PNBFs − frequently described as not specific but probable signs of pulmonary TB and/or TB pleurisy (*e.g.*, Kelley & Micozzi, 1984; Roberts *et al.*, 1994; Santos & Roberts, 2001, 2006; Maczel, 2003; Matos & Santos, 2006; Giacon, 2008; Mariotti *et al.*, 2015) − occurred on the sternal end (left 3^{rd}–6^{th}, right 2^{nd}–3^{rd} and 6^{th}–8^{th}), and occasionally on the body (right 3^{rd}–4^{th}) and vertebral end (right 2^{nd}–3^{rd}) of four left side (3^{rd}–6^{th}) and seven right side (2^{nd}–8^{th}) ribs, exclusively affecting the visceral surfaces. Slight PNBFs were also recorded on the anterior surface of both humeri and radii (predominantly on the distal portion of the shaft), on the posterior surface of the right ulna (all along the shaft), in the supraspinatous fossa of

both scapulae, and on the medial surface of both calcanei, indicating HPO probably related to pulmonary TB (*e.g.*, Mensforth *et al.*, 1978; Kelly *et al.*, 1991; Winland *et al.*, 1997; Rothschild & Rothschild, 1998, 1999; Santos & Roberts, 2001; Hershkovitz *et al.*, 2002; Assis *et al.*, 2011). Although the observed endocranial and postcranial bony changes are not pathognomonic features of TB, the cause of death of Terry No. 254 supports their tuberculous origin.

Similar to the previous case, the skeletal remains of **Terry No. 1030** – a 62-year-old male whose death certificate states pulmonary TB as the cause of death **(Suppl. table 1)** – revealed endocranial bony changes probably resulted from TBM. Multifocal, serpentine branching ABVIs − described by *Schultz* (*e.g.*, 1993, 1999, 2001, 2003) as non-specific vestiges of inflammatory-haemorrhagic processes of the meninges − occurred on the inner surface of the frontal and the left and right parietal **(Fig. 42A)** bones, predominantly along the sagittal sinus. The detected lesions covered more than three-fourths (stage 4) of the inner surfaces. The left and right **(Fig. 42B)** greater wings of the sphenoid bone and the squamous part of the occipital bone **(Fig. 43)** (particularly along the sagittal and transverse sinuses) also showed ABVIs. There were no other bony changes probably associated with TB in the skeleton. Based on the recorded cause of death of Terry No. 1030, the tuberculous origin of the observed ABVIs cannot be excluded.

A) **B)**

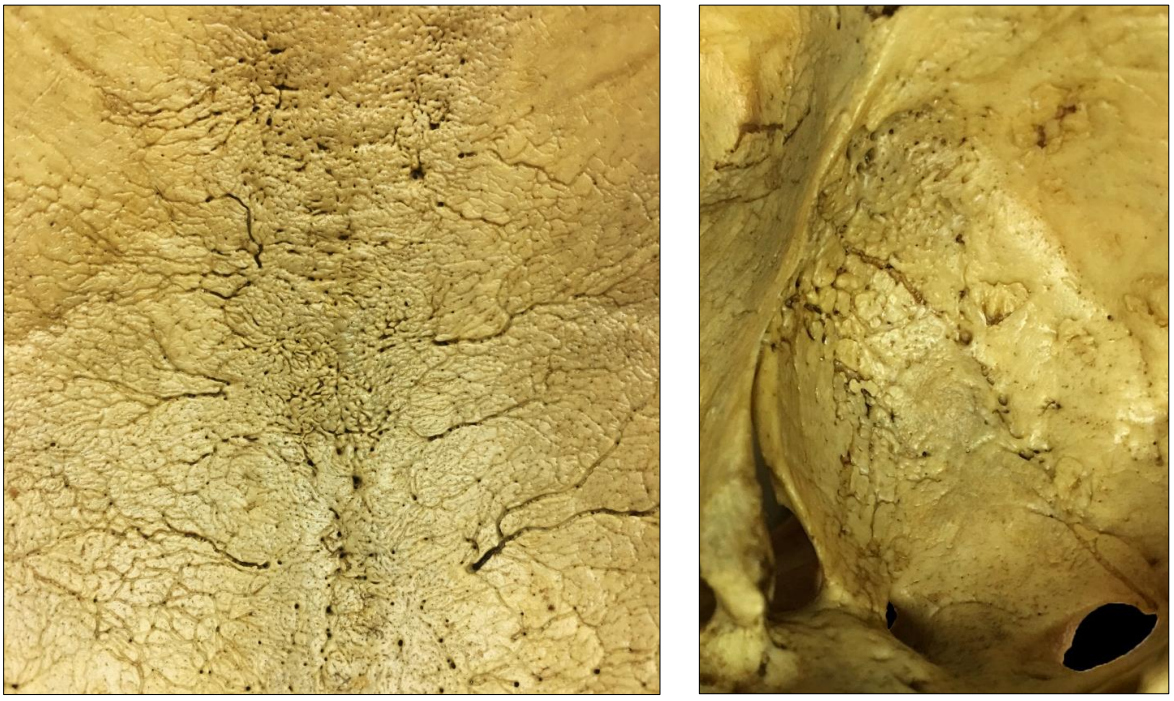


Figure 42: ABVIs A) along the sagittal sinus in the parietal bones and B) on the right greater wing of the sphenoid bone (Terry No. 1030, 62-year-old, male, pulmonary TB).

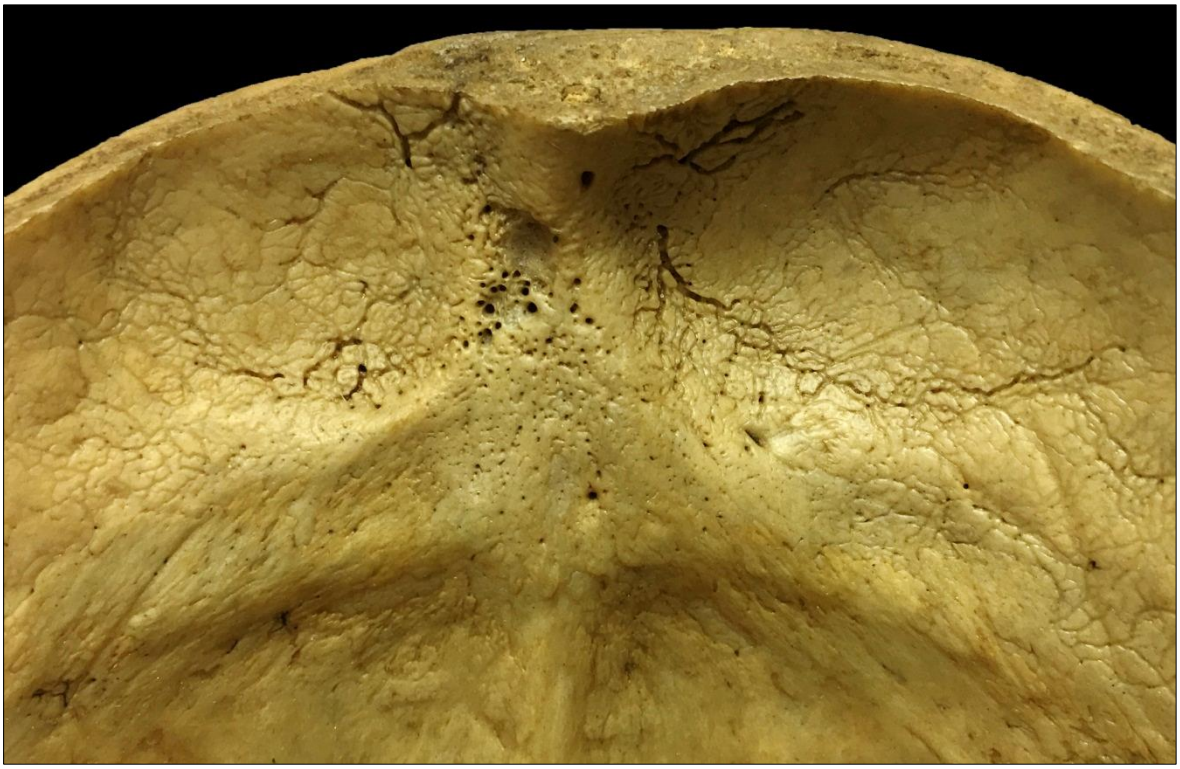


Figure 43: ABVIs along the sagittal and transverse sinuses on the squamous part of the occipital bone (Terry No. 1030, 62-year-old, male, pulmonary TB).

Both the cranial and postcranial remains of **Terry No. 1555** – a 41-year-old female who had died of pulmonary TB **(Suppl. table 1)** – showed different types of pathological bony changes that may be ascribed to tuberculosis. In the skull, shallow APDIs (very slight stage) affecting the squamous part of the frontal and the left and right parietal bones were recorded, referring to eICP possibly due to hydrocephalus that may be related to TBM (*e.g.*, Schultz, 1993, 2001, 2003). Non-specific signs of the inflammatory-haemorrhagic meningeal processes, namely ABVIs (*e.g.*, Schultz, 1993, 1999, 2001, 2003), were noted on the endocranial surface of the frontal and the left and right parietal bones, particularly around their most protruding portions **(Fig. 44)**.

As for the postcranial skeleton, five left (1^{st}–5^{th}) and three right (2^{nd}–4^{th}) side ribs showed slight PNBFs on the visceral surface of the vertebral end that may represent vestiges of an inflammatory response secondary to pulmonary TB and/or TB pleurisy (*e.g.*, Kelley & Micozzi, 1984; Roberts *et al.*, 1994; Santos & Roberts, 2001, 2006; Maczel, 2003; Matos & Santos, 2006; Giacon, 2008; Mariotti *et al.*, 2015). Besides the ribs, the medial and lateral surfaces of both tibiae (predominantly the proximal and distal portions of the shaft), the anterior and posterior surfaces of both fibulae (particularly the middle portion of the shaft), the medial surface of both calcanei, the anterior and medial surfaces of both radii (mainly

the distal portion of the shaft), the supraspinatous fossa of both scapulae, and the palmar surface of both 1st metacarpals (particularly the proximal portion of the shaft) also exhibited slight PNBFs, indicating HPO probably associated with pulmonary TB (*e.g.*, Mensforth *et al.*, 1978; Kelly *et al.*, 1991; Winland *et al.*, 1997; Rothschild & Rothschild, 1998, 1999; Santos & Roberts, 2001; Hershkovitz *et al.*, 2002; Assis *et al.*, 2011). Based on the recorded cause of death of Terry No. 1555, the most likely aetiology of the observed endocranial and postcranial bony changes is tuberculosis.

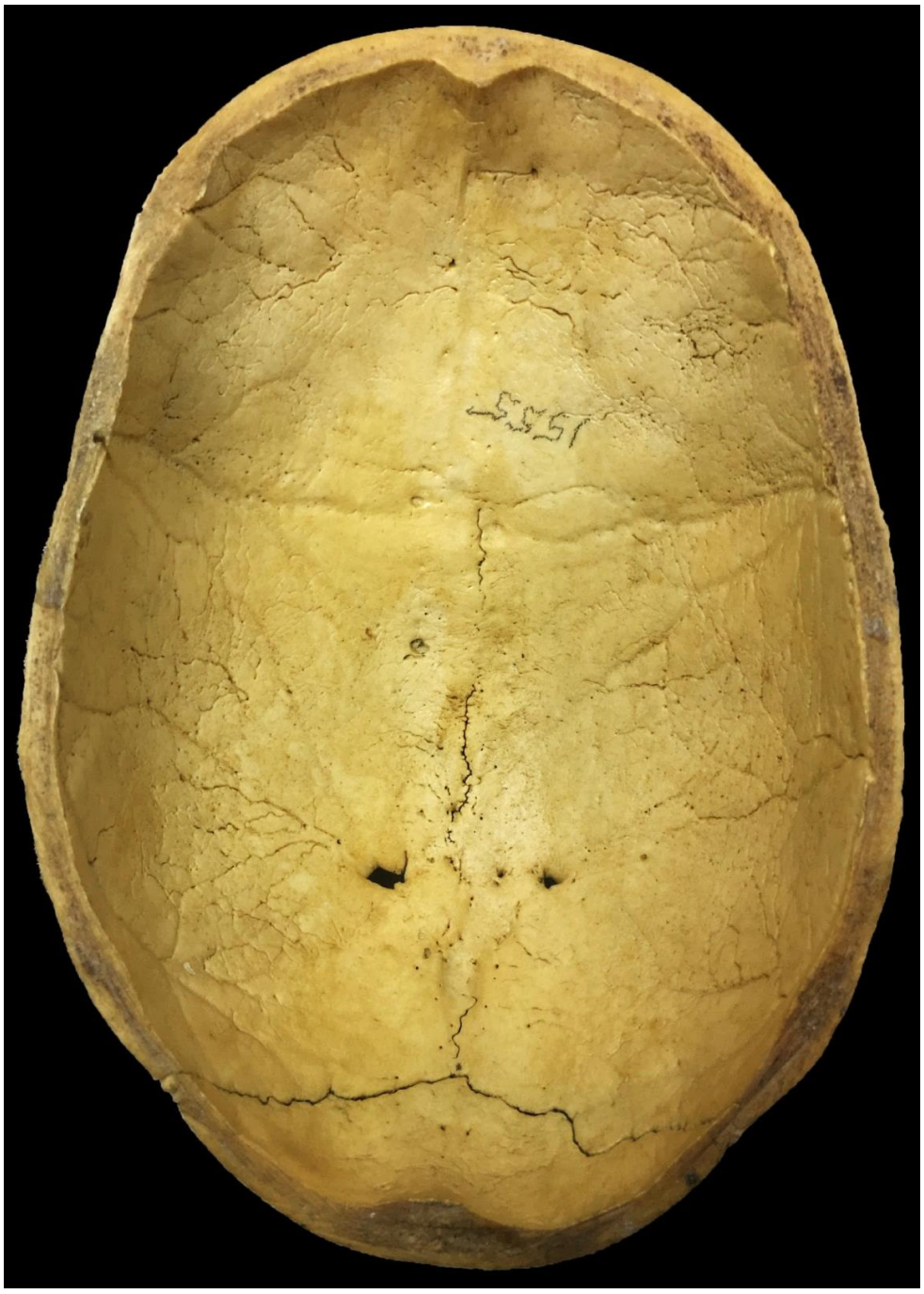


Figure 44: ABVIs on the endocranial surface of the frontal and parietal bones, predominantly affecting the most protruding portions (Terry No. 1555, 41-year-old, female, pulmonary TB).

4.1.4 Granular impressions

Σ=427		TB group		NTB group	
Number of specimens affected by GIs		68/234 (29.06%)		6/193 (3.11%)	
Females	Males	20/65 (30.77%)	48/169 (28.40%)	2/87 (2.30%)	4/106 (3.77%)

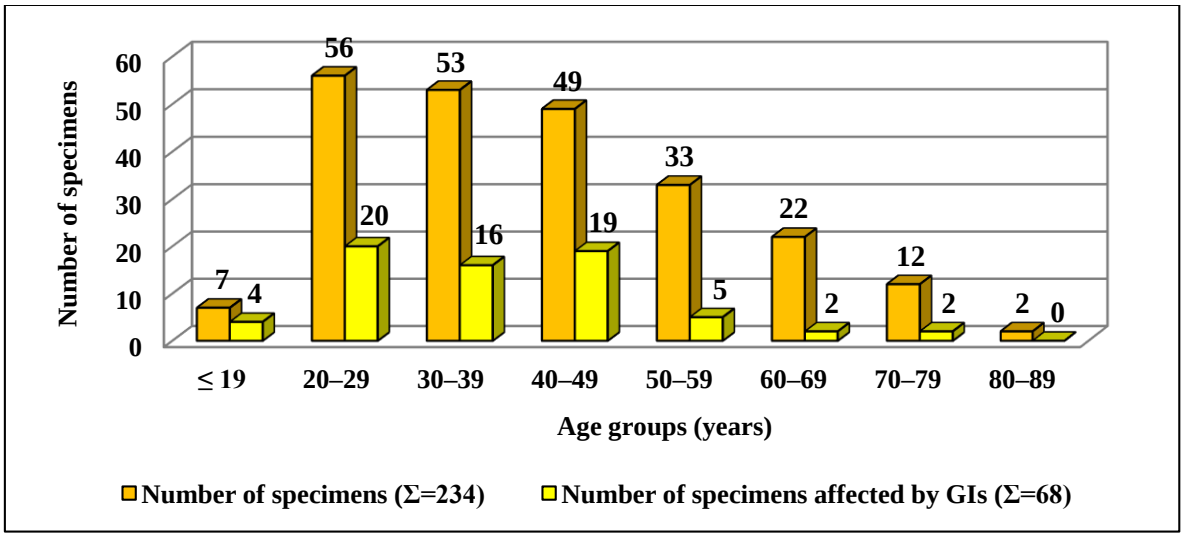
Table 7: Number of specimens exhibiting GIs in the TB group and NTB group by sex.

GIs were detected in 17.33% (74/427) of skeletons examined: in 29.06% (68/234) of the TB group and in 3.11% (6/193) of the NTB group **(Table 7)**. The χ^2 testing of the frequencies of GIs in specimens with TB as the cause of death and individuals with NTB causes of death revealed a statistically extremely significant difference between the two groups (χ^2=47.922, df=1, P<0.0001). When the two groups were compared considering the sex **(Table 7)**, the difference in the frequencies of GIs remained extremely significant for both females (χ^2=22.115, df=1, P<0.0001) and males (χ^2=24.188, df=1, P<0.0001). However, the frequencies of GIs in females and males were very similar in both groups **(Table 7)**; thus, there was no statistically significant difference between the two sexes (TB group: χ^2=0.0386, df=1, P=0.8443; NTB group: χ^2=0.0291, df=1, P=0.8645).

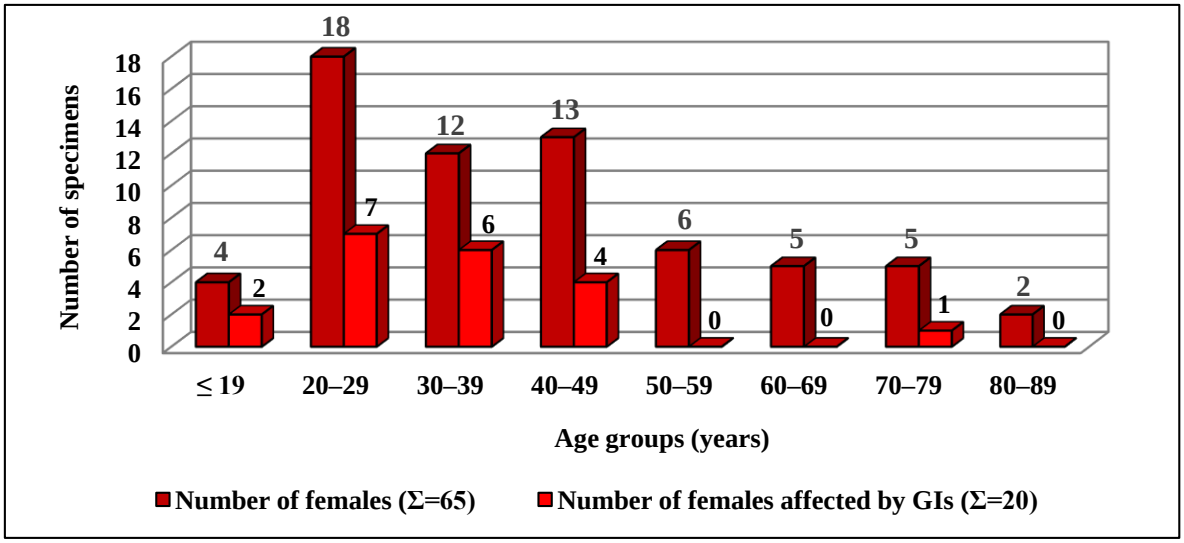
With respect to the distribution of affected specimens by age at death in the TB group, granular impressions occurred with the highest frequency among individuals under the age of 20 years (4/7, 57.14%) **(Fig. 45A)**: with 50.00% (2/4) among females **(Fig. 45B)** and with 66.67% (2/3) among males **(Fig. 45C)**. Nevertheless, more than one-third (55/158, 34.81%) of specimens between 20 and 49 years of age and recorded to have died of TB also exhibited GIs on the endocranial surface of the skull (females: 17/43, 39.53%; males: 38/115, 33.04%) **(Fig. 45A–C)**. Except for males between 50 and 59 years of age (5/27, 18.52%) **(Fig. 45C)**, GIs occurred only in a few cases among individuals above the age of 49 years: in a 73-year-old female, in two males between 60 and 69 years of age, and in a 71-year-old male **(Fig. 45A–C)**. In the NTB group, with the exception of a 25-year-old male, specimens affected by GIs were above the age of 40 years: a female and two males between 40 and 49 years of age, a 54-year-old male, and a 60-year-old female **(Fig. 46A–C)**. The χ^2 testing of the frequencies of GIs between various age groups was not assessed because of the low number of individuals in certain age groups.

Figure 45: Demographic profile of specimens exhibiting GIs in the TB group: A) total sample (68/234, 29.06%), B) females (20/65, 30.77%), and C) males (48/169, 28.40%).

A)



B)



C)

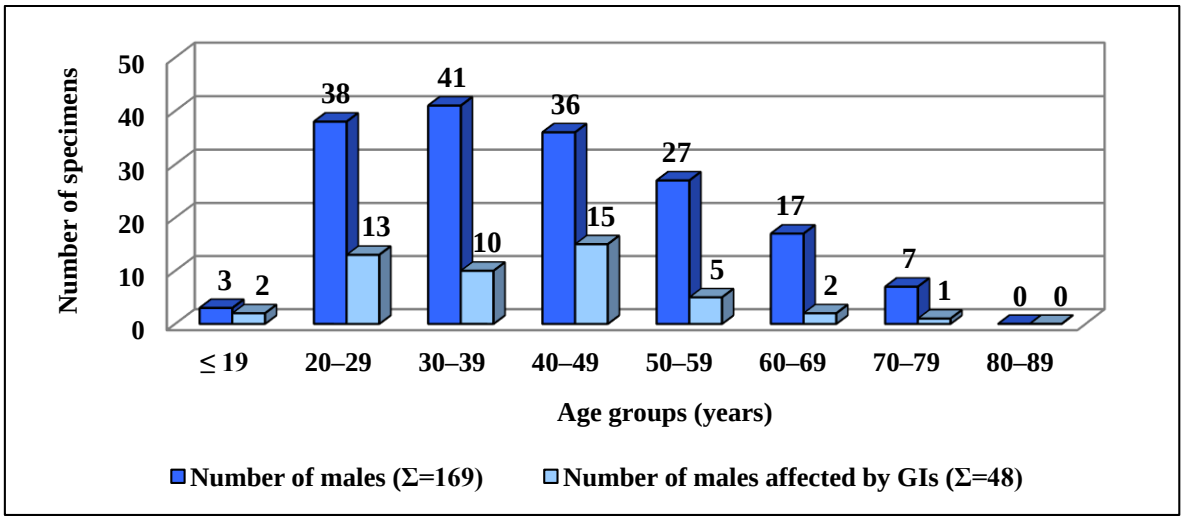
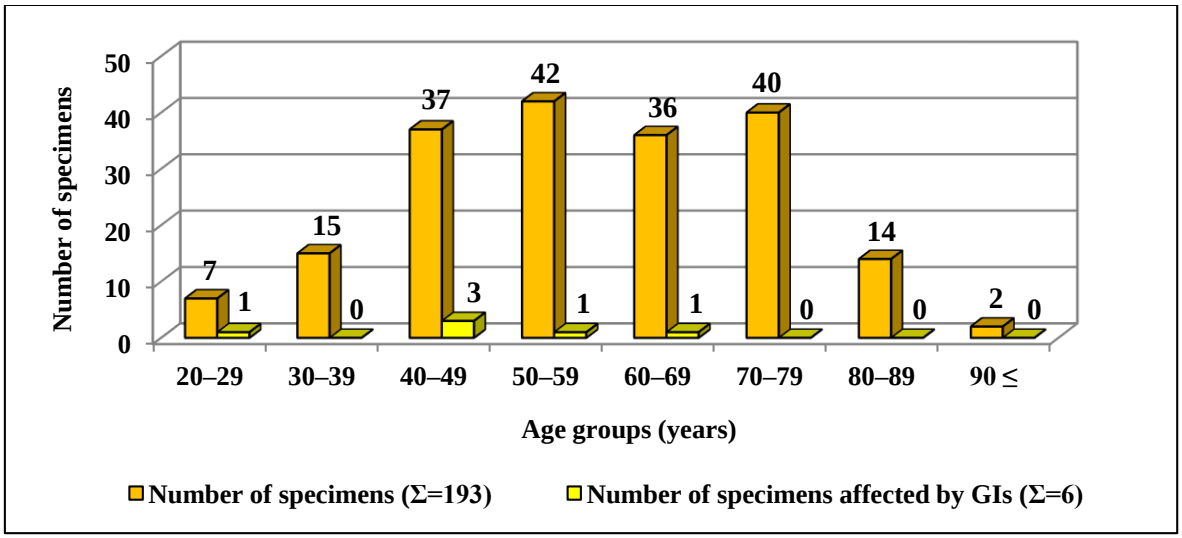
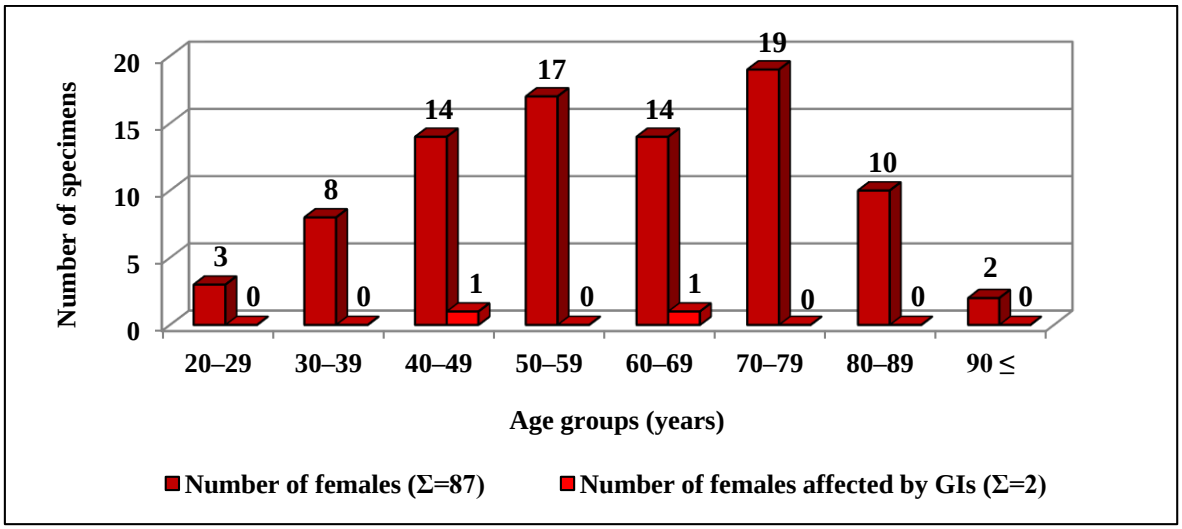


Figure 46: Demographic profile of specimens exhibiting GIs in the NTB group: A) total sample (6/193, 3.11%), B) females (2/87, 2.30%), and C) males (4/106, 3.77%).

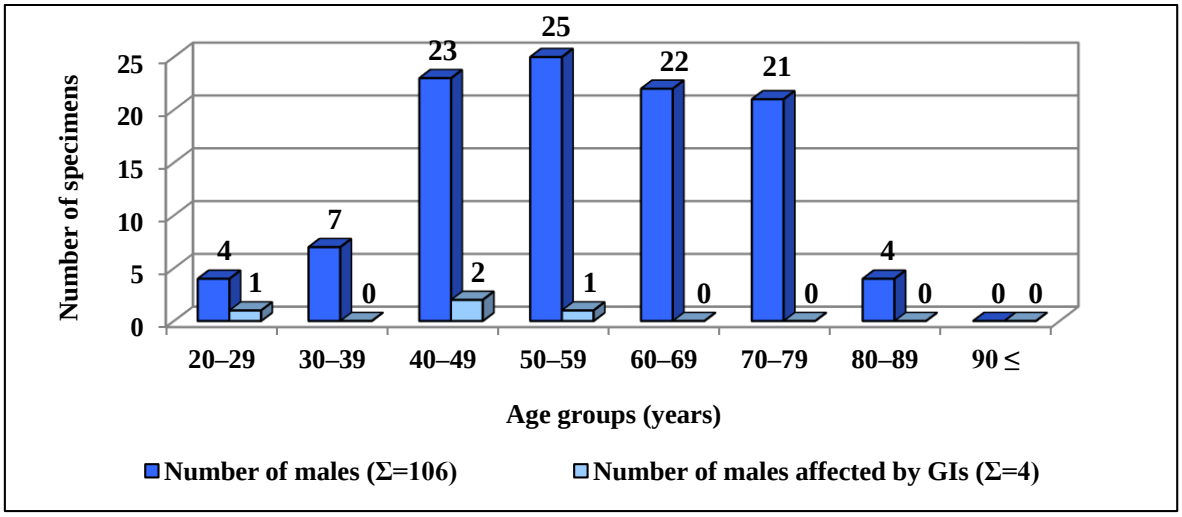
A)



B)



C)



Concerning the localisation of GIs, the most commonly affected area of the inner surface of the skull was the squamous part of the occipital bone **(Fig. 47 – blue)** in both the TB group and NTB group **(Table 8A−B)**. Furthermore, GIs were quite often observed in the orbital part of the frontal bone and in the squamous part of the left and right temporal bones **(Fig. 47 – orange; Table 8A−B)**. Occasionally, the involvement of the left and right greater wings of the sphenoid bone, as well as the left and right parietal bones (predominantly along the squamous suture), was also registered **(Fig. 47 – yellow; Table 8A–B)**.

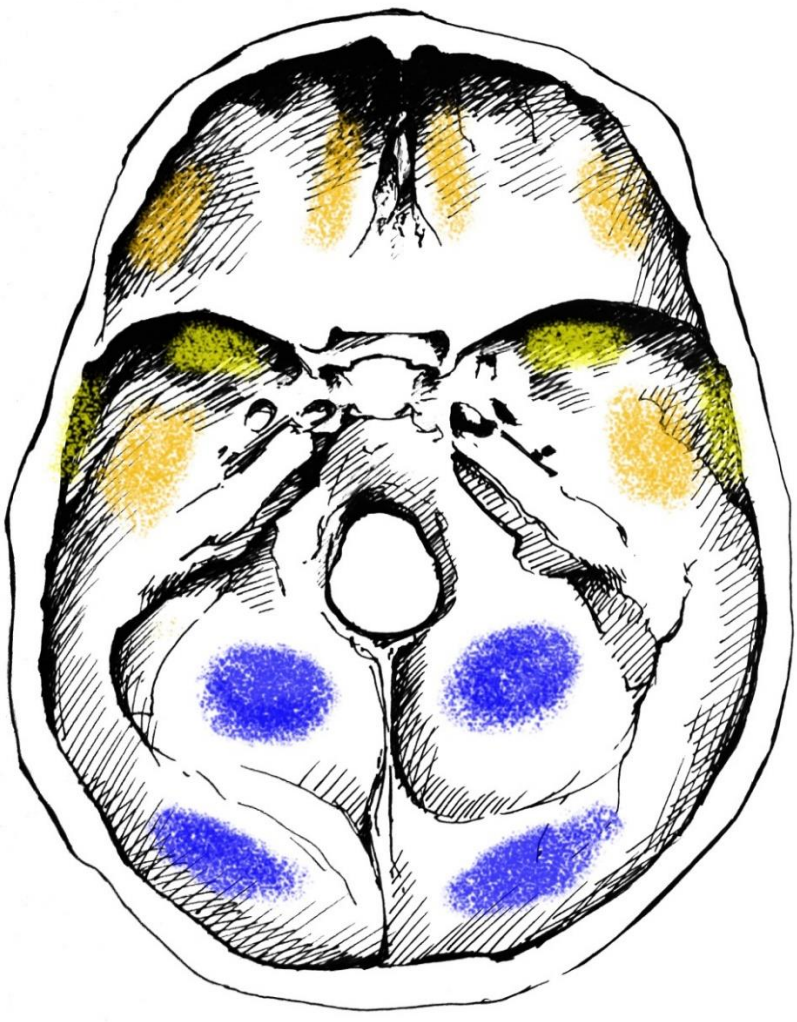


Figure 47: Typical localisations of GIs on the inner surface of the skull base (blue: most commonly affected areas, orange: commonly affected areas, and yellow: less commonly affected areas) (drawing by *Luca Kis*).

In both groups, less than four cranial bones (considering the left and right greater wings of the sphenoid bone as two separate bones) were simultaneously affected by GIs in approximately two-thirds of individuals (TB group: 49/68, 72.06%; NTB group: 4/6, 66.67%) **(Fig. 48A−B)**.

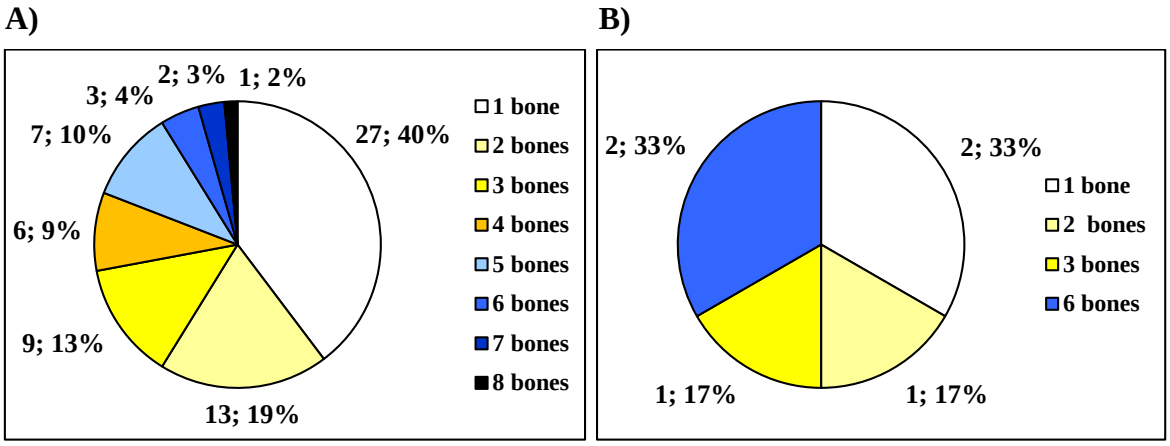


Figure 48: Distribution of specimens affected by GIs in the A) TB group (Σ=68) and B) NTB group (Σ=6) by number of simultaneously involved cranial bones (considering the left and right greater wings of the sphenoid bone as two separate bones).

Regarding the number of presented lesions among specimens identified to have died of TB, GIs were particularly recorded as multifocal bony changes in the occipital and frontal bones, as unifocal alterations on the left and right greater wings of the sphenoid bone and in the left and right parietal bones; whereas the frequencies of unifocal and multifocal GIs were similar in the left and right temporal bones **(Table 8A)**. Among individuals recorded to have died of causes other than TB, only two GIs involving the left and right greater wings of the sphenoid bone were registered as unifocal alterations **(Table 8B)**. As for the extent of detected lesions, the majority of GIs observed in the TB group covered less than one-fourth of the endocranial surfaces in all cranial bones examined **(Table 8A)**. Nonetheless, the extent of GIs in the squamous part of the right temporal bone and on the right greater wing of the sphenoid bone exceeded one-fourth of the inner surfaces quite often: in 30.00% (6/20) and 42.11% (8/19) of cases, respectively **(Table 8A)**. In the NTB group, only three GIs detected on the left and right greater wings of the sphenoid bone and in the squamous part of the occipital bone covered more than one-fourth of the endocranial surfaces **(Table 8B)**.

From a total of 68 individuals with GIs in the TB group, 53 died of pulmonary TB **(Suppl. table 1, 3)**. Five additional specimens died of other types of tuberculosis, such as skeletal TB (three cases), TB meningitis (one case), and peritoneal TB (one case); whereas in the remaining ten cases, the type of tuberculosis as the cause of death was not specified on the morgue record and/or death certificate **(Suppl. table 1, 3)**. Among the NTB causes of death of individuals with GIs, cardiovascular problems (three cases), cancer (two cases), and peritonitis (one case) were recorded **(Suppl. table 2, 4)**.

Table 8: Distribution of specimens exhibiting GIs in the A) TB group and B) NTB group by affected cranial bones (considering the left and right greater wings of the sphenoid bone as two separate bones), extent, and number of lesions (L = left, R = right).

A) TB group (Σ=234)		Frontal bone	Parietal bone (L)	Parietal bone (R)	Temporal bone (L)	Temporal bone (R)	Sphenoid bone (L)	Sphenoid bone (R)	Occipital bone
		32/68 (47.06%)	6/68 (8.82%)	10/68 (14.71%)	20/68 (29.41%)	20/68 (29.41%)	10/68 (14.71%)	19/68 (27.94%)	62/68 (91.18%)
Extent (x) of lesions	x < 25%	31/32 (96.88%)	6/6 (100.00%)	10/10 (100.00%)	18/20 (90.00%)	14/20 (70.00%)	9/10 (90.00%)	11/19 (57.89%)	50/62 (80.65%)
	25% ≤ x < 50%	1/32 (3.13%)	–	–	2/20 (10.00%)	2/20 (10.00%)	1/10 (10.00%)	7/19 (36.84%)	11/62 (17.74%)
	50% ≤ x < 75%	–	–	–	–	4/20 (20.00%)	–	1/19 (5.26%)	1/62 (1.61%)
	75% ≤ x	–	–	–	–	–	–	–	–
Number of lesions	Unifocal	8/32 (25.00%)	4/6 (66.67%)	6/10 (60.00%)	9/20 (45.00%)	9/20 (45.00%)	9/10 (90.00%)	14/19 (73.68%)	9/62 (14.52%)
	Multifocal	24/32 (75.00%)	2/6 (33.33%)	4/10 (40.00%)	11/20 (55.00%)	11/20 (55.00%)	1/10 (10.00%)	5/19 (26.32%)	53/62 (85.48%)

B) NTB group (Σ=193)		Frontal bone	Parietal bone (L)	Parietal bone (R)	Temporal bone (L)	Temporal bone (R)	Sphenoid bone (L)	Sphenoid bone (R)	Occipital bone
		4/6 (66.67%)	1/6 (16.67%)	1/6 (16.67%)	2/6 (33.33%)	3/6 (50.00%)	1/6 (16.67%)	1/6 (16.67%)	6/6 (100.00%)
Extent (x) of lesions	x < 25%	4/4 (100.00%)	1/1 (100.00%)	1/1 (100.00%)	2/2 (100.00%)	3/3 (100.00%)	1/1 (100.00%)	1/1 (100.00%)	5/6 (83.33%)
	25% ≤ x < 50%	–	–	–	–	–	–	–	–
	50% ≤ x < 75%	–	–	–	–	–	–	–	1/6 (16.67%)
	75% ≤ x	–	–	–	–	–	–	–	–
Number of lesions	Unifocal	–	–	–	–	–	1/1 (100.00%)	1/1 (100.00%)	1/6 (16.67%)
	Multifocal	4/4 (100.00%)	1/1 (100.00%)	1/1 (100.00%)	2/2 (100.00%)	3/3 (100.00%)	–	–	5/6 (83.33%)

In the skeleton of **Terry No. 522** – a 30-year-old male recorded to have died of pulmonary TB **(Suppl. table 1) –**, pathological bony changes that may be attributed to tuberculosis were registered in both the cranial and postcranial elements. As for the skull, multifocal GIs − described by *Schultz* (*e.g.*, 1999, 2001, 2003) and *Schultz* & *Schmidt-Schultz* (2015) as pathognomonic signs of TBM, since representing pressure atrophy of the tubercles − were detected on the squamous part of the frontal bone **(Fig. 49A)**, in the right parietal bone along the squamous suture **(Fig. 49B)**, and on the squamous part of the left and right **(Fig. 49B)** temporal bones and of the occipital bone. Furthermore, non-specific vestiges of haemorrhagic and/or inflammatory meningeal reactions − namely multifocal, small, serpentine branching ABVIs accompanied by slight PAs (*e.g.*, Schultz, 1993, 1999, 2001, 2003) − were observed in the left parietal and occipital bones, covering less than one-fourth (stage 1) of the inner surfaces. Moreover, shallow APDIs (very slight stage) were noted on the squamous part of the frontal bone, probably referring to eICP secondary to TBM (*e.g.*, Schultz, 1993, 2001, 2003).

A) **B)**

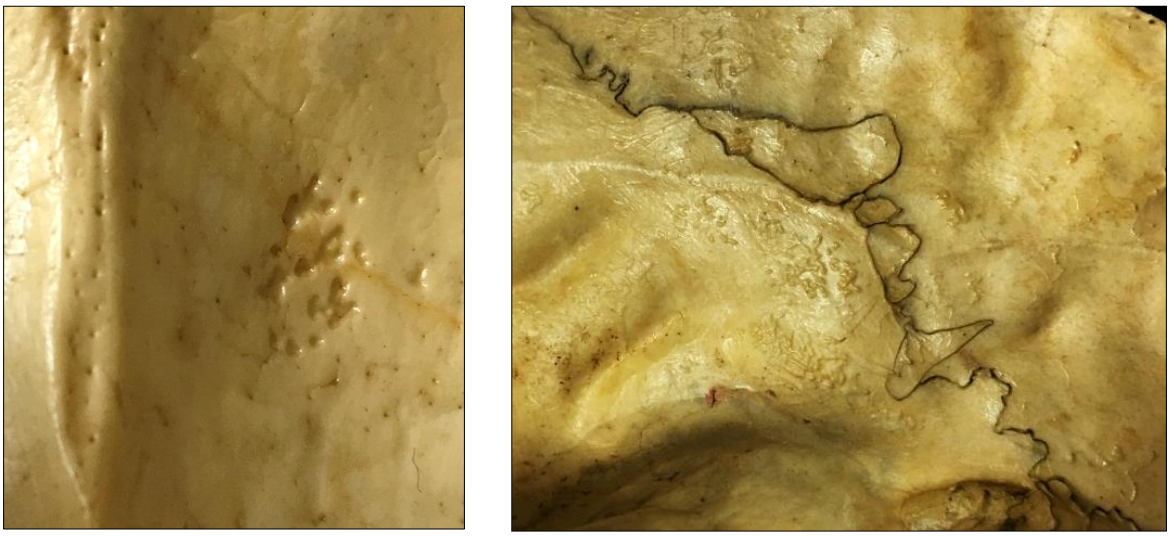


Figure 49: GIs A) on the squamous part of the frontal bone and B) along the squamous suture in the right parietal and temporal bones (Terry No. 522, 30-year-old, male, pulmonary TB).

Besides the endocranial alterations very likely associated with TBM, very slight PNBFs − frequently described as not specific but probable signs of pulmonary TB and/or TB pleurisy (*e.g.*, Kelley & Micozzi, 1984; Roberts *et al.*, 1994; Santos & Roberts, 2001, 2006; Maczel, 2003; Matos & Santos, 2006; Giacon, 2008; Mariotti *et al.*, 2015) − were noted on the visceral surface of the vertebral end of four left side (4^{th}–7^{th}) and ten right side (2^{nd}–11^{th}) ribs. The recorded cause of death of Terry No. 522 supports the tuberculous origin of the detected endocranial and costal changes.

The skeletal remains of **Terry No. 562** − a 17-year-old female whose morgue record states pulmonary TB as the cause of death **(Suppl. table 1)** − exhibited numerous pathological bony changes that probably resulted from tuberculosis. In the skull, multifocal GIs were registered on the orbital part of the frontal bone **(Fig. 50A)** and on the squamous part of the right temporal and occipital **(Fig. 20C** (p. 45)**, 50B)** bones; whereas unifocal GIs were noted on the squamous part of the left temporal bone and on the right greater wing of the sphenoid bone. GIs were described by *Schultz* (*e.g.*, 1999, 2001, 2003) and *Schultz* & *Schmidt-Schultz* (2015) as pathognomonic vestiges of TBM. Furthermore, APDIs (slight stage) affecting the squamous part of the frontal and the left and right parietal bones were recorded, indicating eICP possibly due to hydrocephalus that may be associated with TBM (*e.g.*, Schultz, 1993, 2001, 2003).

A) **B)**

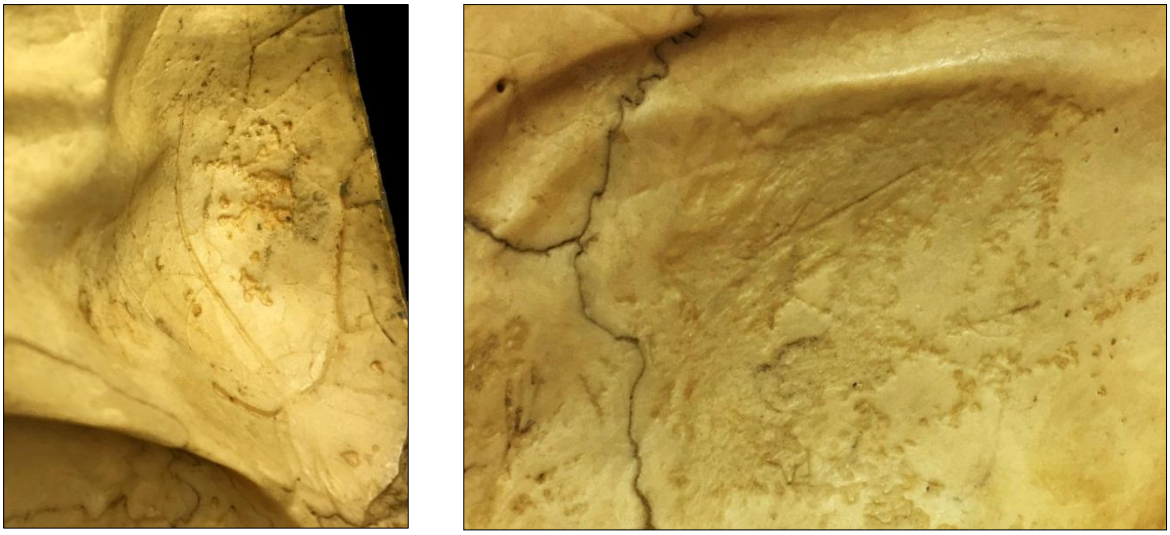


Figure 50: GIs on the right side A) of the orbital part of the frontal bone and B) of the squamous part of the occipital bone (Terry No. 562, 17-year-old, female, pulmonary TB).

With respect to the postcranial skeleton, five left side ribs (2^{nd}–6^{th}) showed slight PNBFs on the visceral surface of the vertebral and sternal ends that may represent vestiges of an inflammatory response secondary to pulmonary TB and/or TB pleurisy (*e.g.*, Kelley & Micozzi, 1984; Roberts *et al.*, 1994; Santos & Roberts, 2001, 2006; Maczel, 2003; Matos & Santos, 2006; Giacon, 2008; Mariotti *et al.*, 2015). In the vertebral column, signs of hypervascularisation possibly referring to early-stage skeletal TB (*e.g.*, Ménard, 1888; Baker, 1999; Maczel, 2003; Giacon, 2008; Mariotti *et al.*, 2015) were registered on the lateral aspects of the lower thoracic (T9–12) and lumbar (L1–5) vertebral bodies. Based on the recorded cause of death of Terry No. 562, the most likely aetiology of the observed endocranial and postcranial bony changes is tuberculosis.

Similar to the previous cases, both the cranial and postcranial remains of **Terry No. 566** − a 40-year-old male who had probably died of TB **(Suppl. table 1)** − revealed different types of pathological bony changes that may be ascribed to tuberculosis. Regarding the skull, the orbital part of the frontal bone, the squamous part of the left temporal and occipital **(Fig. 51A)** bones, and the right greater wing of the sphenoid bone **(Fig. 51B)** exhibited GIs that were described by *Schultz* (*e.g.*, 1999, 2001, 2003) and *Schultz* & *Schmidt-Schultz* (2015) as pathognomonic vestiges of TBM. GIs covered only small areas (stage 1) of the inner surfaces of the affected bones.

A) **B)**

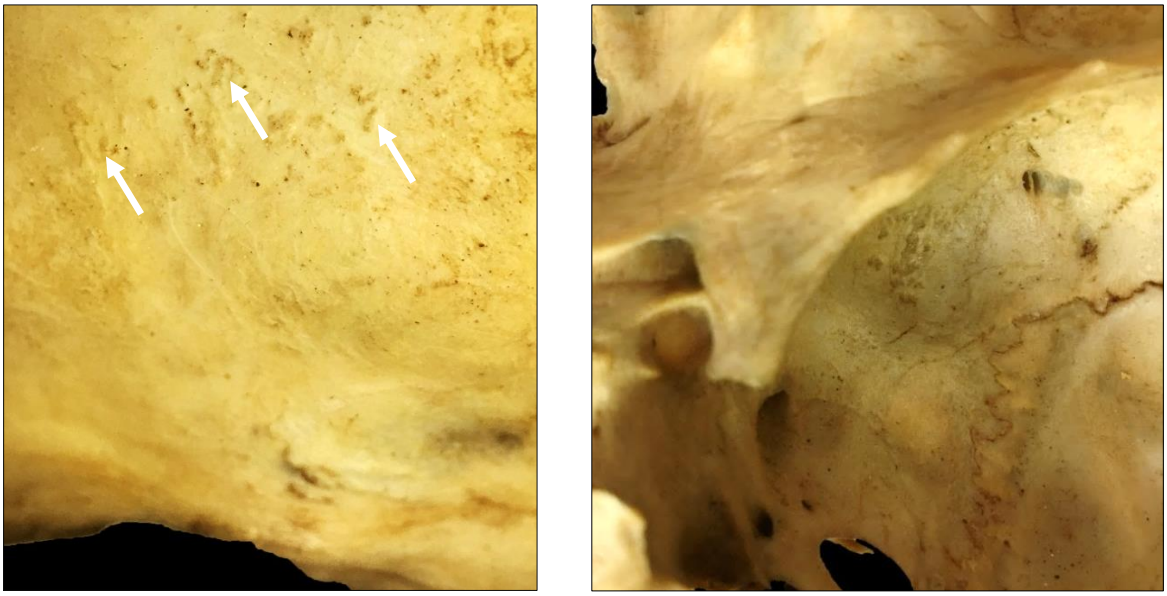


Figure 51: Unifocal GIs A) on the left side of the squamous part of the occipital bone and B) on the right greater wing of the sphenoid bone (Terry No. 566, 40-year-old, male, probable TB).

Concerning the postcranial elements, all right side ribs showed slight PNBFs on the visceral surface of the vertebral end (2^{nd}–12^{th}), body (1^{st}–12^{th}), and/or sternal end (3^{rd}–4^{th}, 6^{th}–7^{th}, and 9^{th}–11^{th}). PNBFs were frequently described as not specific but probable vestiges of pulmonary TB and/or TB pleurisy (*e.g.*, Kelley & Micozzi, 1984; Roberts *et al.*, 1994; Santos & Roberts, 2001, 2006; Maczel, 2003; Matos & Santos, 2006; Giacon, 2008; Mariotti *et al.*, 2015). The indicated cause of death of Terry No. 566 supports the tuberculous origin of the observed endocranial and costal changes.

In the skeleton of **Terry No. 933R** – a 40-year-old male recorded to have died of peritoneal TB **(Suppl. table 1)** –, numerous pathological bony changes that probably resulted from tuberculosis were noted. In the skull, the orbital **(Fig. 52A)** and squamous **(Fig. 52B)** parts of the frontal bone, the left and right parietal bones along the squamous suture,

and the squamous part of the occipital bone **(Fig. 20B** (p. 45)**)** revealed multifocal GIs; whereas the squamous part of the left and right temporal bones, and the left and right greater wings of the sphenoid bone displayed unifocal GIs, described by *Schultz* (*e.g.*, 1999, 2001, 2003) and *Schultz* & *Schmidt-Schultz* (2015) as specific signs of TBM. Moreover, multifocal, small, serpentine branching ABVIs representing non-specific vestiges of haemorrhagic and/or inflammatory meningeal processes (*e.g.*, Schultz, 1993, 1999, 2001, 2003) were detected on the squamous part of the left frontal bone, covering about one-third (stage 2) of the inner surface. Furthermore, shallow APDIs (very slight stage) affecting the squamous part of the frontal bone were recorded, indicating eICP possibly due to hydrocephalus that may be associated with TBM (*e.g.*, Schultz, 1993, 2001, 2003).

A) **B)**

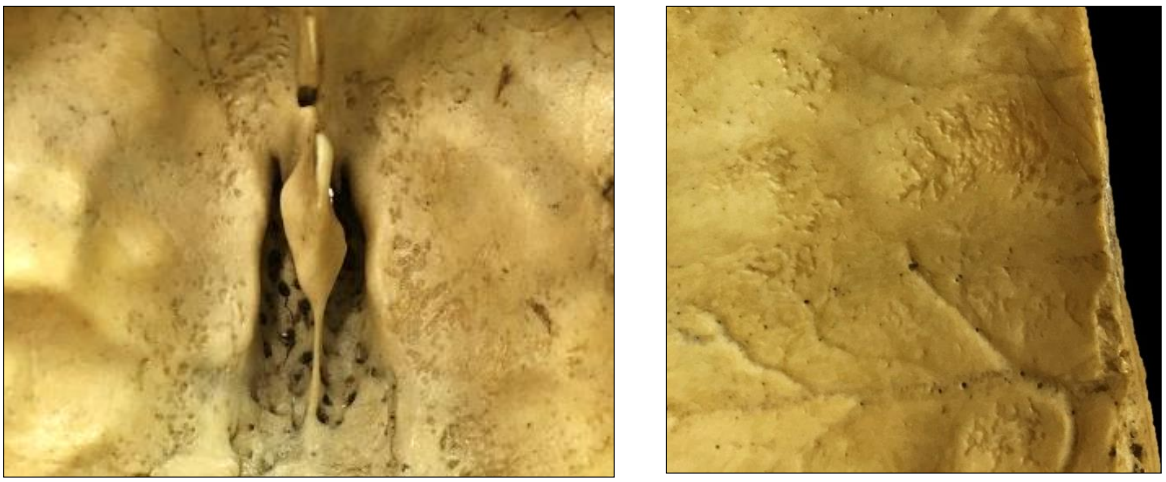


Figure 52: Multifocal GIs on the A) orbital and B) squamous parts of the frontal bone (Terry No. 933R, 40-year-old, male, peritoneal TB).

In the postcranial skeleton, the vertebral column exhibited signs of hypervascularisation in the form of circumferential pitting on the lateral and anterior aspects of the lower cervical (C6–7) and thoracic (T1–12), as well as on the lateral aspects of the upper lumbar (L1–2) vertebral bodies. Although vertebral hypervascularisation is not a specific feature of tuberculosis, it has been described in relation to early-stage skeletal TB in a number of studies (*e.g.*, Ménard, 1888; Baker, 1999; Maczel, 2003; Giacon, 2008; Mariotti *et al.*, 2015). Moreover, PNBFs – probably representing vestiges of an inflammatory response secondary to pulmonary TB and/or TB pleurisy (*e.g.*, Kelley & Micozzi, 1984; Roberts *et al.*, 1994; Santos & Roberts, 2001, 2006; Maczel, 2003; Matos & Santos, 2006; Giacon, 2008; Mariotti *et al.*, 2015) – were noted on the visceral surface of the body of the 11th right side rib. Based on the recorded cause of death of Terry No. 933R, the most likely aetiology of the observed endocranial and postcranial bony changes is TB.

4.2 Co-occurrence of endocranial alterations probably associated with tuberculosis

Σ=427		TB group		NTB group	
Number of specimens exhibiting at least two different types of endocranial alterations		96/234 (41.03%)		15/193 (7.77%)	
Females	Males	28/65 (43.08%)	68/169 (40.24%)	7/87 (8.05%)	8/106 (7.55%)

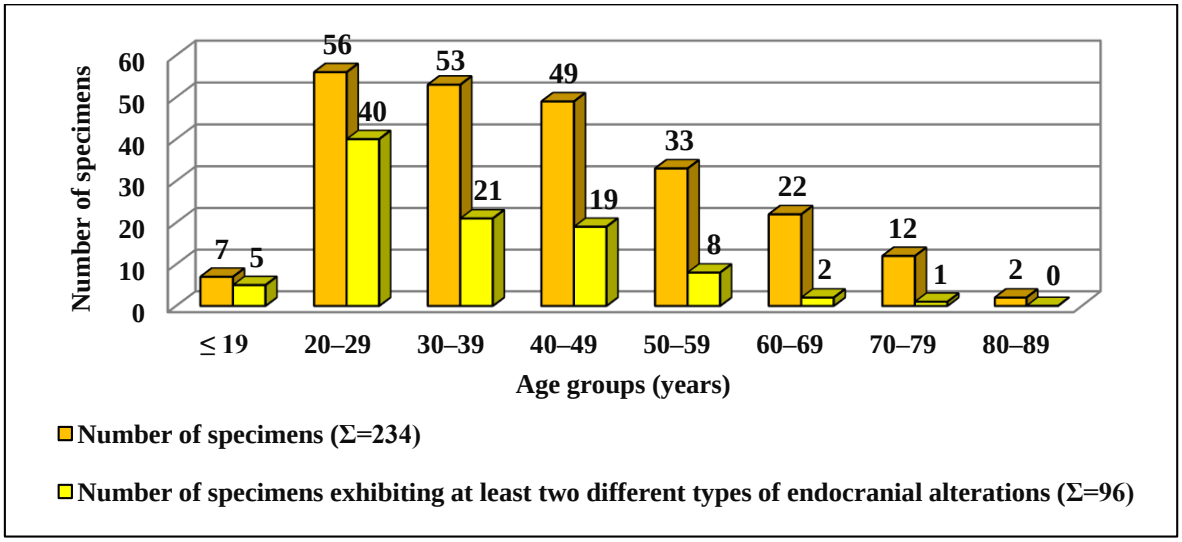
Table 9: Number of specimens exhibiting at least two different types of endocranial alterations probably related to TBM in the TB group and NTB group by sex.

From a total of 427 skeletons evaluated, 111 (26.00%) showed at least two different types of the examined endocranial alterations: 96 (41.03%) of 234 individuals recorded to have died of TB and 15 (7.77%) of 193 specimens identified to have died of causes other than TB **(Table 9)**; thus, there was a statistically extremely significant difference in the frequencies of the co-occurrence of endocranial lesions probably related to TBM between the TB group and NTB group (χ^2=59.079, df=1, P<0.0001). When the two groups were compared considering the sex **(Table 9)**, the difference in the frequencies of the association of the evaluated endocranial alteration types remained extremely significant for both females (χ^2=23.820, df=1, P<0.0001) and males (χ^2=33.192, df=1, P<0.0001). However, the frequencies of the co-occurrence of the examined endocranial lesion types among females and males were very similar in both groups **(Table 9)**; therefore, there was no statistically significant difference between the two sexes (TB group: χ^2=0.0611, df=1, P=0.8047; NTB group: χ^2=0.0200, df=1, P=0.8876).

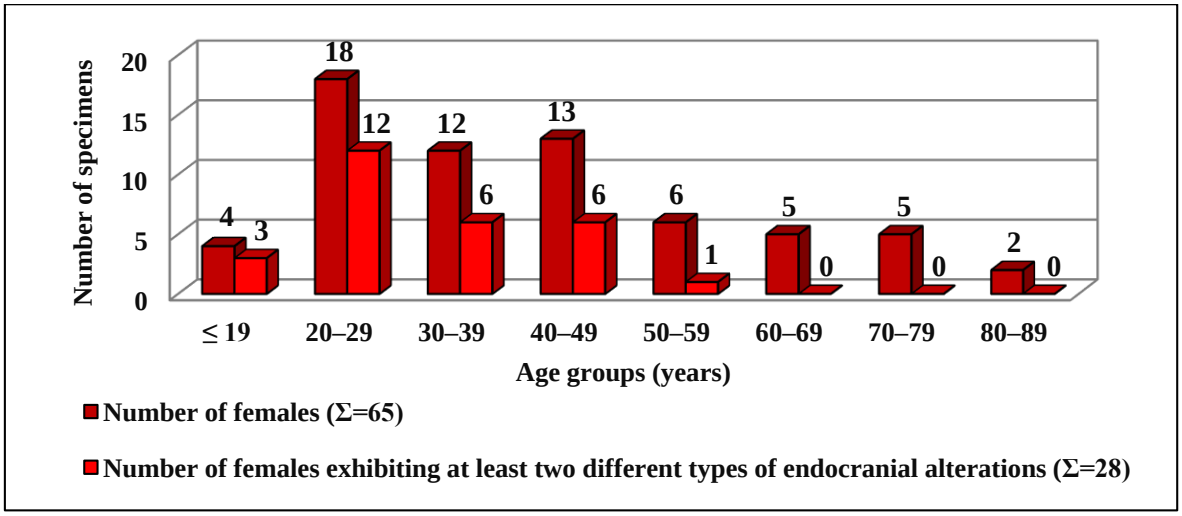
As for the distribution of individuals exhibiting at least two different types of endocranial alterations probably related to TBM by age at death, the association of these bony changes occurred with the highest frequency among specimens under the age of 30 years (45/63, 71.43%) in the TB group **(Fig. 53A)**: with 68.18% (15/22) among females **(Fig. 53B)** and with 73.17% (30/41) among males **(Fig. 53C)**. Nevertheless, more than one-third (40/102, 39.22%) of individuals between 30 and 49 years of age and recorded to have died of TB were also affected by at least two different types of the evaluated endocranial lesions (females: 12/25, 48.00%; males: 28/77, 36.36%) **(Fig. 53A–C)**. In the NTB group, with the exception of a 25-year-old male, specimens exhibiting association of the examined endocranial lesion types were above the age of 40 years **(Fig. 54A–C)**. The χ^2 testing of the frequencies of the co-occurrence of evaluated endocranial alteration types between various age groups was not assessed because of the low number of individuals in certain age groups.

Figure 53: Demographic profile of specimens exhibiting at least two different types of endocranial alterations probably related to TBM in the TB group:
A) total sample (96/234, 41.03%), B) females (28/65, 43.08%), and C) males (68/169, 40.24%).

A)



B)



C)

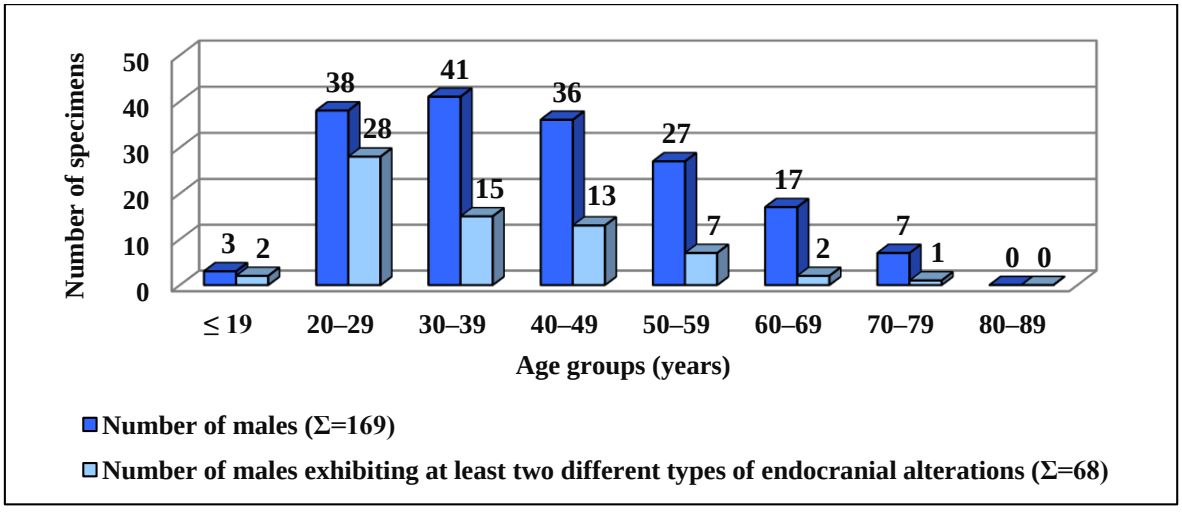
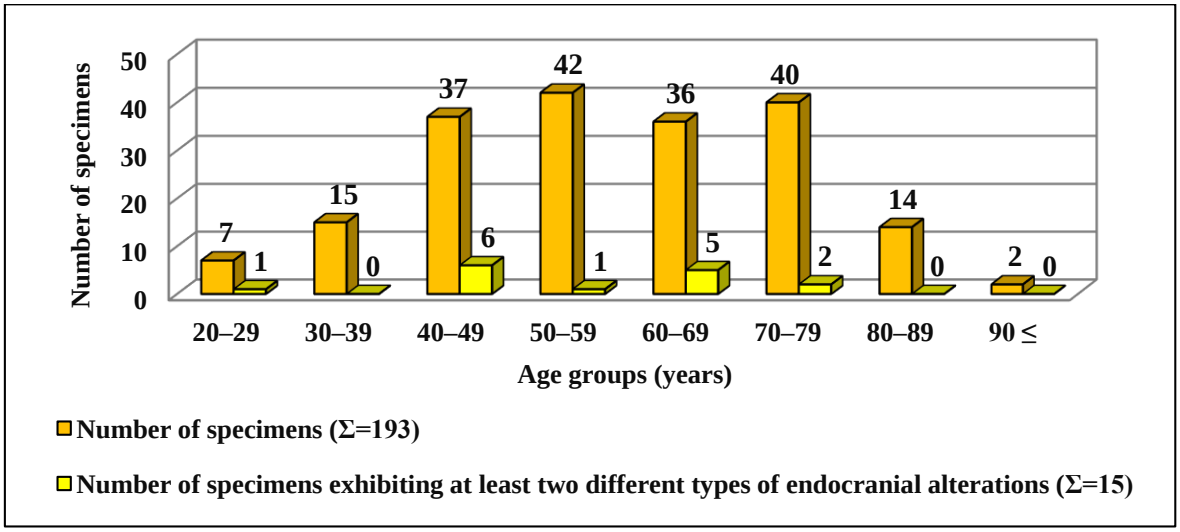
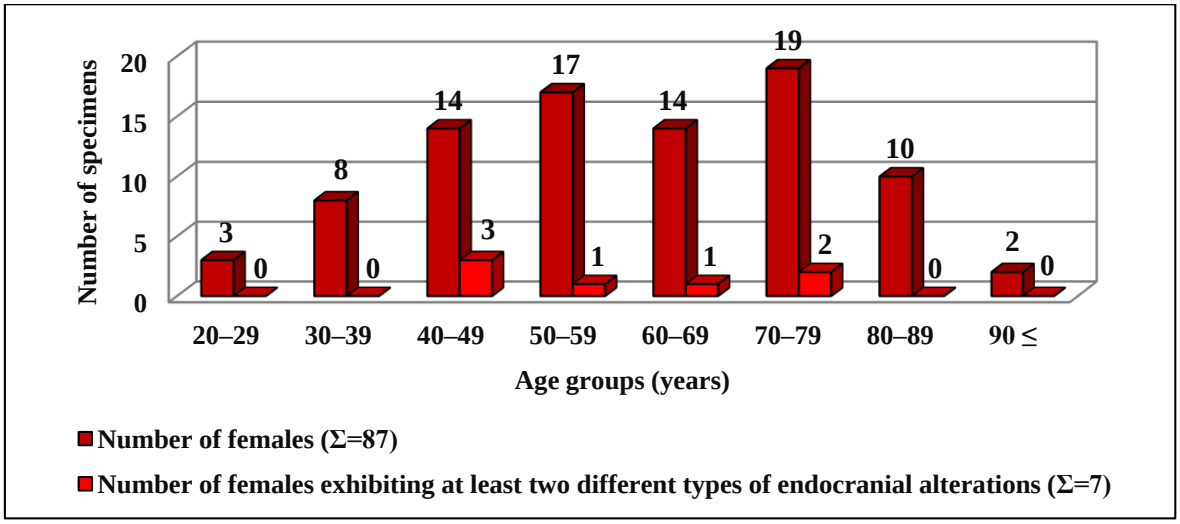


Figure 54: Demographic profile of specimens exhibiting at least two different types of endocranial alterations probably related to TBM in the NTB group:
A) total sample (15/193, 7.77%), B) females (7/87, 8.05%), and C) males (8/106, 7.55%).

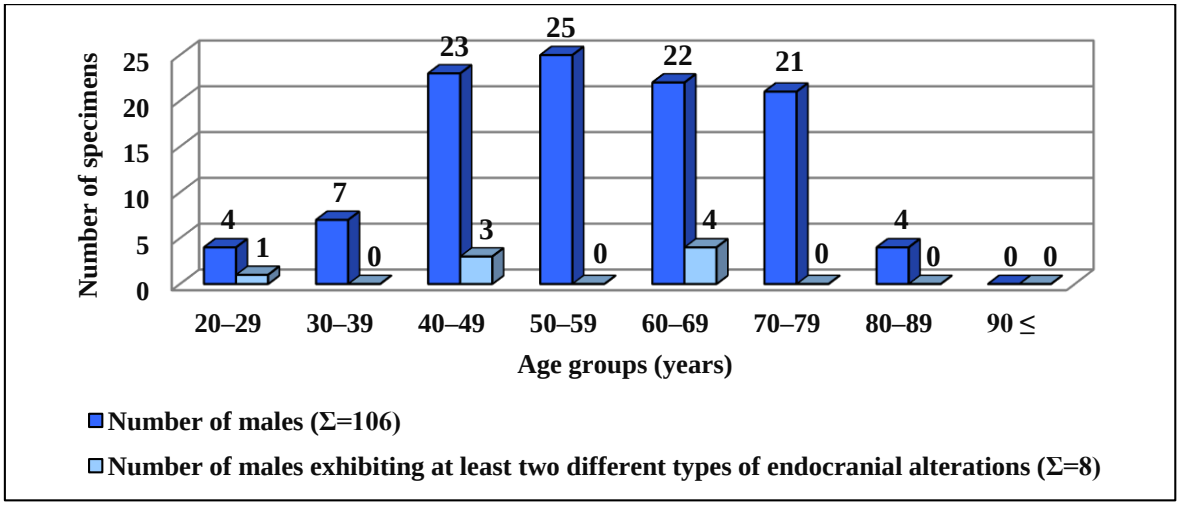
A)



B)



C)



Regarding the number of probable TBM-related lesion types simultaneously affecting the inner surface of the skull, from a total of 427 specimens examined, more than one-third (162/427, 37.94%) exhibited no signs of endocranial alterations possibly associated with TBM: 22.65% (53/234) in the TB group **(Fig. 55A)** and 56.48% (109/193) **(Fig. 55B)** in the NTB group. In a further one-third of individuals evaluated (154/427, 36.07%), only one probable TBM-related lesion type occurred on the inner surface of the skull: in 85 cases with TB as the cause of death (85/234, 36.32%) **(Fig. 55A)** and in 69 cases with NTB causes of death (69/193, 35.75%) **(Fig. 55B)**. Of the 96 specimens showing association of endocranial alteration types probably related to TBM in the TB group, 58 (60.42%), 34 (35.41%), and four (4.17%) exhibited co-occurrence of two, three, and four types of these lesions **(Fig. 55A)**, respectively. In the NTB group, with the exception of a 49-year-old female who was affected by three different types of probable TBM-related endocranial alterations, individuals revealing association of these bony changes displayed co-occurrence of only two types **(Fig. 55B)**.

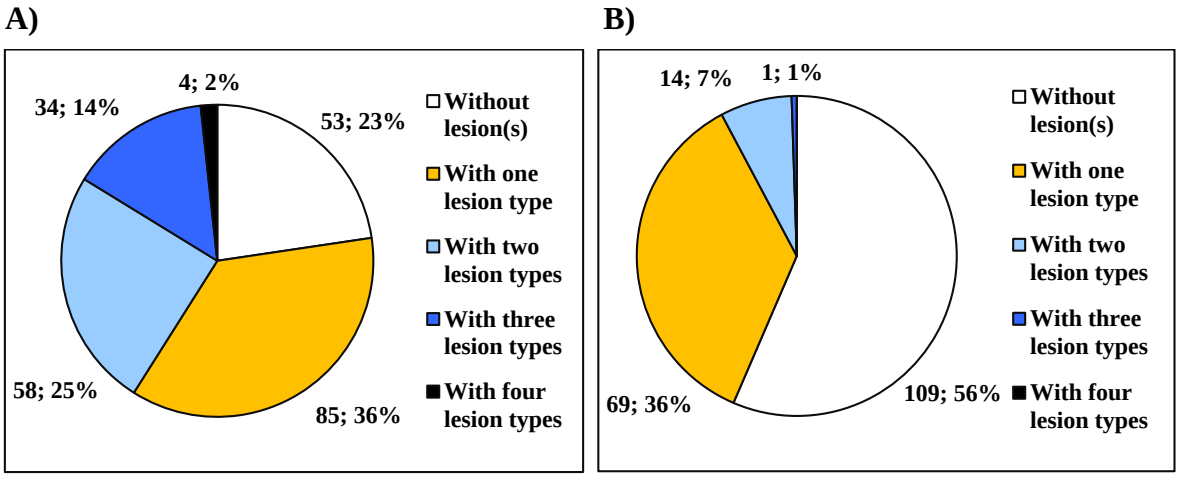


Figure 55: Distribution of specimens by number of presented probable TBM-related endocranial alteration types in the A) TB group (Σ=234) and B) NTB group (Σ=193).

Among specimens exhibiting co-occurrence of probable TBM-associated endocranial alteration types in the TB group, 74 were identified to have died of pulmonary TB **(Suppl. table 1, 3)**. Nine additional individuals died of other types of tuberculosis, such as skeletal TB (three cases), peritoneal TB (two cases), TB meningitis (two cases), TB sinusitis (one case), and miliary TB (one case); whereas in the remaining 13 cases, the type of tuberculosis as the cause of death was not specified on the morgue record and/or death certificate **(Suppl. table 1, 3)**. In the NTB group, the most frequently registered NTB causes of death were cardiovascular problems **(Suppl. table 2, 4)** among specimens showing association of endocranial alteration types probably related to TBM.

The skeletal remains of **Terry No. 304** − a 20-year-old female whose death certificate states pulmonary TB as the cause of death **(Suppl. table 1)** − revealed both cranial and postcranial bony changes that probably resulted from tuberculosis. In the skull, APDIs (slight stage) were registered all over the inner surface of the skullcap and skull base, indicating eICP possibly due to hydrocephalus that may be associated with TBM (*e.g.*, Schultz, 1993, 2001, 2003). Furthermore, non-specific vestiges of inflammatory-haemorrhagic meningeal processes − namely multifocal, small, serpentine branching ABVIs accompanied by slight PAs (*e.g.*, Schultz, 1993, 1999, 2001, 2003) − were detected in the APDIs in the frontal **(Fig. 56)** and the left and right parietal bones, covering about three-fourths (stage 4) of the inner surfaces. Multifocal PAs were also noted on the squamous part of the temporal and occipital bones.

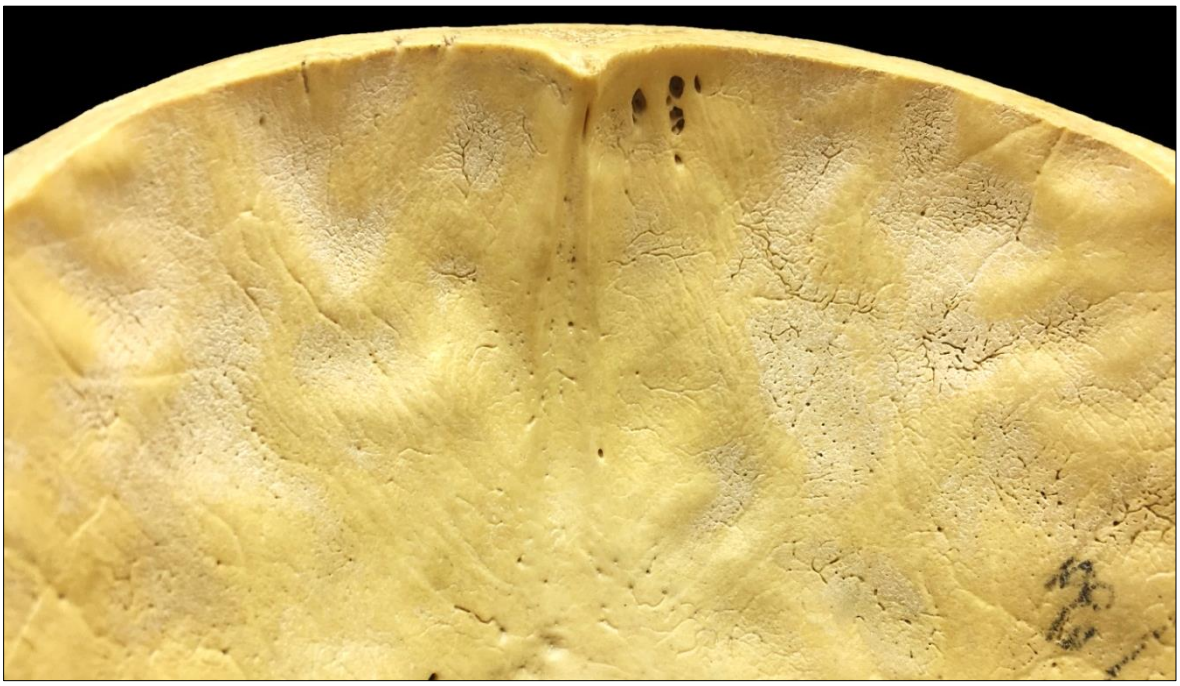


Figure 56: Multifocal ABVIs and PAs in the slight APDIs on the squamous part of the frontal bone (Terry No. 304, 20-year-old, female, pulmonary TB).

With respect to the postcranial skeleton, the vertebral column showed multiple, smooth-walled resorptive pits often connected by horizontal, superficial vascular channels on the lateral aspects of the thoracic (T4–12) vertebral bodies. The lateral aspects of the lumbar (L1–5) vertebral bodies and the ventral surface of the sacrum (S4–5) also exhibited signs of hypervascularisation, possibly referring to early-stage skeletal TB (*e.g.*, Ménard, 1888; Baker, 1999; Maczel, 2003; Giacon, 2008; Mariotti *et al.*, 2015). Although the observed endocranial and vertebral changes are not pathognomonic features of TB, the cause of death of Terry No. 304 supports their tuberculous origin.

Similar to the previous case, both the cranial and postcranial remains of **Terry No. 1159** − a 26-year-old male who had died of pulmonary TB **(Suppl. table 1)** − displayed different types of pathological bony changes that may be ascribed to tuberculosis. Regarding the skull, GIs – described by *Schultz* (*e.g.*, 1999, 2001, 2003) and *Schultz* & *Schmidt-Schultz* (2015) as pathognomonic vestiges of TBM – were recorded on the orbital part of the frontal bone **(Fig. 18C** (p. 42)**, 57)** and on the squamous part of the occipital bone, covering less than one-fourth (stage 1) of the inner surfaces. Moreover, non-specific vestiges of haemorrhagic and/or inflammatory processes of the meninges – namely multifocal, small patches of PAs (*e.g.*, Schultz, 1993, 1999, 2001, 2003) − were detected on the squamous and orbital **(Fig. 57)** parts of the frontal bone, along the sagittal suture in the left and right parietal bones, and on the squamous part of the temporal and occipital bones. Furthermore, shallow APDIs (very slight stage) were registered all over the inner surface of the skullcap and skull base, indicating eICP secondary to TBM (*e.g.*, Schultz, 1993, 2001, 2003).

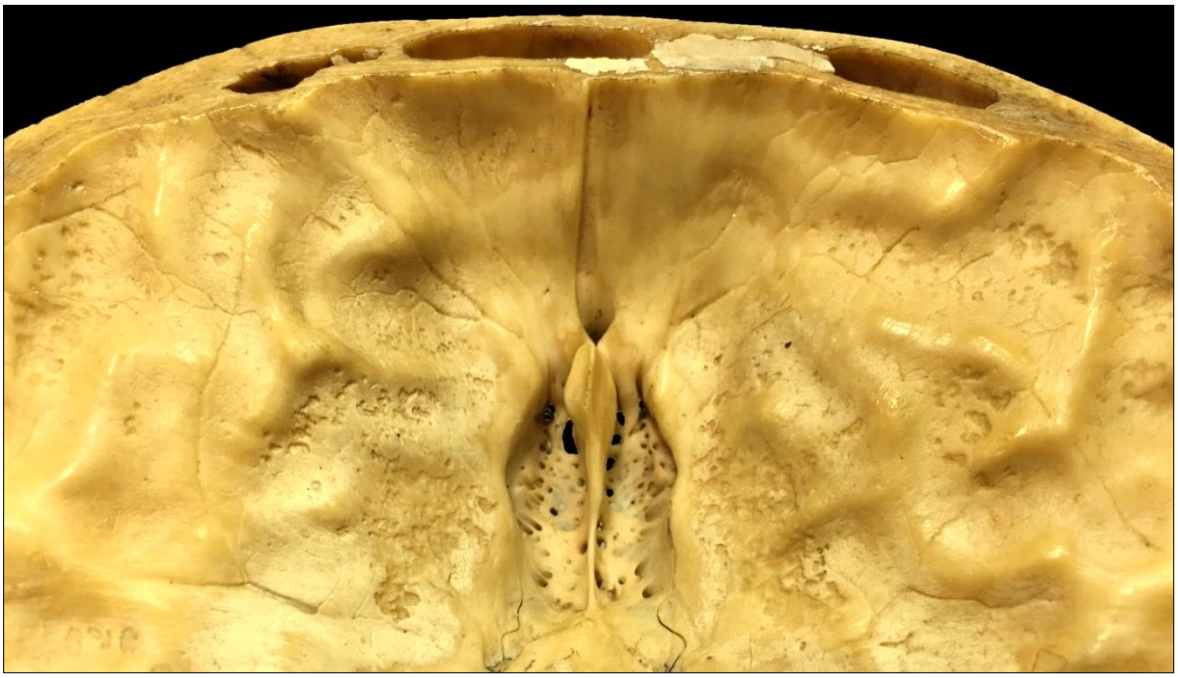


Figure 57: Multifocal PAs and GIs in the APDIs on the orbital part of the frontal bone (Terry No. 1159, 26-year-old, male, pulmonary TB).

Concerning the postcranial elements, the vertebral column exhibited signs of hypervascularisation in the form of circumferential pitting on the anterior aspect of the upper thoracic (T1–4) and on the lateral aspect of the middle and lower thoracic (T5–12) and upper lumbar (L1–3) vertebral bodies, possibly referring to early-stage skeletal TB (*e.g.*, Ménard, 1888; Baker, 1999; Maczel, 2003; Giacon, 2008; Mariotti *et al.*, 2015). Moreover, ten left side ribs (2^{nd}–11^{th}) showed very slight PNBFs on the visceral surface of the vertebral end

(2nd–4th and 8th–9th), body (2nd–3rd, 6th, and 9th–11th), and/or sternal end (2nd–10th) that may represent vestiges of an inflammatory response secondary to pulmonary TB and/or TB pleurisy (*e.g.*, Kelley & Micozzi, 1984; Roberts *et al.*, 1994; Santos & Roberts, 2001, 2006; Maczel, 2003; Matos & Santos, 2006; Giacon, 2008; Mariotti *et al.*, 2015). Besides the ribs, the lateral and posterior surfaces of both tibiae (predominantly the proximal portion of the shaft), the anterior surface of both humeri (particularly the distal portion of the shaft), and the supraspinatous fossa of the right scapula also revealed slight PNBFs, indicating HPO associated with pulmonary TB (*e.g.*, Mensforth *et al.*, 1978; Kelly *et al.*, 1991; Winland *et al.*, 1997; Rothschild & Rothschild, 1998, 1999; Santos & Roberts, 2001; Hershkovitz *et al.*, 2002; Assis *et al.*, 2011). Based on the recorded cause of death of Terry No. 1159, the most likely aetiology of the observed endocranial and postcranial bony changes is tuberculosis.

In the skeleton of **Terry No. 1222** − a 28-year-old female recorded to have died of pulmonary TB **(Suppl. table 1)** −, pathological bony changes that may be attributed to tuberculosis were registered in the cranial elements. GIs, described by *Schultz* (1999, 2001, 2003) and *Schultz* & *Schmidt-Schultz* (2015) as pathognomonic features of TBM, were detected on the left greater wing of the sphenoid bone and on the squamous part of the occipital bone **(Fig. 58)**, covering less than one-fourth (stage 1) of the inner surfaces.

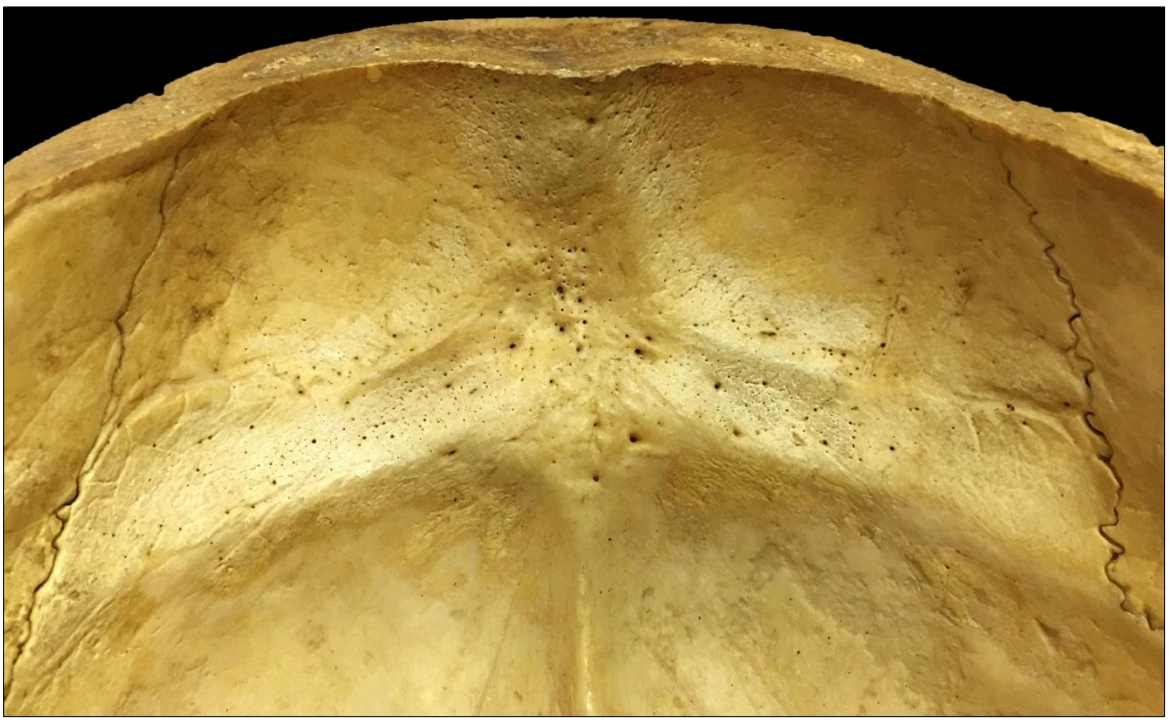


Figure 58: Multifocal GIs and PAs on the squamous part of the occipital bone (Terry No. 1222, 28-year-old, female, pulmonary TB).

Moreover, multifocal, small, serpentine branching ABVIs accompanied by slight PAs, referring to non-specific vestiges of inflammatory-haemorrhagic meningeal processes (*e.g.*, Schultz, 1993, 1999, 2001, 2003), were noted along the sagittal sinus and around the most protruding portions of the frontal and the left and right **(Fig. 59)** parietal bones, covering more than two-thirds (stage 4) of the inner surfaces. The squamous part of the occipital and temporal bones, and the left and right greater wings of the sphenoid bone also revealed multifocal PAs. Shallow APDIs (very slight stage) were noted on the squamous part of the frontal bone and in the left and right parietal bones, indicating eICP secondary to TBM (*e.g.*, Schultz, 1993, 2001, 2003). The postcranial skeleton showed no signs of bony changes probably associated with TB. The recorded cause of death of Terry No. 1222 supports the tuberculous origin of the observed endocranial alterations.

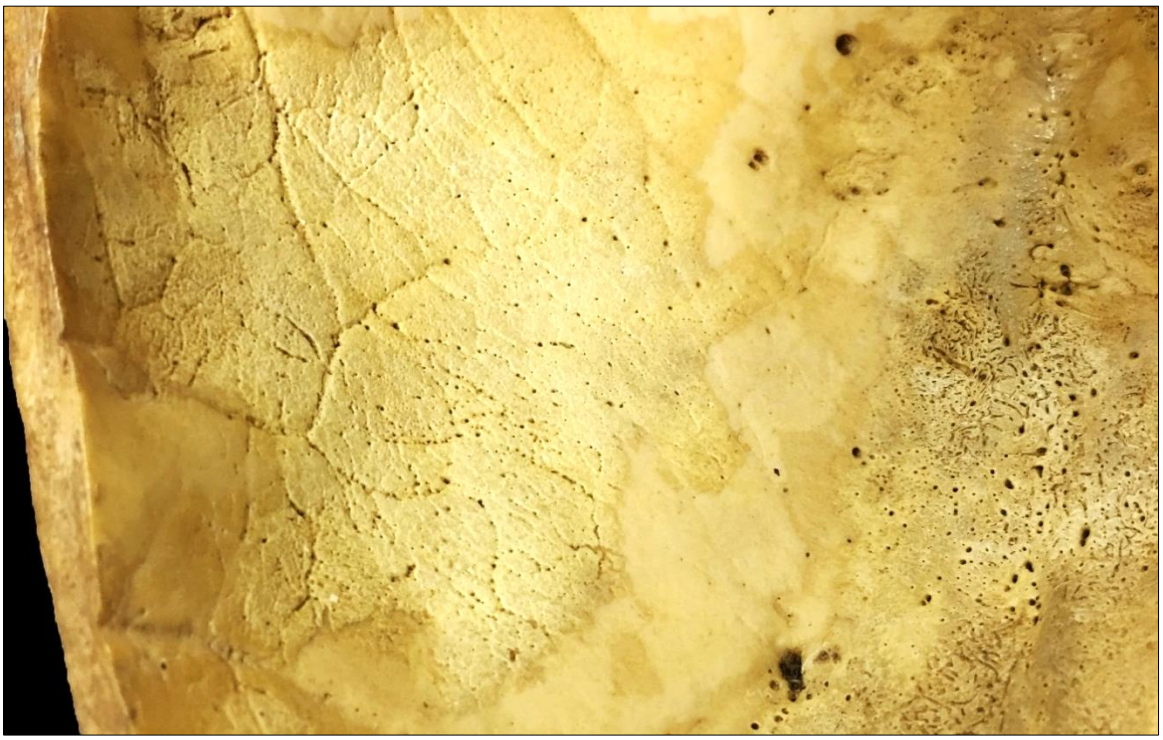


Figure 59: Multifocal ABVIs covered by PAs on the inner surface of the right parietal bone (Terry No. 1222, 28-year-old, female, pulmonary TB).

The skeletal remains of **Terry No. 1322** − a 34-year-old male whose morgue record states pulmonary TB as the cause of death **(Suppl. table 1)** − displayed numerous pathological bony changes that probably resulted from tuberculosis. In the skull, deep APDIs (pronounced stage) were registered all over the inner surface of the skullcap and skull base, probably referring to eICP due to tuberculous involvement of the CNS (*e.g.*, Schultz, 1993, 2001, 2003). Furthermore, non-specific vestiges of haemorrhagic and/or inflammatory

meningeal processes − namely multifocal, small, serpentine branching ABVIs accompanied by slight PAs (*e.g.*, Schultz, 1993, 1999, 2001, 2003) − were detected in the deep DIs and along the sagittal suture in the frontal **(Fig. 19A** (p. 44)**)** and the left and right parietal bones. Multifocal ABVIs covered by thin layers of newly formed bone (PAs) were also noted along the sagittal **(Fig. 60A–B)** and left transverse **(Fig. 60B)** sinuses in the occipital bone, and along the left sigmoid sinus **(Fig. 60B)** in the left temporal bone. Moreover, unifocal PAs occurred on the squamous part of the right temporal bone and on the left and right greater wings of the sphenoid bone.

A) **B)**

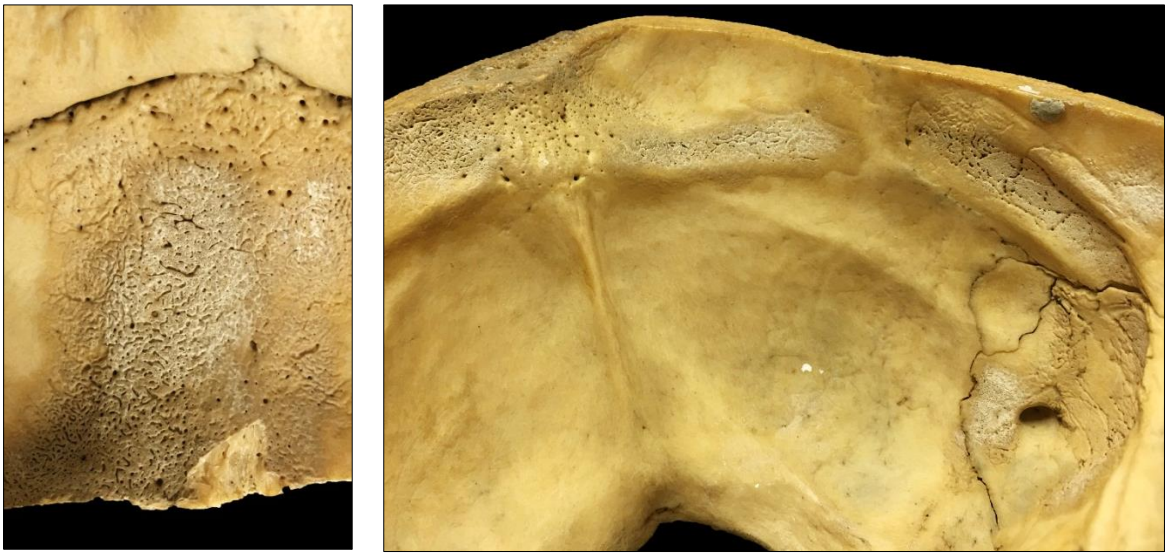


Figure 60: Multifocal ABVIs accompanied by PAs A) along the sagittal sinus (occipital bone) and B) along the left transverse (occipital bone) and sigmoid (left temporal bone) sinuses (Terry No. 1322, 34-year-old, male, pulmonary TB).

Regarding the postcranial skeleton, three left side ribs (4^{th}–6^{th}) showed very slight PNBFs on the visceral surface of the vertebral (5^{th}–6^{th}) or sternal (4^{th}) end that may represent signs of an inflammatory response secondary to pulmonary TB and/or TB pleurisy (*e.g.*, Kelley & Micozzi, 1984; Roberts *et al.*, 1994; Santos & Roberts, 2001, 2006; Maczel, 2003; Matos & Santos, 2006; Giacon, 2008; Mariotti *et al.*, 2015). In the vertebral column, multiple, smooth-walled resorptive pits often connected by horizontal, superficial vascular channels were recognised on the lateral aspects of the thoracic (T3–12) and lumbar (L1–5) vertebral bodies, indicating early-stage skeletal TB (*e.g.*, Ménard, 1888; Baker, 1999; Maczel, 2003; Giacon, 2008; Mariotti *et al.*, 2015). Although the observed endocranial and postcranial bony changes are not pathognomonic features of TB, the cause of death of Terry No. 1322 supports their tuberculous origin.

4.3 Association of endocranial and non-endocranial lesions likely related to tuberculosis

Σ=265		TB group		NTB group	
Number of specimens exhibiting co-occurrence of probable TB-related endocranial and non-endocranial bony changes		145/181 (80.11%)		22/84 (26.19%)	
Females	Males	32/45 (71.11%)	113/136 (83.09%)	8/28 (28.57%)	14/56 (25.00%)

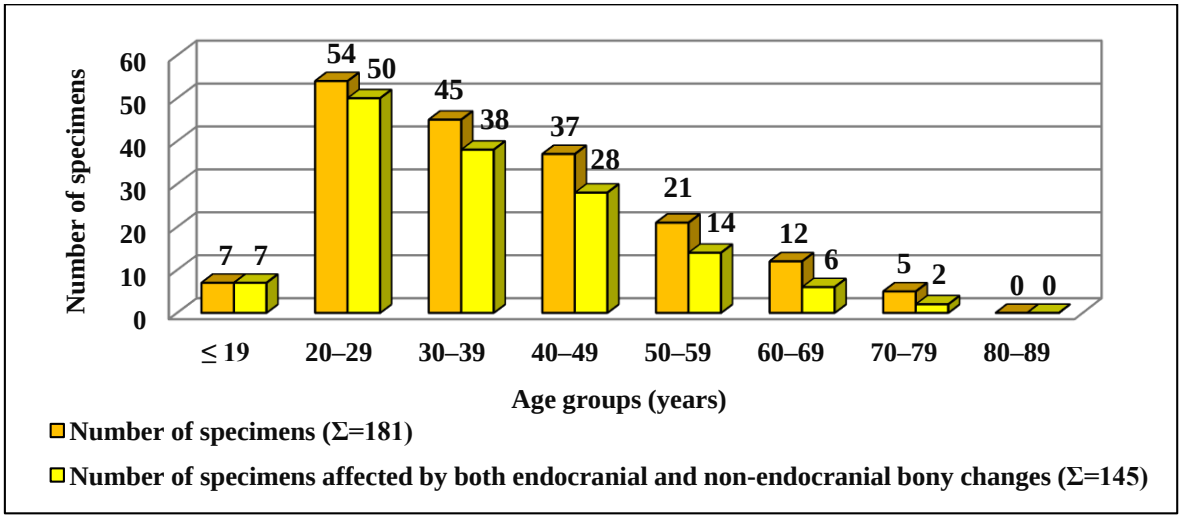
Table 10: Number of specimens exhibiting association of endocranial and non-endocranial bony changes probably related to tuberculosis in the TB group and NTB group by sex.

From a total of 265 skeletons showing at least one type of probable TBM-associated endocranial alterations, 167 (63.02%) exhibited co-occurrence of possible TB-related endocranial and non-endocranial bony changes: 145 (80.11%) of 181 individuals in the TB group and 22 (26.19%) of 84 specimens in the NTB group **(Table 10)**; therefore, there was a statistically extremely significant difference in the frequencies of the association of endocranial and non-endocranial lesions probably related to TB between the two groups (χ^2=69.280, df=1, P<0.0001). When the two groups were compared considering the sex **(Table 10)**, the difference in the frequencies of the co-occurrence of possible TB-associated endocranial and non-endocranial alterations remained significant for both females (χ^2=10.951, df=1, P=0.0009) and males (χ^2=57.205, df=1, P<0.0001). However, the frequencies of the association of these bony changes in females and males were similar in both groups **(Table 10)**; thus, there was no statistically significant difference between the two sexes (TB group: χ^2=2.339, df=1, P=0.1262; NTB group: χ^2=0.00296, df=1, P=0.9566).

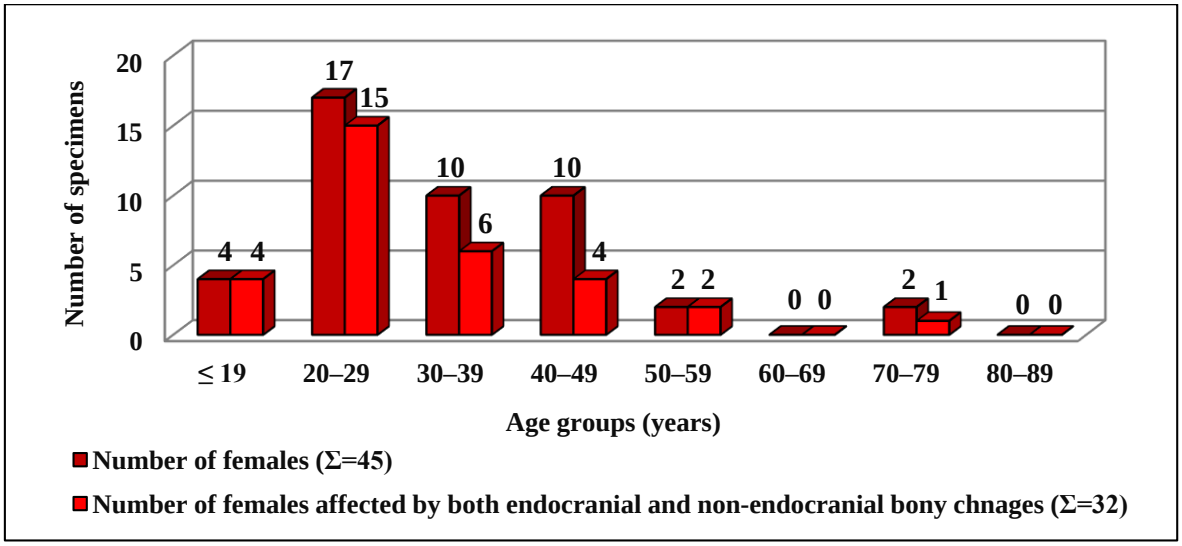
Regarding the distribution of individuals showing co-occurrence of probable TB-related endocranial and non-endocranial lesions by age at death, the association of these bony changes occurred with the highest frequency among specimens under the age of 40 years (104/119, 87.39%): with 89.62% (95/106) **(Fig. 61A)** and 69.23% (9/13) **(Fig. 62A)** in the TB group and NTB group, respectively. Among individuals recorded to have died of TB, more than 90% of females under the age of 30 years (19/21, 90.48%) **(Fig. 61B)** and of males under the age of 50 years (94/102, 92.16%) **(Fig. 61C)** showed association of possible TB-related endocranial and non-endocranial alterations; whereas among specimens identified to have died of causes other than TB, females (4/5, 80.00%) **(Fig. 62B)** and males (5/8, 62.50%) **(Fig. 62C)** under the age of 40 years were most frequently affected. The χ^2 testing of the frequencies of the co-occurrence of probable TB-associated endocranial and non-endocranial lesions between various age groups was not assessed because of the low number of individuals in certain age groups.

Figure 61: Demographic profile of specimens exhibiting co-occurrence of endocranial and non-endocranial bony changes probably related to tuberculosis in the TB group: A) total sample (145/181, 80.11%), B) females (32/45, 71.11%), and C) males (113/136, 83.09%).

A)



B)



C)

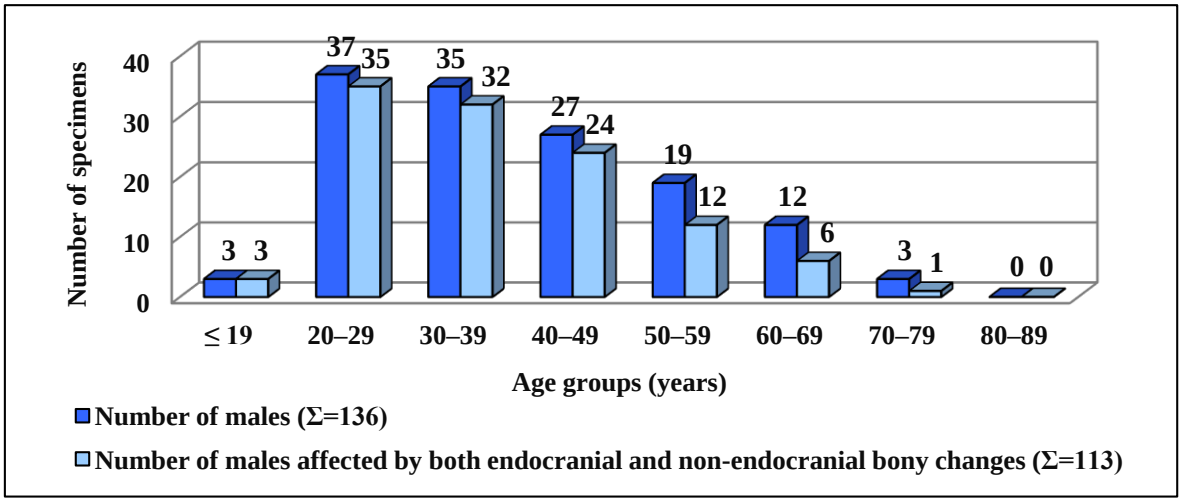
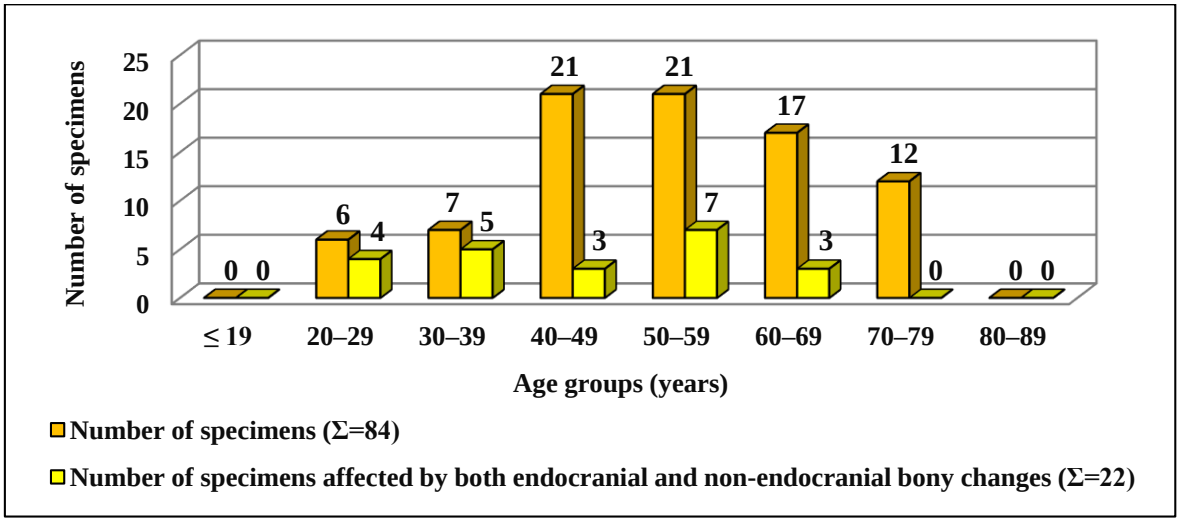
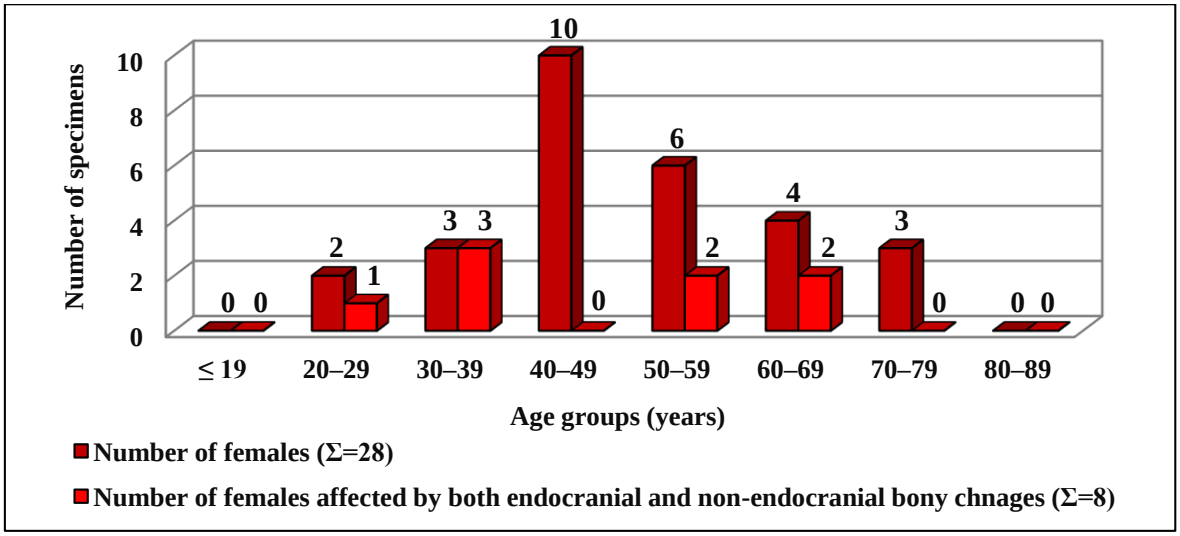


Figure 62: Demographic profile of specimens exhibiting co-occurrence of endocranial and non-endocranial bony changes probably related to tuberculosis in the NTB group: A) total sample (22/84, 26.19%), B) females (8/28, 28.57%), and C) males (14/56, 25.00%).

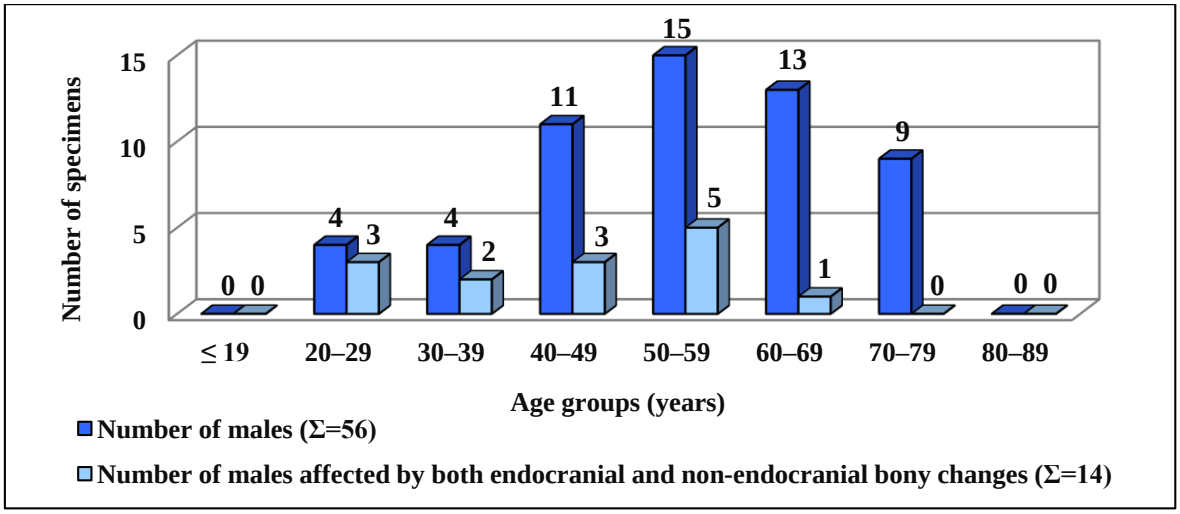
A)



B)



C)



As for the number of probable TB-related non-endocranial lesion types simultaneously affecting the skeleton, from a total of 265 specimens showing at least one type of possible TBM-associated endocranial alterations, more than one-third (98/265, 36.98%) exhibited no signs of non-endocranial bony changes: 19.89% (36/181) in the TB group **(Fig. 63A)** and 73.81% (62/84) **(Fig. 63B)** in the NTB group. In a further one-fourth of individuals evaluated (61/265, 23.02%), only one probable TB-associated non-endocranial lesion type occurred in the skeleton: in 47 cases with TB as the cause of death (47/181, 25.97%) **(Fig. 63A)** and in 14 cases with NTB causes of death (14/84, 16.67%) **(Fig. 63B)**. Of the 106 specimens showing association of non-endocranial alteration types probably related to TB (106/265, 40.00%), about two-thirds (70/106, 66.04%) exhibited co-occurrence of two types of these bony changes: 67.35% (66/98) in the TB group **(Fig. 63A)** and 50.00% (4/8) in the NTB group **(Fig. 63B)**. The association of more than two possible TB-related non-endocranial lesions was detected in about one-third (36/106, 33.96%) of individuals exhibiting co-occurrence of these alterations: in 32 cases (32/98, 32.65%) with TB as the cause of death **(Fig. 63A)** and in four cases (4/8, 50.00%) with NTB causes of death **(Fig. 63B)**. Nevertheless, the number of probable TB-related non-endocranial bony changes concurrently affecting the skeleton varied from two to seven in the TB group and from two to four in the NTB group **(Fig. 63A−B)**.

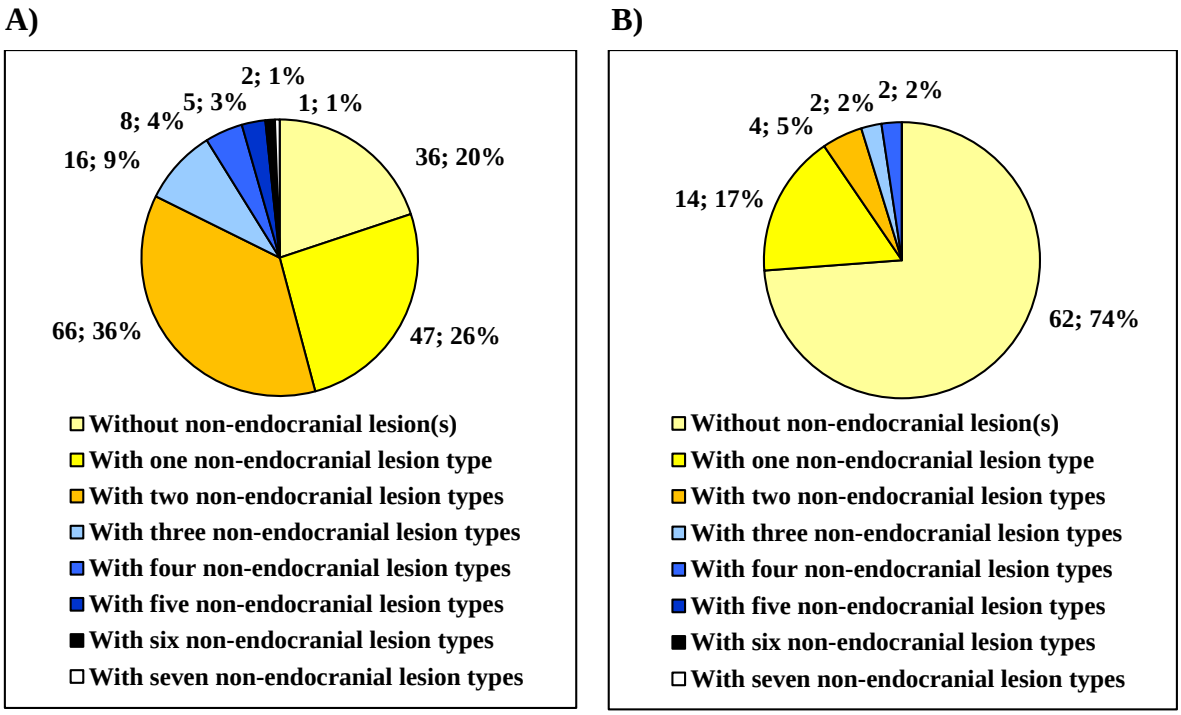


Figure 63: Distribution of specimens with at least one type of probable TBM-related endocranial alterations by number of presented possible TB-associated non-endocranial alteration types in the A) TB group (Σ=181) and B) NTB group (Σ=84).

Concerning the frequencies of different types of possible TB-associated non-endocranial bony changes affecting specimens with at least one type of probable TBM-related endocranial alterations in the TB group, PNBFs on the visceral surface of ribs (111/181, 61.33%) and signs of hypervascularisation on the anterior and/or lateral aspects of vertebral bodies (102/181, 56.35%) were the most frequently detected lesions; whereas TB involvement of the extra-spinal bones (*i.e.*, TB osteomyelitis) affecting the ribs, hip bones, cranial bones or sternum (13/181, 7.18%), as well as of the extra-spinal joints (*i.e.*, TB arthritis) – such as of the sacroiliac joint and/or pubic symphysis (11/181, 6.08%) –, was registered in only a few cases **(Fig. 64A)**. In the NTB group, circumferential, multiple, smooth-walled resorptive lesions often connected by horizontal vascular impressions on the anterior and lateral aspects of the vertebral bodies (13/84, 15.48%) represented the most frequently observed non-endocranial bony changes possibly associated with TB **(Fig. 64B)**.

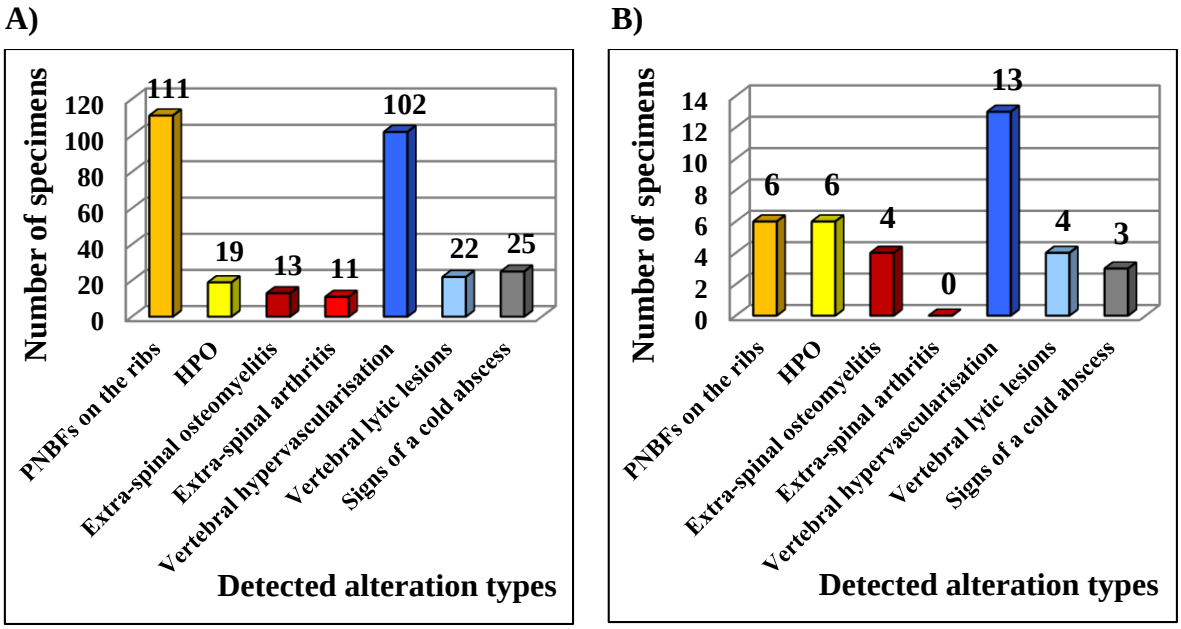


Figure 64: Number of specimens with at least one type of probable TBM-related endocranial alterations and showing different types of possible TB-associated non-endocranial bony changes in the A) TB group (Σ=181) and B) NTB group (Σ=84).

Among individuals with association of probable TB-related endocranial and non-endocranial bony changes in the TB group, the type of tuberculosis as the cause of death was not specified on the morgue record and/or death certificate in 21 cases **(Suppl. table 1, 5)**. In 114 cases, pulmonary TB was registered as the cause of death **(Suppl. table 1, 5)**; whereas the remaining ten individuals have died of skeletal TB (three cases), peritoneal TB (three cases), TB meningitis (two cases), TB sinusitis (one case) or miliary TB (one case) **(Suppl. table 1, 5)**. Among specimens with co-occurrence of possible TB-associated endocranial

and non-endocranial bony changes in the NTB group, the most frequently registered NTB causes of death were cardiovascular problems **(Suppl. table 2, 6)**.

In the skeleton of **Terry No. 468** – a 23-year-old male recorded to have died of pulmonary and spinal TB **(Suppl. table 1)** –, pathological bony changes that may be attributed to tuberculosis were registered both in the cranial and postcranial elements (Spekker *et al*., 2018). In the skull, APDIs (very slight stage) were registered all over the inner surface of the skullcap and skull base, indicating eICP very likely due to hydrocephalus that may be associated with TBM (*e.g*., Schultz, 1993, 2001, 2003).

Concerning the postcranial bone remains, PNBFs − frequently described as not pathognomonic but probable signs of pulmonary TB and/or TB pleurisy (*e.g*., Kelley & Micozzi, 1984; Roberts *et al*., 1994; Santos & Roberts, 2001, 2006; Maczel, 2003; Matos & Santos, 2006; Giacon, 2008; Mariotti *et al*., 2015) − occurred on the vertebral (11^{th}–12^{th}) **(Fig. 65)** and/or sternal (12^{th}) ends of two left side ribs (11^{th}–12^{th}), exclusively affecting the visceral surfaces.

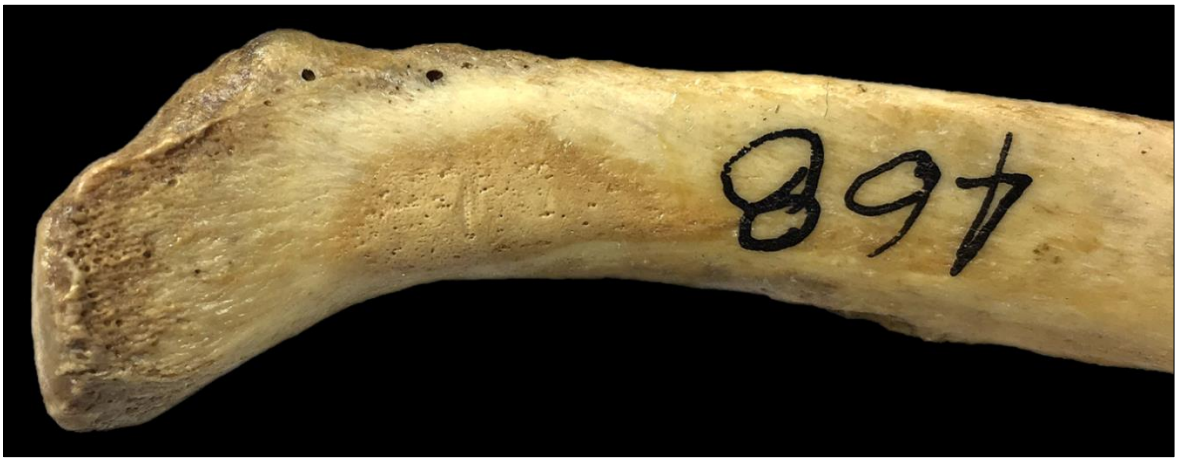


Figure 65: Slight PNBFs on the visceral surface of the vertebral end of the 11^{th} left rib (Terry No. 468, 23-year-old, male, pulmonary and spinal TB) (Spekker *et al*., 2018).

Besides the above-mentioned rib lesions, vertebral alterations very likely associated with the anterior subligamentous form of tuberculous spondylitis (Sorrel & Sorrel-Dejerine, 1932; Aufderheide & Rodríguez-Martín, 1998; Palmer, 2002; Ortner, 2003; Kumar, 2005; Spiegel *et al*., 2005; Agrawal *et al*., 2010; Garg & Somvanshi, 2011; Rivas-Garcia *et al*., 2013) were observed in the thoracic (T6–12) and lumbar (L1–5) regions. The anterior and occasionally the lateral aspects of the middle and lower thoracic (T6–12) vertebral bodies revealed slight erosion and reactive new bone formations exclusively affecting the cortical bone layers. In addition to the aforementioned superficial changes, the lower thoracic

(T8−12) vertebral bodies exhibited small, shallow erosive lesions, particularly localised on the anterior and right lateral aspects **(Fig. 66A−B)**. Similar to the thoracic region of the spine, the anterior and lateral aspects of the lumbar (L1–4) vertebral bodies **(Fig. 67A−C)** displayed severe destructive remodelling of the cortical bone layers, occasionally extending towards the posterior vertebral elements. Moreover, multiple, tunnel- or groove-like erosive lesions involving the anterior, lateral, superior, and/or inferior surfaces, as well as remarkable new bone formations and bony bridges interconnecting the anterior aspects of the adjacent lumbar vertebral bodies (L1–4) **(Fig. 67A−C)**, were detected. The L5 body was also affected by the pathological process: a shallow erosive lesion in the middle of the postero-superior surface, signs of slight hypervascularisation in the form of circumferential pitting on the anterior and lateral aspects, and reactive new bone formations extending towards the posterior vertebral elements on both lateral aspects were noted.

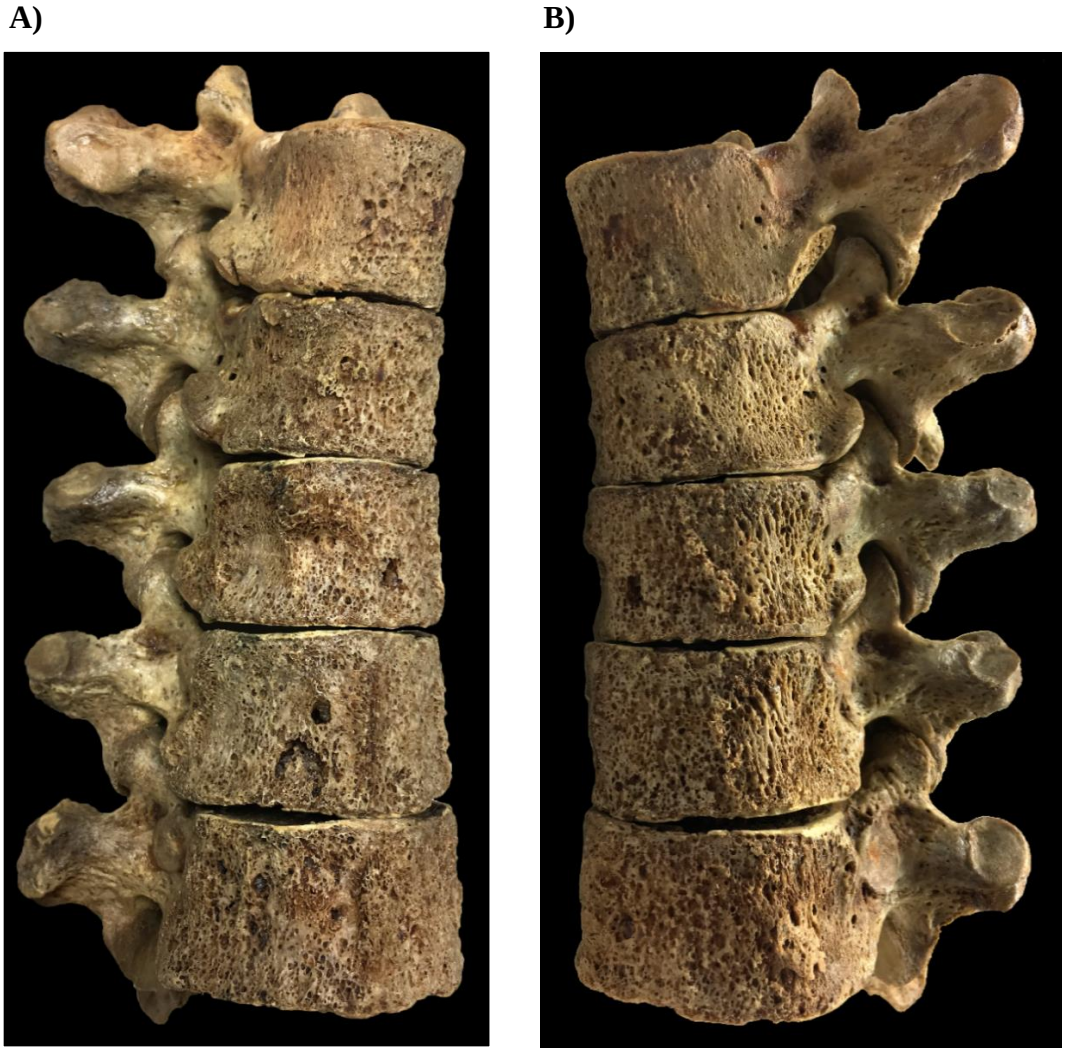


Figure 66: Slight cortical erosion accompanied by PNBFs on the anterior and lateral aspects of the T6–10 vertebral bodies: A) right antero-lateral view and B) left antero-lateral view (Terry No. 468, 23-year-old, male, pulmonary and spinal TB) (Spekker *et al.*, 2018).

Figure 67: Deep, spherical, tunnel- or groove-like erosive lesions and bony bridges interconnecting the adjacent vertebral bodies in the lumbar region (L1–4): A) right antero-lateral view, B) anterior view, and C) left antero-lateral view (Terry No. 468, 23-year-old, male, pulmonary and spinal TB) (Spekker *et al*., 2018).

A) **B)** **C)**

Probably in response to an overlying extra-vertebral cold abscess that is a common complication in tuberculous spondylitis (Aufderheide & Rodríguez-Martín, 1998; Ortner, 2003; Pálfi *et al*., 2012), an erosive lesion accompanied by PNBFs was detected on the anterior surface of the left and right **(Fig. 68A)** hip bones, adjacent to the medial and middle parts of the iliac crest. Furthermore, the iliac and sacral articular surfaces of the left and right **(Fig. 68A)** sacroiliac joints showed a slightly porous appearance, possibly referring to bilateral TB sacroiliitis. Nevertheless, tuberculous involvement of the sacroiliac joint is rather uncommon, affecting approximately 3 to 10% of all cases with osteoarticular TB and usually results from direct extension of a spinal TB focus (Aufderheide & Rodríguez-Martín, 1998; Ortner, 2003; Gupta *et al*., 2005; Papagelopoulos *et al*., 2005). The two pubic symphyses were also affected by the pathological process: both the left **(Fig. 68B)** and right adjoining surfaces exhibited severe destruction that is suggestive of TB symphysitis, representing an unusual site of the disease (Ortner, 2003; Lal *et al*., 2013; Meena & Gangary, 2015).

A) **B)**

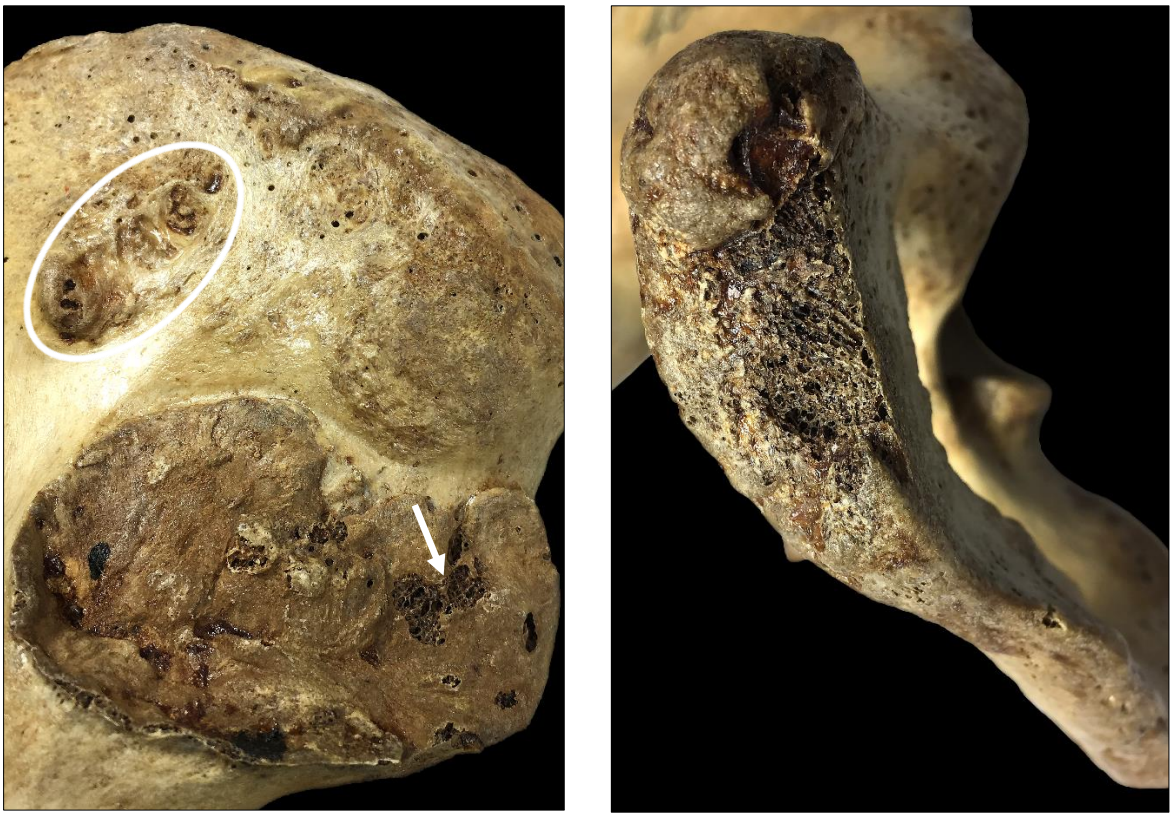


Figure 68: A) shallow, roundish erosive lesion accompanied by PNBFs on the anterior surface of the right hip bone, adjacent to the iliac crest (white circle), as well as slight erosive lesions on the iliac articular surface of the right sacroiliac joint (white arrow), and B) severe destruction of the adjoining surface of the left pubic symphysis (Terry No. 468, 23-year-old, male, pulmonary and spinal TB) (Spekker *et al*., 2018).

Similar to the previous case, both the cranial and postcranial remains of **Terry No. 902** – an approximately 36-year-old male who had died of pulmonary TB **(Suppl. table 1)** – showed different types of pathological bony changes that may be ascribed to tuberculosis (Spekker *et al*., 2018). Concerning the skull, multifocal, small, serpentine branching ABVIs − described by *Schultz* (*e.g*., Schultz, 1993, 1999, 2001, 2003) as non-specific vestiges of haemorrhagic and/or inflammatory processes of the meninges − were registered on the endocranial surface of the frontal **(Fig. 69A)** and the left and right **(Fig. 69B)** parietal bones. Although ABVIs are not pathognomonic features of tuberculosis, they may result from TBM (*e.g*., Schultz, 1993, 1999, 2001, 2003; Hershkovitz *et al*., 2002; Lewis, 2004).

A) **B)**

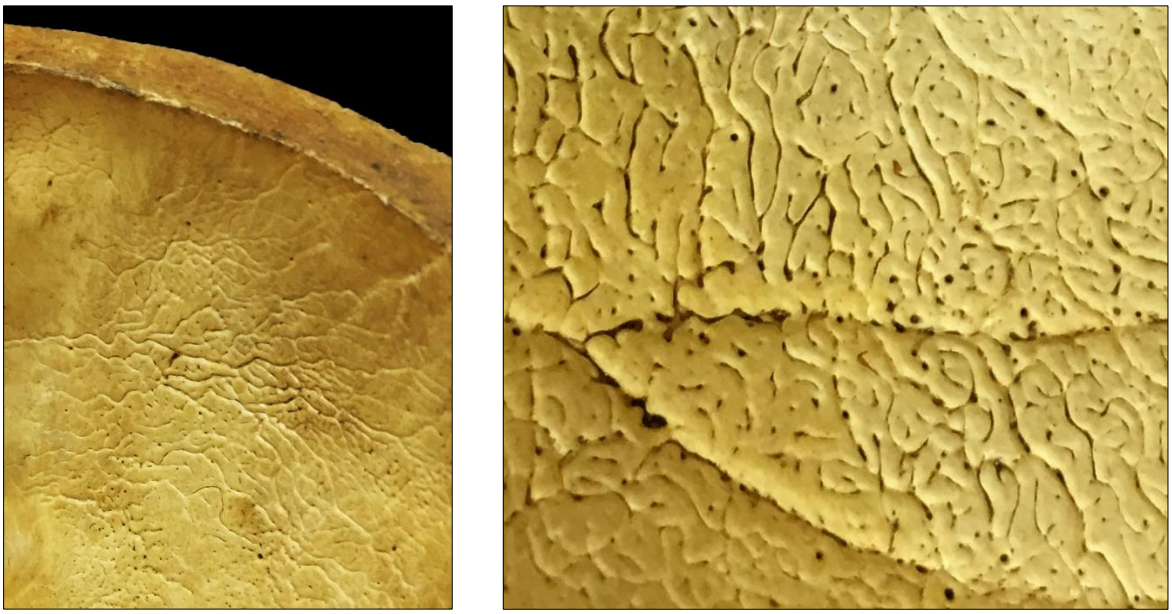


Figure 69: Multifocal, small, serpentine branching ABVIs on the endocranial surface A) of the left side of the squamous part of the frontal bone and B) of the right parietal bone (Terry No. 902, 36-year-old, male, pulmonary TB) (Spekker *et al*., 2018).

Regarding the postcranial elements, four non-contiguous foci of probable tuberculous spondylitis were identified: the left atlanto-occipital joint, the middle thoracic region (T4–7), the T12 vertebra, and the lower lumbar region (L4–5). The articular surfaces of the left atlanto-occipital joint **(Fig. 70A−B)** – especially the one located on the C1 – showed a rough porous appearance and severe destruction. Moreover, reactive new bone formations were registered posteriorly to the left condyle of the occipital bone, adjacent to the *foramen magnum* **(Fig. 70A)**. The articular surfaces of the left facet joint between the T4–5 vertebrae **(Fig. 70C−D)** were also affected by the pathological process, exhibiting a rough porous appearance and slight destruction. The above-mentioned articular lesions may represent the

articular form of tuberculous spondylitis (Ortner, 2003; Garg & Somvanshi, 2011; Fuentes Ferrer *et al*., 2012; Qureshi *et al*., 2013; Mansukhani *et al*., 2014).

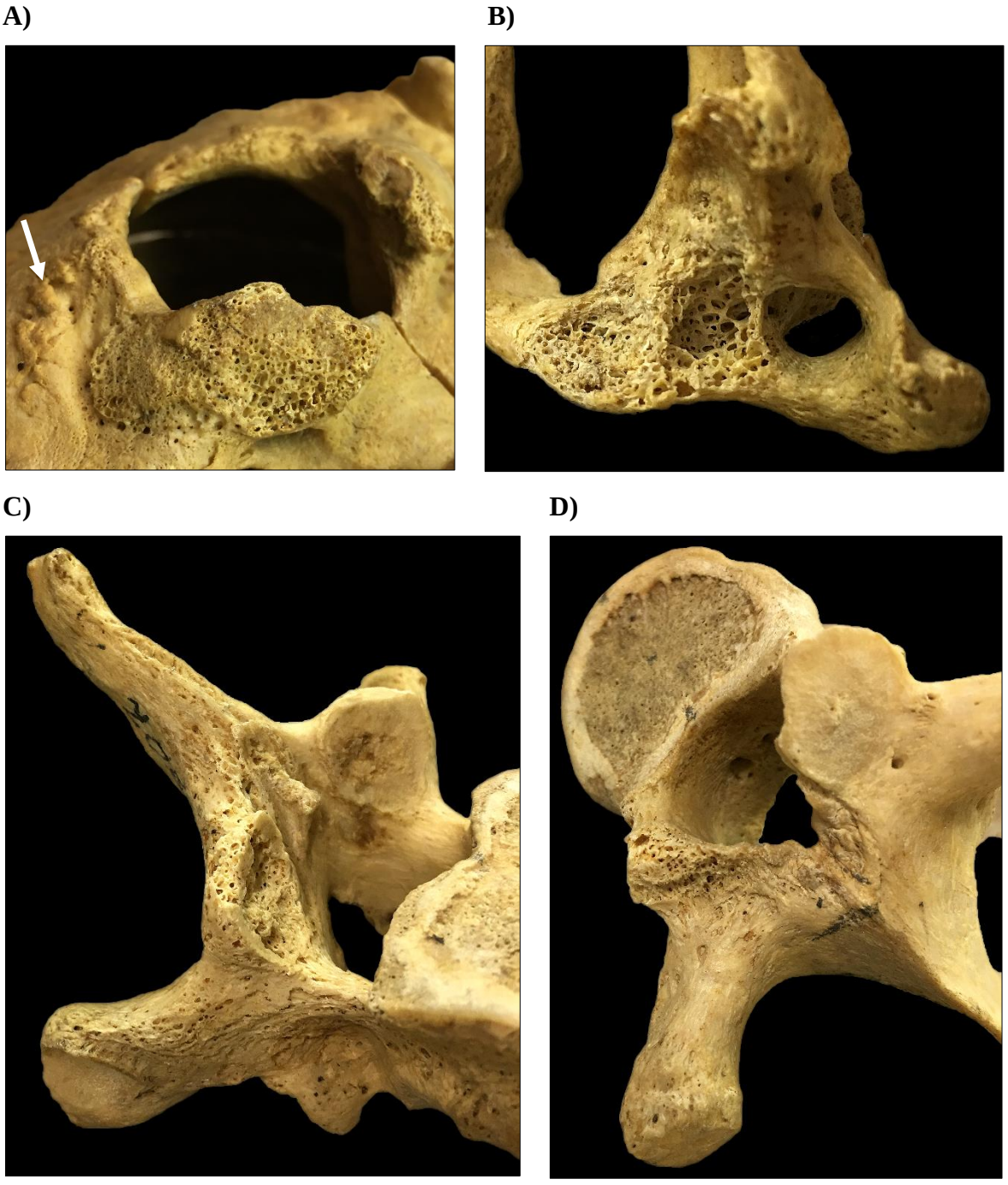


Figure 70: Erosion of the adjoining articular surfaces in the left atlanto-occipital joint: A) occipital bone (with new bone formations adjacent to the *foramen magnum* – white arrow) and B) C1, as well as in the left facet joint between the T4−5 vertebrae: C) T4 and D) T5 (Terry No. 902, 36-year-old, male, pulmonary TB) (Spekker *et al*., 2018).

Furthermore, the anterior aspect of the T5–6 bodies **(Fig. 71A)** revealed slight remodelling of the cortical bone accompanied by small, abnormal, worm-like blood vessel impressions. Erosive lesions involving the left lamina and the adjoining part of the spinous

process of T4 **(Fig. 71B)**, as well as the right lateral aspect of the T7 body, were also recorded. On the anterior aspect of the T12 and L4–5 vertebral bodies, slight remodelling of the cortical bone was detected. Moreover, the right lateral aspect of the T12 body **(Fig. 71C)** and the left lateral aspect of the L5 body **(Fig. 71D)** revealed erosive lesions accompanied by reactive new bone formations. The aforementioned superficial vertebral changes may indicate the presence of extra-vertebral TB abscesses that may extend from the affected joints into the posterior vertebral elements and/or descend down beneath the anterior longitudinal ligament into lower areas of the spine, probably representing the anterior subligamentous form of tuberculous spondylitis (Sorrel & Sorrel-Dejerine, 1932; Aufderheide & Rodríguez-Martín, 1998; Palmer, 2002; Ortner, 2003; Kumar, 2005; Spiegel *et al*., 2005; Agrawal *et al.*, 2010; Garg & Somvanshi, 2011; Rivas-Garcia *et al*., 2013).

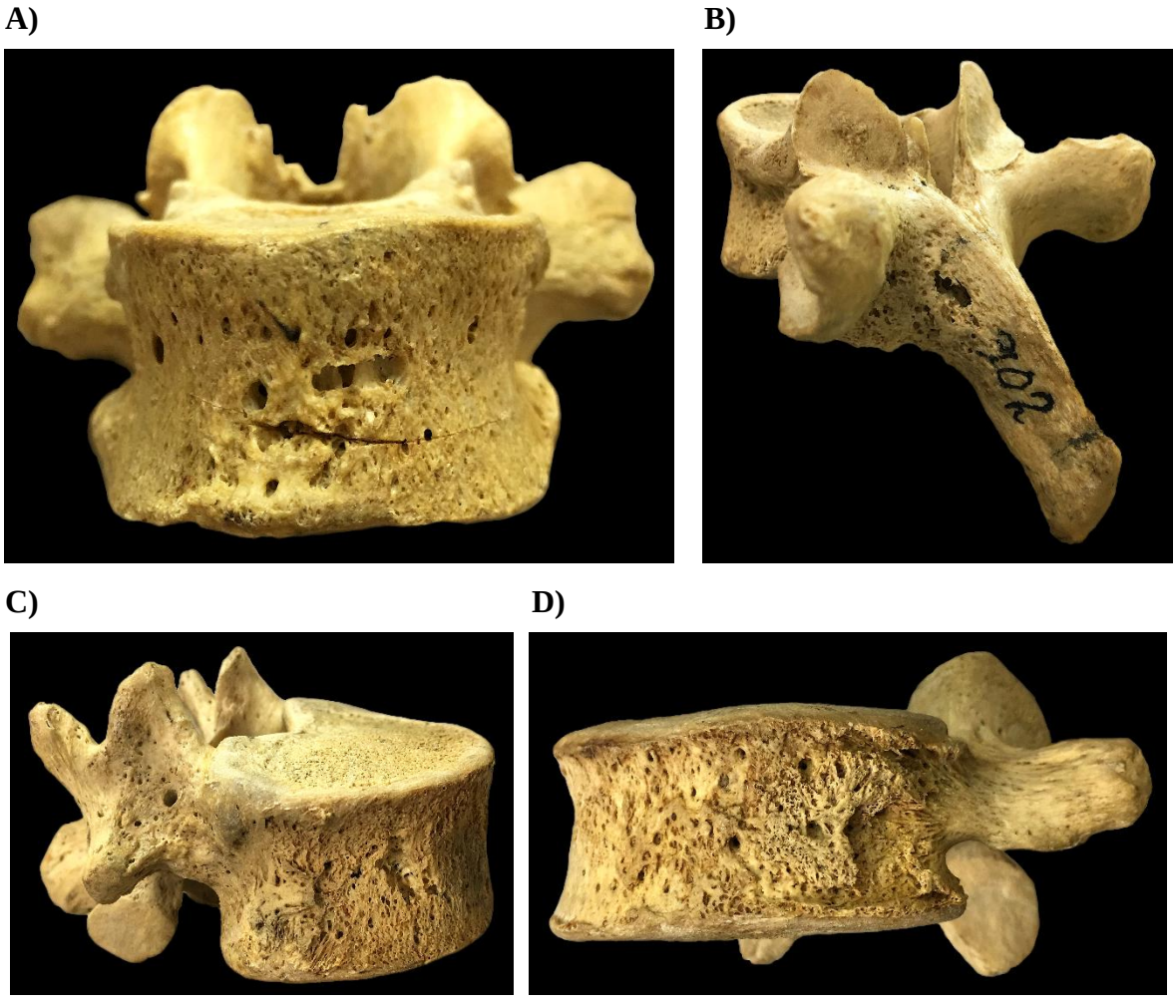


Figure 71: Superficial vertebral changes: A) slight cortical remodelling and small, horizontal abnormal blood vessel impressions on the anterior aspect of T6; and erosive lesions accompanied by reactive new bone formations on the B) left lamina and spinous process of T4, C) right lateral aspect of T12, and D) left lateral aspect of L5 (Terry No. 902, 36-year-old, male, pulmonary TB) (Spekker *et al*., 2018).

Moreover, signs of hypervascularisation were noted in the form of circumferential pitting on the lateral aspects of the lower thoracic (T10–12) and lumbar (L1–5) vertebral bodies. Although vertebral hypervascularisation is not a specific feature of tuberculosis, it has been described in relation to early-stage skeletal TB in a number of studies (*e.g*., Ménard, 1888; Baker, 1999; Maczel, 2003; Giacon, 2008; Mariotti *et al*., 2015).

Besides the vertebral changes, multiple perforating lytic lesions, as well as remodelling and destruction of the cortical surfaces on both the external **(Fig. 72A)** and internal **(Fig. 72B)** surfaces of the body of the sternum were detected, probably indicating TB osteomyelitis of the sternum. However, TB involvement of the sternum is fairly uncommon, accounting for less than 2% of all cases with extra-spinal TB osteomyelitis (Aufderheide & Rodríguez-Martín, 1998; Ortner, 2003; Vasa *et al*., 2009; Sachdeva *et al*., 2013).

A) **B)**

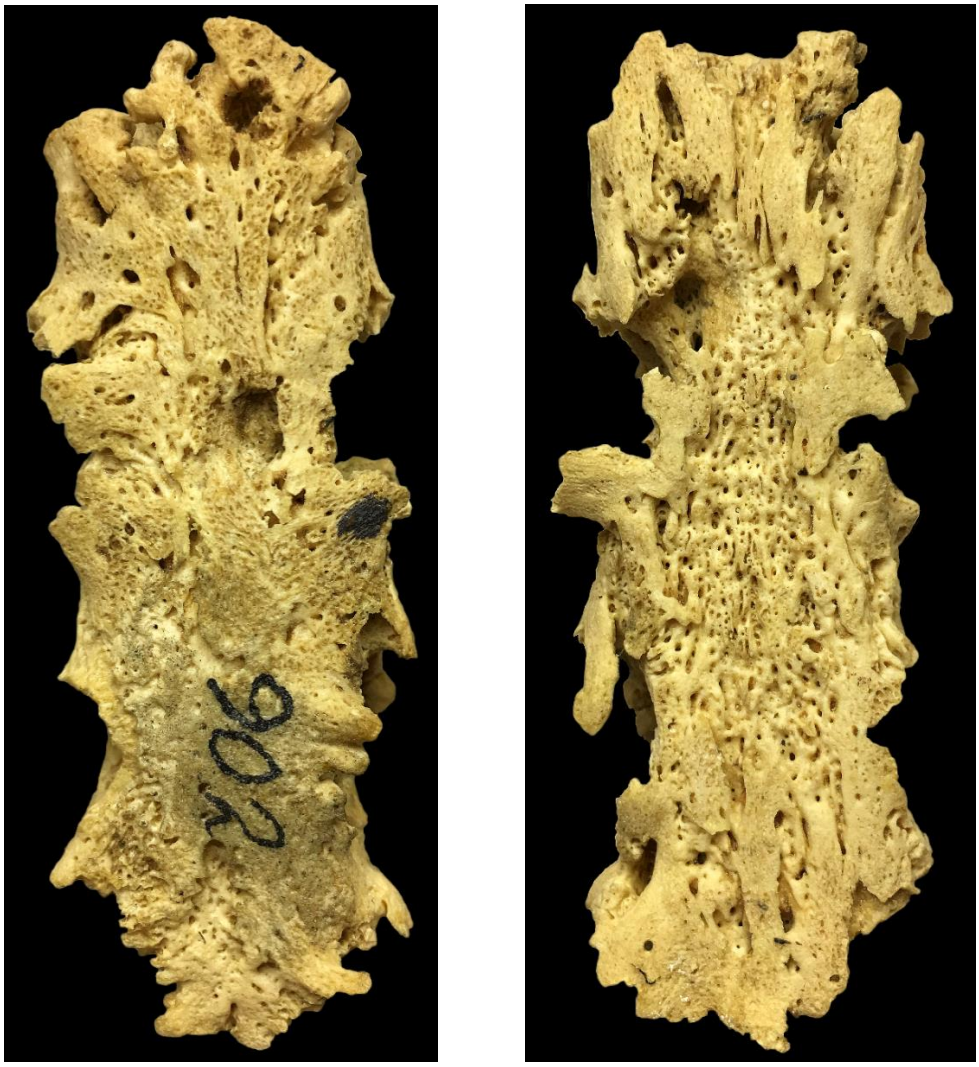


Figure 72: Severe destruction and remodelling of the A) external and B) internal surfaces of the body of the sternum, with multiple perforating lytic lesions (Terry No. 902, 36-year-old, male, pulmonary TB) (Spekker *et al*., 2018).

In addition, very slight PNBFs were recognised on the vertebral end of six right side (3^{rd}–8^{th}) and two left side (4^{th}–5^{th}) ribs, exclusively affecting the visceral surfaces. Furthermore, solitary erosive lesions were observed on the body (left 3^{rd} and right 4^{th}) and/or sternal end (left 4^{th}–7^{th}) of six ribs **(Fig. 73)**. According to the results of previous palaeopathological studies performed on human bone remains from documented skeletal collections (*e.g.*, Kelley & Micozzi, 1984; Roberts *et al.*, 1994; Santos & Roberts, 2001, 2006; Maczel, 2003; Matos & Santos, 2006; Giacon, 2008; Mariotti *et al.*, 2015), the above-mentioned rib lesions may represent signs of an inflammatory response secondary to pulmonary TB and/or TB pleurisy.

Figure 73: Small erosive lesion in the costal groove of the 4^{th} left side rib (Terry No. 902, 36-year-old, male, pulmonary TB) (Spekker *et al.*, 2018).

All surfaces of both tibiae (predominantly the middle and distal portions of the shaft) **(Fig. 74)** and fibulae (all along the shaft), and the palmar surfaces of four left side (2^{nd}–5^{th}) and four right side (1^{st}–4^{th}) metacarpals (mainly the middle and distal portions of the shaft) also exhibited slight PNBFs, presumably referring to HPO associated with pulmonary TB (*e.g.*, Kelly *et al.*, 1991; Winland *et al.*, 1997; Rothschild & Rothschild, 1998, 1999; Santos & Roberts, 2001; Hershkovitz *et al.*, 2002; Assis *et al.*, 2011).

Figure 74: Slight PNBFs on the medial surface of the mid-shaft of the left tibia (Terry No. 902, 36-year-old, male, pulmonary TB) (Spekker *et al.*, 2018).

Similar to the previous case, signs of an overlying TB cold abscess (Aufderheide & Rodríguez-Martín, 1998; Ortner, 2003; Pálfi *et al*., 2012) were noted in the form of small erosive lesions accompanied by PNBFs on the anterior surface of the right hip bone, adjacent to the middle part of the iliac crest. Moreover, both the iliac **(Fig. 75A)** and sacral **(Fig. 75B)** articular surfaces of the left sacroiliac joint showed a rough porous appearance, very likely suggesting unilateral TB sacroiliitis (Aufderheide & Rodríguez-Martín, 1998; Ortner, 2003; Gupta *et al*., 2005; Papagelopoulos *et al*., 2005).

A) **B)**

Figure 75: Slight erosion on the A) iliac and B) sacral articular surfaces of the left sacroiliac joint (Terry No. 902, 36-year-old, male, pulmonary TB) (Spekker *et al*., 2018).

5 DISCUSSION & CONCLUSIONS

Tuberculosis is one of the oldest known infectious diseases that has been plaguing mankind for thousands of years (Galagan, 2014). The palaeopathological research of TB essentially based upon the macromorphological diagnosis of the disease in ancient human bone remains may provide invaluable data on the different manifestations of tuberculosis, as well as on the effects of TB upon human mortality and morbidity around the world throughout prehistoric and historic times (Maczel, 2003; Santos & Roberts, 2006; Pálfi *et al*., 2015).

Using modern medical knowledge, palaeopathologists attempt to establish a retrospective diagnosis of prehistoric and historic cases with tuberculosis by macroscopically identifying pathological conditions (*e.g*., spinal TB and TB arthritis of the large, weight-bearing joints) in skeletons of people lived in the past that may be related to the disease. However, utilisation of modern diagnostic criteria for tuberculosis in the palaeopathological practice may not be appropriate, since on the one hand, probable TB-related bony changes observed in recent cases may differ from those of detectable in ancient human bone remains, due in part to the introduction of antibiotics in the treatment of tuberculosis. On the other hand, in modern medical TB cases, bony changes cannot be surveyed with macromorphological methods but with medical imaging techniques (*e.g*., X-ray radiography, computed tomography, and magnetic resonance imaging) only; nevertheless, subtle bony alterations may be impossible to be visualised by the latter ones. Therefore, they are not relevant to the diagnosis of tuberculosis in recent cases and are not described as diagnostic criteria for the disease by physicians in the modern medical literature, even if they can be potentially important elements of TB identification for palaeopathologists. Furthermore, the assessment of TB prevalence in past human populations has traditionally relied upon the palaeopathological diagnosis of spinal TB and/or TB arthritis of the large, weight-bearing joints only. Since osteoarticular TB occurs in less than 2% of all patients with active tuberculosis and according to estimates, accounted for approximately 3 to 5% of all TB cases in prehistoric and historic times, it is difficult to assess the true prevalence of the disease in human osteoarchaeological material from the pre-antibiotic era based only on the above-mentioned diagnostic criteria (Kelley & Micozzi, 1984; Roberts *et al*., 1994; Santos & Roberts, 2001, 2006; Maczel, 2003; Ortner, 2003; Roberts & Buikstra, 2003; Matos & Santos, 2006; Pálfi *et al*., 2012; Mariotti *et al*., 2015).

In order to contribute to facilitating the establishment of a more reliable and accurate palaeopathological diagnosis of TB and the assessment of a more relevant disease prevalence in past human populations, a number of palaeopathological and palaeomicrobiological

studies (*e.g.*, Ménard, 1888; Kelley & Micozzi, 1984; Schultz, 1993, 1999, 2001, 2003; Roberts *et al.*, 1994; Templin & Schultz, 1994; Teschler-Nicola *et al.*, 1994, 2015; Jankauskas & Schultz, 1995; Winland *et al.*, 1997; Rothschild & Rothschild, 1998, 1999; Baker, 1999; Jankauskas, 1999; Haas *et al.*, 2000; Santos & Roberts, 2001, 2006; Hershkovitz *et al.*, 2002; Maczel, 2003; Matos & Santos, 2006; Giacon, 2008; Pálfi *et al.*, 2012; Mariotti *et al.*, 2015; Masson *et al.*, 2015; Molnár *et al.*, 2015; Schultz & Schmidt-Schultz, 2015) were performed on osteoarchaeological series and documented skeletal collections since the late 20th century that have revealed a positive correlation between different types of tuberculosis (*e.g.*, skeletal TB, pulmonary TB and/or TB pleurisy, and TBM) and subtle bony alterations, including vertebral hypervascularisation, PNBFs on the visceral surface of ribs, and endocranial alterations (*i.e.*, abnormally pronounced digital impressions; periosteal appositions; abnormal blood vessel impressions, including *serpens endocrania symmetrica*; and granular impressions). However, the diagnostic value of different endocranial alteration types possibly associated with TBM has more recently been questioned (*e.g.*, Lewis, 2004; Roberts *et al.*, 2009; Janovic *et al.*, 2015), as their precise aetiology is still a matter of controversy, and additionally, similar or even the same morphological features can be found in non-TB-related cases, such as in non-specific inflammatory (*e.g.*, non-specific meningitis) and haemorrhagic (*e.g.*, epidural haematoma) processes.

Detailed analysis of well-documented collections of pre-antibiotic era skeletons of known cause of death (*e.g.*, *Hamann–Todd Human Osteological Collection*, *Robert J. Terry Anatomical Skeletal Collection*, and *Coimbra Identified Skeletal Collection*) can serve as a unique and important basis for determining the appropriate palaeopathological diagnostic criteria for TB in past human populations, since bone remains of specimens identified to have died of tuberculosis and not treated with antibiotics may exhibit similar TB-related bony changes to those of observable in skeletons of people lived in the past; in contrast to recent cases with tuberculosis, they can be surveyed not only with medical imaging techniques but also directly with macromorphological methods; and even subtle bony changes can be recognised in them (Santos & Roberts, 2001, 2006; Hunt & Albanese, 2005; Matos & Santos, 2006; Mariotti *et al.*, 2015). In the last three decades, the *Terry Collection* has been used to define and refine palaeopathological diagnostic criteria for tuberculosis in several studies (*e.g.*, Roberts *et al.*, 1994; Winland *et al.*, 1997; Rothschild & Rothschild, 1998, 1999; Pálfi *et al.*, 2012); nevertheless, the possible TBM-associated endocranial alteration types were beyond the scope of the aforementioned research projects.

The main aim of the current PhD dissertation was to expand knowledge and understanding about the development of the four probable TBM-related endocranial alteration types (*i.e*., APDIs, PAs, ABVIs, and GIs) and to improve their palaeopathological interpretation, as well as to contribute to strengthening their diagnostic value in the identification of tuberculosis in human osteoarchaeological material. Therefore, review of the modern medical and palaeopathological literature regarding tuberculosis was conducted, with special attention to bony changes likely associated with TB. Moreover, for the first time, a detailed investigation focusing on the macromorphological characteristics and frequencies of the aforementioned endocranial alterations, as well as of their co-occurrence with each other and with non-endocranial bony changes probably related to TB, was performed on all individuals (N=302) recorded to have died of different types of tuberculosis (*e.g*., pulmonary TB, miliary TB, peritoneal TB, and skeletal TB) in the *Terry Collection*, and on a control group consisting of randomly selected specimens (N=302) from the remaining skeletons of the *Terry Collection*, identified to have died of causes other than TB (*e.g*., other infectious diseases, cardiovascular problems, cancer, and external causes, such as suicide and homicide). Nonetheless, it must be noted that the disease registered as the cause of death on the morgue record and/or death certificate of the 604 individuals selected for the above-mentioned research project from the *Terry Collection* may not have been the only medical condition present in the specimens; thus, even if another medical condition was registered as the cause of death on the morgue record and/or death certificate of individuals recorded to have died of causes other than TB from the *Terry Collection*, they could still have suffered from tuberculosis at death (Roberts *et al*., 1994; Santos & Roberts, 2001).

From the 604 selected skeletons surveyed in the *Terry Collection*, 177 were excluded from the examination considering the four endocranial alteration types possibly associated with TBM: the skullcap was missing in two cases and the skull was not sectioned in a further 173 cases; therefore, precluding the accurate observation of the inner surface of the skull; whereas the age at death was uncertain in two additional cases; thus, compromising the statistical analysis of data. The remaining 427 individuals with skulls sectioned in the transverse plane and occasionally also in the mid-sagittal plane were divided into two main groups on the basis of their causes of death: one composed of 234 specimens with TB as the cause of death (TB group) and the other consisting of 193 individuals with NTB causes of death (NTB group).

The present PhD dissertation focused on the macromorphological and statistical results of the aforementioned research project, with objectives of the dissertation being the following:

1) To macroscopically evaluate the 427 selected skeletons with sectioned skulls from the *Terry Collection* for the presence of the four types of probable TBM-related endocranial alterations, as well as for their co-occurrence with each other and with non-endocranial bony changes possibly associated with tuberculosis;

2) To compare the frequencies of the four types of probable TBM-related endocranial alterations, as well as of their co-occurrence with each other and with non-endocranial bony changes possibly associated with tuberculosis, between the 234 individuals recorded to have died of TB (TB group) and the 193 specimens identified to have died of causes other than TB (NTB group), considering sex and age at death of individuals;

3) To macromorphologically characterise the four probable TBM-related endocranial alteration types detected in the 427 selected skeletons with sectioned skulls from the *Terry Collection*, regarding the prominence (APDIs), as well as the localisation, extent, and number (PAs, ABVIs, and GIs) of lesions on the affected cranial bone(s);

4) To provide example cases showing the most important macromorphological characteristics of the four types of possible TBM-associated endocranial alterations; and

5) To evaluate the diagnostic value of the four probable TBM-related endocranial alteration types examined in the 427 selected skeletons with sectioned skulls from the *Terry Collection*.

The subsequent section of the current PhD dissertation provides detailed discussion of the macromorphological and statistical results of the research project conducted on the 427 selected skeletons with sectioned skulls from the *Terry Collection* and draws conclusions deriving from the findings in order of the above-mentioned objectives.

1) During the macromorphological evaluation of the 427 selected skeletons with sectioned skulls from the *Terry Collection*, 50.59% (216/427), 15.69% (67/427), 14.52% (62/427), and 17.33% (74/427) of the surveyed individuals exhibited APDIs, PAs, ABVIs, and GIs, respectively. Therefore, APDIs represented the most frequently detected type of possible TBM-associated endocranial alterations; whereas PAs, ABVIs, and GIs occurred in similar proportions of the examined specimens. Furthermore, of the 427 skeletons, more than

one-third (162/427, 37.94%) displayed no signs of endocranial alterations probably related to TBM. In a further one-third (154/427, 36.07%) of individuals, only one possible TBM-associated endocranial alteration type was registered on the inner surface of the skull; whereas the remaining less than one-third (111/427, 25.99%) of specimens showed co-occurrence of at least two different types of endocranial alterations likely related to TBM, with the majority of individuals (72/111, 64.86%) revealing association of only two types of the evaluated lesions affecting the inner surface of the skull.

In the 265 out of the 427 selected skeletons with sectioned skulls from the *Terry Collection* that exhibited at least one type of possible TBM-associated endocranial alterations, PNBFs on the visceral surface of ribs, vertebral hypervascularisation, and vertebral lytic lesions, as well as signs of HPO, extra-spinal TB osteomyelitis and arthritis, and TB cold abscesses, were recorded as non-endocranial bony changes likely related to TB: in 44.15% (117/265), 43.40% (115/265), 9.81% (26/265), 9.43% (25/265), 6.42% (17/265), 4.15% (11/265), and 10.57% (28/265) of the aforementioned specimens, respectively. Thus, PNBFs on the visceral surface of ribs and vertebral hypervascularisation affecting the anterior and/or lateral aspects of the bodies represented the most commonly detected types of possible TB-associated non-endocranial bony changes in the 265 selected skeletons with sectioned skulls from the *Terry Collection* displaying at least one probable TBM-related endocranial alteration type. Moreover, of the 265 skeletons, about one-third (98/265, 36.98%) showed no signs of non-endocranial bony changes likely associated with TB; whereas the remaining two-thirds (167/265, 63.02%) of individuals exhibited association of probable TB-related endocranial and non-endocranial bony changes, with the majority (106/167, 63.47%) of skeletons revealing simultaneous occurrence of at least two different types of possible TB-associated non-endocranial bony changes; nevertheless, the number of non-endocranial bony changes probably related to TB and concurrently affecting the above-mentioned specimens varied form two to seven.

In summary, at least one type of endocranial alterations likely associated with TBM was registered in about two-thirds (265/427, 62.06%) of the 427 selected skeletons with sectioned skulls from the *Terry Collection* that were macroscopically evaluated for the presence of the aforementioned lesions affecting the inner surface of the skull, without prior knowledge of the cause of death of individuals. In addition, the co-occurrence of probable TBM-related endocranial alteration types with each other and with possible TB-associated non-endocranial bony changes was detected in about one-fourth (111/427, 25.99%) and more than one-third (167/427, 39.11%) of the surveyed specimens, respectively.

2) After the detailed macromorphological evaluation of the 427 selected skeletons with sectioned skulls from the *Terry Collection*, subsequent statistical analysis of data was performed: absolute and percentage frequencies of the four types of endocranial alterations probably related to TBM, as well as of their co-occurrence with each other and with non-endocranial bony changes likely associated with TB, were calculated in both the TB group (Σ= 234) and NTB group (Σ=193), considering the sex and age at death of individuals; and χ^2 testing of data to determine the significance of differences (if any) in frequencies of the four examined lesion types affecting the inner surface of the skull, as well as of their association with each other and with possible TB-related non-endocranial bony changes between the two groups, was undertaken.

APDIs, PAs, ABVIs, and GIs were registered in both the TB group and NTB group: in 65.81% (154/234) versus 32.12% (62/193), 20.09% (47/234) versus 10.36% (20/193), 21.37% (50/234) versus 6.22% (12/193), and 29.06% (68/234) versus 3.11% (6/193) of specimens surveyed, respectively. Therefore, every evaluated endocranial alteration type likely associated with TBM occurred more frequently in the TB group than in the NTB group. Whereas APDIs and PAs affected individuals with TB as the cause of death about twice as often as specimens with NTB causes of death, ABVIs and GIs were approximately three and a half times and ten times more common in individuals recorded to have died of TB than in specimens identified to have died of causes other than TB, respectively. The co-occurrence of the four examined lesion types affecting the inner surface of the skull with each other and with non-endocranial bony changes possibly related to TB were detected in both the TB group and NTB group: in 41.03% (96/234) versus 7.77% (15/193) and 80.11% (145/181) versus 26.19% (22/84) of individuals surveyed, respectively. Thus, the co-occurrence of at least two types of probable TBM-associated endocranial alterations was about five times more frequent in the TB group than in the NTB group; whereas the association of likely TB-related endocranial and non-endocranial bony changes occurred approximately three times more commonly in specimens with TB as the cause of death than in individuals with NTB causes of death.

Furthermore, the χ^2 comparison of the frequencies of APDIs, PAs, ABVIs, and GIs, as well as of their co-occurrence with each other and with probable TB-associated non-endocranial bony changes, revealed a statistically significant difference between the TB group and NTB group (χ^2=46.680, df=1, P<0.0001; χ^2=6.841, df=1, P=0.0089; χ^2=18.357, df=1, P<0.0001; χ^2=47.922, df=1, P<0.0001; χ^2=59.079, df=1, P<0.0001; and χ^2=69.280, df=1, P<0.0001, respectively); therefore – similar to the results of previous

palaeopathological and palaeomicrobiological studies performed on osteoarchaeological series and documented skeletal collections (*e.g.*, Schultz, 1993, 1999, 2001, 2003; Templin & Schultz, 1994; Teschler-Nicola *et al.*, 1994, 2015; Jankauskas & Schultz, 1995; Jankauskas, 1999; Hershkovitz *et al.*, 2002; Maczel, 2003; Pálfi *et al.*, 2012; Masson *et al.*, 2015; Molnár *et al.*, 2015; Schultz & Schmidt-Schultz, 2015) –, constituting evidence that there may be a positive correlation between the above-mentioned lesions and tuberculosis. Thus, APDIs, PAs, ABVIs, and GIs can be used as diagnostic criteria for TBM in the palaeopathological practice. Although not all of them may be considered as specific vestiges of the disease – since pathological conditions other than tuberculosis (*e.g.*, bacterial meningitis, trauma, scurvy, and epidural haematoma) may also result in the development of similar or even the same morphological features –, palaeopathologists could still use them to identify TB in osteoarchaeological material from the pre-antibiotic era, especially when they simultaneously occur with each other and/or with non-endocranial bony changes possibly related to TB.

Considering the sex of the 427 selected skeletons with sectioned skulls from the *Terry Collection*, APDIs, PAs, ABVIs, and GIs were registered among both females (Σ=65) and males (Σ=169) in the TB group: in 52.31% (34/65) versus 71.01% (120/169), 23.08% (15/65) versus 18.93% (32/169), 30.77% (20/65) versus 17.75% (30/169), and 30.77% (20/65) versus 28.40% (48/169) of specimens surveyed, respectively. Similar to the TB group, APDIs, PAs, ABVIs, and GIs were recorded among both females (Σ=87) and males (Σ=106) in the NTB group: in 21.84% (19/87) versus 40.57% (43/106), 10.34% (9/87) versus 10.38% (11/106), 6.90% (6/87) versus 5.66% (6/106), and 2.30% (2/87) versus 3.77% (4/106) of individuals examined, respectively. Therefore, every evaluated endocranial alteration type likely associated with TBM occurred more frequently in the TB group than in the NTB group among both females and males. The co-occurrence of the four examined lesion types affecting the inner surface of the skull with each other and with non-endocranial bony changes probably related to TB were detected among both females and males in the TB group: in 43.08% (28/65) versus 40.24% (68/169) and 71.11% (32/45) versus 83.09% (113/136) of specimens surveyed, respectively. Similar to the TB group, the co-occurrence of the four examined lesion types affecting the inner surface of the skull with each other and with non-endocranial bony changes possibly associated with TB were observed among both females and males in the NTB group: in 8.05% (7/87) versus 7.55% (8/106) and 28.57% (8/28) versus 25.00% (14/56) of individuals examined, respectively. Thus, the co-occurrence of at least two types of probable TBM-related endocranial alterations, as well as the

association of endocranial and non-endocranial bony changes likely related to TB, were more commonly registered in specimens with TB as the cause of death than in individuals with NTB causes of death among both females and males.

Moreover, when the two groups were compared considering the sex of the surveyed specimens, the difference in the frequencies of APDIs, ABVIs, and GIs, as well as of the co-occurrence of the four evaluated lesion types affecting the inner surface of the skull with each other and with probable TB-associated non-endocranial bony changes remained significant for both females (χ^2=13.896, df=1, P=0.0002; χ^2=13.317, df=1, P=0.0003; χ^2=22.115, df=1, P<0.0001; χ^2=23.820, df=1, P<0.0001; and χ^2=10.951, df=1, P=0.0009, respectively) and males (χ^2=23.759, df=1, P<0.0001; χ^2=7.342, df=1, P=0.0067; χ^2=24.188, df=1, P<0.0001; χ^2=33.192, df=1, P<0.0001; and χ^2=57.205, df=1, P<0.0001, respectively); whereas the χ^2 comparison of the frequencies of PAs between individuals with TB as the cause of death and specimens with NTB causes of death revealed no statistically significant difference among both females (χ^2=3.629, df=1, P=0.0568) and males (χ^2=2.997, df=1, P=0.0834). The frequencies of PAs and GIs, as well as of the co-occurrence of the four evaluated lesion types affecting the inner surface of the skull with each other and with likely TB-related non-endocranial bony changes, were very similar among females and males in both the TB group and NTB group; thus, there was no statistically significant difference between the two sexes (TB group: χ^2=0.277, df=1, P=0.5987 and NTB group: χ^2=0.0529, df=1, P=0.8181; TB group: χ^2=0.0386, df=1, P=0.8443 and NTB group: χ^2=0.0291, df=1, P=0.8645; TB group: χ^2=0.0611, df=1, P=0.8047 and NTB group: χ^2=0.0200, df=1, P=0.8876; and TB group: χ^2=2.339, df=1, P=0.1262 and NTB group: χ^2=0.00296, df=1, P=0.9566, respectively). Nevertheless, in both the TB group and NTB group, an approximately 20 percentage point difference (male predominance: 52.31% versus 71.01% and 21.84% versus 40.57%, respectively) in the frequencies of APDIs was found between females and males; and the χ^2 comparison of the frequencies of APDIs between the two sexes revealed a statistically significant difference in both specimens identified to have died of TB (χ^2=6.487, df=1, P=0.0109) and individuals recorded to have died of causes other than TB (χ^2=6.850, df=1, P=0.0089). Unfortunately, there may be no appropriate scientific explanation for these findings in the two groups, as according to the results of recent medical studies (*e.g.*, Brodsky, 2010; Dendane *et al.*, 2013; Salekeen *et al.*, 2013; Smith *et al.*, 2013; Bir *et al.*, 2016; Tyagi *et al.*, 2016), there may be no statistically significant difference between the two sexes or there may be a slight female or male predominance in adult patients with TBM or with other underlying medical conditions that may result in the development

of eICP with consequent formation of APDIs on the inner surface of the skull. Furthermore, an about 13 percentage point difference (female predominance: 30.77% versus 17.75%) in the frequencies of ABVIs between females and males was found in the TB group; and the χ^2 comparison of the frequencies of ABVIs between the two sexes in the TB group revealed a statistically significant difference (χ^2=3.992, df=1, P=0.0457). Unfortunately, no data were found in the modern medical literature that would appropriately explain the above-mentioned findings. Nonetheless, the frequencies of ABVIs among females and males were very similar in the NTB group; therefore, there was no statistically significant difference between the two sexes (χ^2=0.00295, df=1, P=0.9567).

Regarding the distribution of affected specimens by age at death, APDIs occurred with the highest frequency among individuals under the age of 30 years (61/70, 87.14%): with 88.89% (56/63) in the TB group and with 71.43% (5/7) in the NTB group. Similar to the APDIs, PAs, and ABVIs affected most commonly specimens under the age of 30 years in the TB group: more than two-fifths of the aforementioned individuals revealed PAs (26/63, 41.27%) or ABVIs (28/63, 44.44%) on the inner surface of the skull. Nevertheless, in the NTB group, the majority of specimens exhibiting PAs (18/20, 90.00%) or ABVIs (11/12, 91.67%) were above the age of 40 years. GIs occurred with the highest frequency among individuals under the age of 20 years (4/7, 57.14%) in the TB group; nonetheless, more than one-third (55/158, 34.81%) of specimens between 20 and 49 years of age and with TB as the cause of death also showed GIs on the inner surface of the skull. Similar to the PAs and ABVIs, GIs affected almost exclusively individuals above the age of 40 years (5/6, 83.33%) in the NTB group. As for the co-occurrence of at least two different types of endocranial alterations probably related to TBM, specimens under the age of 30 years (45/63, 71.43%) were most frequently affected by it in the TB group; nevertheless, more than one-third (40/102, 39.22%) of individuals between 30 and 49 years of age and recorded to have died of TB were also concurrently affected by at least two different types of endocranial alterations possibly associated with TBM. In the NTB group, the vast majority of specimens (5/6, 83.33%) exhibiting co-occurrence of at least two different types of endocranial alterations likely related to TBM were above the age of 40 years. The simultaneous occurrence of probable TB-associated endocranial and non-endocranial bony changes was recorded with the highest frequency among individuals above the age of 40 years (104/119, 87.39%): with 89.62% (95/106) and 69.23% (9/13) in the TB group and NTB group, respectively. The χ^2 testing of the frequencies of APDIs, PAs, ABVIs, and GIs, as well as of the co-occurrence of the four evaluated lesion types affecting the inner surface of the skull

with each other and with likely TB-related non-endocranial bony changes, between the various age groups was not assessed because of the low number of specimens in certain age groups.

3) During the macromorphological evaluation of the 427 selected skeletons with sectioned skulls from the *Terry Collection*, concerning the observed APDIs, their prominence was registered according to a 3-level scale (very slight: shallow DIs (< 2mm in depth) predominantly over the anterior portion of the endocranial surface; slight: deeper DIs (2–4 mm in depth) particularly over the anterior and middle portions of the endocranial surface; and pronounced: deep DIs (4 mm < in depth) all over the endocranial surface); whereas regarding the detected PAs, ABVIs, and GIs, the affected cranial bone(s); the number of recorded lesions in the affected cranial bone(s) (unifocal or multifocal); and the extent of the endocranial surface area the observed lesion(s) covered (x) in the affected cranial bone(s) (4-level scale: 1) $x < 25\%$, 2) $25\% \leq x < 50\%$, 3) $50\% \leq x < 75\%$, and 4) $75\% \leq x$) were noted.

As for the prominence of APDIs detected in 216 out of the 427 selected skeletons with sectioned skulls from the *Terry Collection*, very slight APDIs occurred in more than two-thirds (148/216, 68.52%) of the above-mentioned individuals. Whereas very slight APDIs were more commonly registered in specimens with NTB causes of death, slight and pronounced APDIs were more frequently recorded in individuals with TB as the cause of death: in 62.34% (96/154) versus 83.87% (52/62), 27.27% (42/154) versus 14.52% (9/62), and 10.39% (16/154) versus 1.61% (1/62), respectively.

Regarding the localisation of PAs and ABVIs on the inner surface of the skull, the frontal bone (predominantly its most protruding portions and/or orbital part) and the parietal bones (particularly their most protruding portion and/or their part along the superior sagittal sinus) represented the most common sites of involvement in both the TB group and NTB group. Occasionally, the occipital bone (generally its squamous part along the superior sagittal and/or transverse sinuses), the temporal bones (mostly their squamous part), and the greater wings of the sphenoid bone were also affected. Considering the left and right greater wings of the sphenoid bone as two separate bones, in more than one-half of specimens with TB as the cause of death and PAs or ABVIs, at least three or four cranial bones were simultaneously affected: in 53.19% (25/47) and 64.00% (32/50), respectively; whereas in the majority of individuals with NTB causes of death and PAs or ABVIs, less than three or four cranial bones were concomitantly involved: in 65.00% (13/20) and 75.00% (9/12),

respectively. In contrast to the PAs and ABVIs, GIs occurred most frequently on the squamous part of the occipital bone in both the TB group and NTB group. Moreover, GIs were quite often observed in the orbital part of the frontal bone and in the squamous part of the temporal bones; whereas involvement of the greater wings of the sphenoid bone, as well as of the parietal bones (predominantly along the squamous suture) by GIs, was registered in only the minority of skeletons surveyed. In both the TB group and NTB group, less than four cranial bones (considering the left and right greater wings of the sphenoid bone as two separate bones) were concurrently affected by GIs in approximately two-thirds of specimens exhibiting the aforementioned probable TBM-associated endocranial alteration type: in 72.06% (49/68) and 66.67% (4/6), respectively.

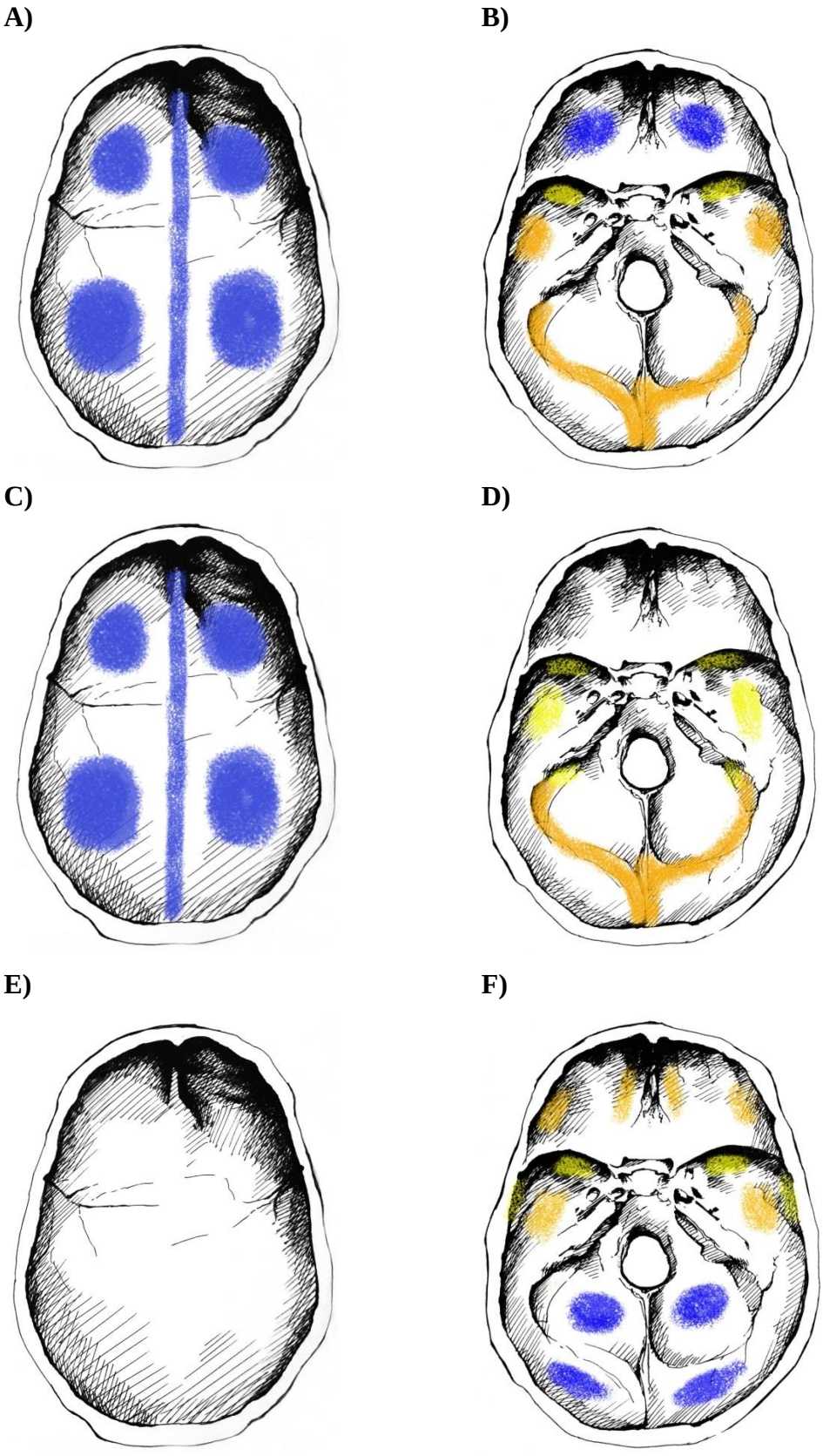
Concerning the extent of the detected lesions, the majority of PAs and ABVIs (observed in 67 and 62 out of the 427 selected skeletons with sectioned skulls from the *Terry Collection*, respectively) covered less than one-half of the endocranial surfaces in all cranial bones examined. Nonetheless, the extent of PAs and ABVIs recorded in the frontal and parietal bones exceeded one-half of the inner surfaces quite frequently. In contrast to the PAs and ABVIs, the majority of GIs registered in 74 out of the 427 selected skeletons with sectioned skulls from the *Terry Collection* covered only less than one-fourth of the endocranial surfaces in all cranial bones examined. Nevertheless, the extent of GIs detected in the sphenoid and temporal bones exceeded one-fourth of the inner surfaces quite commonly. With respect to the number of lesions, in the 67 and 62 cases exhibiting PAs and ABVIs, respectively, the above-mentioned endocranial alterations likely related to TBM occurred almost exclusively as multifocal bony changes on the inner surface of the skull in all cranial bones evaluated, and only occasionally were observed as unifocal lesions. Similar to the PAs and ABVIs, in the 74 affected cases, GIs were particularly recorded as multifocal bony changes in the frontal and occipital bones; nonetheless, they were registered as unifocal alterations in the parietal, sphenoid, and temporal bones quite often.

In summary, in more than two-thirds of 216 out of the 427 selected skeletons with sectioned skulls from the *Terry Collection* that exhibited APDIs, the very slight stage of the aforementioned lesion was detected. As for the localisation of PAs, ABVIs, and GIs, findings of the current PhD dissertation were similar to those of previous studies (*e.g.*, Mensforth *et al.*, 1978; Schultz, 1993, 1999; Hershkovitz *et al.*, 2002; Schultz & Schmidt-Schultz, 2015): PAs and ABVIs were situated particularly on the inner surface of the frontal and parietal bones, with their most protruding portion and/or part along the superior sagittal sinus being the most commonly affected areas; whereas GIs were localised predominantly on the

endocranial surface of the skull base and lateral skull vault, mostly on the squamous part of the occipital and temporal bones, as well as on the orbital part of the frontal bone, with the pattern and distribution of GIs resembling that of most often observed in the affected meninges during the pathogenesis of TBM **(Fig. 76A–F)**. Considering the left and right greater wings of the sphenoid bone as two separate bones, in more than one-half of individuals with TB as the cause of death and PAs or ABVIs, at least three or four cranial bones were simultaneously affected, respectively; whereas in the majority of specimens with NTB causes of death and PAs or ABVIs, less than three or four cranial bones were concomitantly involved, respectively. In both groups, less than four cranial bones were concurrently affected by GIs in about two-thirds of individuals exhibiting the above-mentioned probable TBM-associated endocranial alteration type. Regarding the extent of lesions, whereas the majority of the detected PAs and ABVIs covered less than one-half of the endocranial surfaces in all cranial bones examined, the extent of the endocranial surface area the observed GIs covered in the affected cranial bones only occasionally exceeded one-fourth of the inner surfaces. Concerning the number of lesions, PAs, ABVIs, and GIs were registered most frequently as multifocal alterations in all cranial bones evaluated.

4) In the present PhD dissertation (at the end of each section of the RESULTS & CASE STUDIES chapter), example cases were provided that showed the most important macromorphological characteristics of the four evaluated endocranial alteration types probably related to TBM, as well as of their co-occurrence with each other and/or with non-endocranial bony changes likely associated with TB. Terry No. 30R, 382R, and 1033 were used to represent the very slight, slight, and pronounced stages of the prominence of APDIs, respectively. The most characteristic localisations of PAs, ABVIs, and GIs on the inner surface of the cranial bones were illustrated by Terry No. 987, 1027, and 1300; Terry No. 254, 1030, and 1555; and Terry No. 522, 562, 566, and 933R, respectively. Six further example cases were used to demonstrate the co-occurrence of the four possible TBM-related endocranial alteration types with each other (Terry no. 304, 1159, 1222, and 1322) and with non-endocranial bony changes probably associated with TB (Terry No. 468 and 902). The detailed case studies presented in the current PhD dissertation may give a better insight into the macromorphological characteristics of the examined lesions affecting the inner surface of the skull, and may provide palaeopathologists with a stronger basis for establishing a more reliable and accurate diagnosis of TBM in ancient human bone remains that exhibit bony changes resembling those of the example cases presented here.

Figure 76: Typical localisations of PAs, ABVIs, and GIs on the inner surface of the skullcap: A), C), and E), respectively; and of the skull base: B), D), and F), respectively (blue: most commonly affected areas, orange: commonly affected areas, and yellow: less commonly affected areas) (drawings by *Luca Kis*).



5) On the basis of the findings obtained from the research project performed on the 427 selected skeletons with sectioned skulls from the *Terry Collection*, the four evaluated endocranial alteration types (*i.e.*, APDIs, PAs, ABVIs, and GIs) can be used as diagnostic criteria for TBM in the palaeopathological practice, as all of them occurred more frequently in the TB group than in the NTB group; and the χ^2 comparison of the frequencies of APDIs, PAs, ABVIs, and GIs, as well as of their co-occurrence with each other and with likely TB-related non-endocranial bony changes, revealed a statistically significant difference between the two groups; thus, indicating that there may be a positive correlation between the examined lesions and TBM. However, the diagnostic value of the aforementioned endocranial alteration types is not equal.

In comparison with the three other endocranial alteration types possibly associated with TBM (*i.e.*, APDIs, ABVIs, and GIs), PAs have the weakest diagnostic value in the palaeopathological identification of TBM in ancient human bone remains based on the findings of the present PhD dissertation, since even if they were detected in specimens with TB as the cause of death about twice as often as in individuals with NTB causes of death, the χ^2 comparison of the frequencies of PAs revealed a statistically only significant difference between the TB group and NTB group (χ^2=6.841, df=1, P=0.0089), suggesting a weaker correlation between PAs and TBM. Furthermore, the results obtained from the research project performed on the 427 selected skeletons with sectioned skulls from the *Terry Collection* may support those of previous studies (*e.g.*, Mensforth *et al.*, 1978; Schultz, 1993, 1999, 2001, 2003) regarding the specificity of the above-mentioned endocranial alteration type for TBM, as PAs were observed in more than 10% (20/193) of the 193 skeletons composing the NTB group; and thus, indicating that they cannot be considered as specific vestiges of TBM. In one-half (10/20, 50.00%) of the specimens with PAs in the NTB group, probable TBM-related endocranial alterations other than PAs (APDIs: eight cases, ABVIs: one case, and GIs: one case) and/or likely TB-associated non-endocranial bony changes (PNBFs: one case and vertebral hypervascularisation: one case) were also noted. Since the disease registered as the cause of death on the morgue record and/or death certificate may not have been the only medical condition present in the individuals surveyed in the *Terry Collection*, specimens identified to have died of causes other than TB could still have suffered from tuberculosis at death (Roberts *et al.*, 1994; Santos & Roberts, 2001). Thus, in the aforementioned ten individuals with PAs in the NTB group, the tuberculous origin of the recorded endocranial and non-endocranial lesions cannot be excluded. However, it is also possible that in these ten cases – similar to the other one-half (10/20,

50.00%) of specimens with PAs in the NTB group, where no signs of probable TBM-related endocranial alterations other than PAs or of likely TB-associated non-endocranial bony changes were observed –, medical conditions other than TB (*e.g.*, bacterial meningitis, trauma, and scurvy) may result in the development of the detected lesions.

On the basis of the findings obtained from the research project performed on the 427 selected skeletons with sectioned skulls from the *Terry Collection*, APDIs have a stronger diagnostic value in the palaeopathological identification of TBM in past human populations than PAs, since – similar to the PAs – APDIs were registered in individuals recorded to have died of TB approximately twice as frequently as in specimens identified to have died of causes other than TB; but – in contrast to the PAs – the χ^2 comparison of the frequencies of APDIs revealed a statistically not only significant but extremely significant difference between the TB group and NTB group (χ^2=46.680, df=1, P<0.0001); therefore, indicating a strong correlation between APDIs and TBM. Nevertheless, the results of the present PhD dissertation fit in with those of previous studies (*e.g.*, Schultz, 1993, 1999, 2001, 2003) concerning the specificity of the above-mentioned endocranial alteration type for TBM, as about one-third (62/193, 32.12%) of the 193 skeletons constituting the NTB group revealed APDIs on the inner surface of the skull; thus, suggesting that APDIs cannot be considered as pathognomonic features of TBM. In less than one-half (28/62, 45.16%) of the individuals with APDIs in the NTB group, probable TBM-related endocranial alterations other than APDIs (PAs: seven cases, ABVIs: three cases, and GIs: four cases) and/or likely TB-associated non-endocranial bony changes (PNBFs: four cases, vertebral hypervascularisation: 12 cases, vertebral lytic lesions: three cases, signs of extra-spinal osteomyelitis: three cases, signs of HPO: four cases, and signs of cold abscesses: two cases) were also registered. It must be noted that even if the recorded cause of death of specimens surveyed in the *Terry Collection* may not have been tuberculosis, individuals could still have suffered from the disease but their death was attributed to another medical condition (Roberts *et al.*, 1994; Santos & Roberts, 2001); therefore, it cannot be excluded that in the aforementioned 28 specimens with APDIs in the NTB group, the observed endocranial and non-endocranial bony changes might result from TB. However, in the other one-half (34/62, 54.84%) of individuals with APDIs in the NTB group, where no signs of probable TBM-related endocranial alterations other than APDIs or of possible TB-associated non-endocranial bony changes were detected, the NTB origin (*e.g.*, other CNS infections, brain tumours, and haemorrhages) of the noted lesions is much more likely.

In comparison with the APDIs and PAs, ABVIs have a stronger diagnostic value in the palaepathological identification of TBM in osteoarchaeological material from the pre-antibiotic era based on the findings of the current PhD dissertation, since they were about three and a half times more common in specimens with TB as the cause of death than in individuals with NTB causes of death; and the χ^2 comparison of the frequencies of ABVIs revealed a statistically extremely significant difference between the TB group and NTB group (χ^2=18.357, df=1, P<0.0001); therefore, suggesting a strong correlation between ABVIs and TBM. Nonetheless, the results of the research project conducted on the 427 selected skeletons with sectioned skulls from the *Terry Collection* may support those of previous studies (*e.g.*, Schultz, 1993, 1999, 2001, 2003) regarding the specificity of the above-mentioned endocranial alteration type for TBM, as ABVIs were observed in more than 6% (12/193) of the 193 skeletons composing the NTB group; thus, indicating that they cannot be considered as specific vestiges of TBM. In more than one-half (7/12, 58.33%) of the individuals with ABVIs in the NTB group, probable TBM-related endocranial alterations other than ABVIs (APDIs: three cases and PAs: two cases) and/or likely TB-associated non-endocranial bony changes (PNBFs: one case, signs of extra-spinal osteomyelitis: one case, signs of HPO: one case, and signs of cold abscesses: one case) were also noted. Since the disease registered as the cause of death on the morgue record and/or death certificate may not have been the only medical condition present in the specimens surveyed in the *Terry Collection*, individuals recorded to have died of causes other than TB could still have suffered from tuberculosis at death (Roberts *et al*., 1994; Santos & Roberts, 2001). Therefore, in the aforementioned seven specimens with ABVIs in the NTB group, the tuberculous origin of the detected endocranial and non-endocranial lesions cannot be excluded. However, it is also possible that in these seven cases – similar to the other one-half (5/12, 41.67%) of individuals with ABVIs in the NTB group, where no signs of probable TBM-related endocranial alterations other than ABVIs or of likely TB-associated non-endocranial bony changes were observed –, medical conditions other than TB (*e.g*., bacterial meningitis, trauma, and scurvy) may result in the development of the observed lesions, since most of them cannot be considered as pathognomonic features of TB.

On the basis of the results obtained from the research project performed on the 427 selected skeletons with sectioned skulls from the *Terry Collection*, among the four possible TBM-related endocranial lesion types, GIs have the strongest diagnostic value in the palaeopathological identification of TBM in past human populations, since they occurred approximately ten times more often in specimens with TB as the cause of death than in

individuals with NTB causes of death; and the χ^2 comparison of the frequencies of GIs revealed a statistically extremely significant difference between the TB group and NTB group (χ^2=47.922, df=1, P<0.0001). Moreover, the findings of the present PhD dissertation fit in with those of previous studies (*e.g.*, Schultz, 1999, 2001, 2003; Schultz & Schmidt-Schultz, 2015) concerning the specificity of the above-mentioned endocranial alteration type for TBM, as – in contrast to the previously discussed lesions affecting the inner surface of the skull (*i.e.*, APDIs, PAs, and ABVIs) – GIs affected only the minority (6/193, 3.11%) of the 193 skeletons constituting the NTB group, and in the vast majority of the above-mentioned six specimens (5/6, 83.33%), probable TBM-associated endocranial alterations other than GIs (APDIs: four cases and PAs: one case) and/or likely TB-related non-endocranial bony changes (PNBFs: two cases, vertebral hypervascularisation: two cases, signs of extra-spinal osteomyelitis: two cases, and signs of HPO: one case) were also recorded. It must be noted that even if the registered cause of death of individuals surveyed in the *Terry Collection* may not have been tuberculosis, specimens could still have suffered from the disease but their death was attributed to another medical condition (Roberts *et al.*, 1994; Santos & Roberts, 2001); thus, it is very likely that in the aforementioned six cases, the observed endocranial and non-endocranial bony changes might result from TB.

In summary, even if PAs, APDIs, and ABVIs cannot be considered as pathognomonic features of TBM, palaeopathologists could still use them – with necessary circumspection – to identify the disease in human osteoarchaeological material from the pre-antibiotic era, especially when they simultaneously occur with each other and/or with possible TB-related non-endocranial bony changes. Furthermore, the results of the current PhD dissertation may confirm those of *Schultz* (*e.g.*, 1999, 2001, 2003) and *Schmidt-Schultz* (2015) that GIs can be considered as pathognomonic features of TBM; and therefore, the palaeopathological diagnosis of TBM can be established with a high certainty when GIs are present in ancient human bone remains.

6 RESEARCH SIGNIFICANCE & PERSPECTIVES

Despite significant advances in the global fight against tuberculosis, it still presents a health emergency; therefore, a renewed interest and funding to the research of the disease and of its aetiological agents has sparked during the last few decades in order to eliminate or at least control TB in the future. Since the beginning of the 21st century, a number of molecular evolutionary studies (*e.g.*, Brosch *et al.*, 2002; Mostowy *et al.*, 2002; Gutierrez *et al.*, 2005; Brisse *et al.*, 2006; Huard *et al.*, 2006; Smith, 2006; Hershberg *et al.*, 2008; Wirth *et al.*, 2008; Comas *et al.*, 2013; Bos *et al.*, 2014) have improved our knowledge on the origin and evolutionary history of the MTBC, as well as on the co-evolution of its members with the human and various wild and domesticated animal hosts; however, the results of the aforementioned research projects are unfortunately insufficient and controversial for the time being (Stone *et al.*, 2009; Gagneux, 2012; Coscolla & Gagneux, 2014; Galagan, 2014; Bañuls *et al.*, 2015; Brites & Gagneux, 2015; Pálfi *et al.*, 2015; Pai *et al.*, 2016; WHO, 2017).

In addition, palaeomicrobiological analyses of biological remains of TB bacteria extracted from skeletons and mummies of people lived in the past (*e.g.*, DNA, proteins, and lipid biomarkers) (*e.g.*, Spigelman & Lemma, 1993; Salo *et al.*, 1994; Arriaza *et al.*, 1995; Haas *et al.*, 2000; Donoghue *et al.*, 2005; Zink *et al.*, 2007; Chan *et al.*, 2013; Hershkovitz *et al.*, 2015; Schmidt-Schultz & Schultz, 2015) have provided invaluable novel data not only on the evolution of tuberculosis but also on its palaeoepidemiology throughout prehistoric and historic times. Nevertheless, findings of recent palaeoepidemiological studies on human osteoarchaeological series from the pre-antibiotic era (*e.g.*, Masson *et al.*, 2015; Molnár *et al.*, 2015; Pósa *et al.*, 2015) have confirmed the complementarity of palaeomicrobiological and traditional, macromorphology-based palaeopathological analyses, as their combined application may contribute to facilitating the establishment of a more reliable and accurate palaeopathological diagnosis of TB in ancient human bone remains and the assessment of a more relevant prevalence of the disease in past human populations (Stone *et al.*, 2009; Donoghue *et al.*, 2015; Minnikin *et al.*, 2015; Pálfi *et al.*, 2015).

The above-mentioned examinations require excessive scientific knowledge on the macromorphological diagnostics of tuberculosis that underlines the importance of the present research project conducted on skeletons of known cause of death from the *Terry Collection*, since its results may provide palaeopathologists with a stronger basis for identifying TB and with a more sensitive means of assessing the prevalence of the disease in human osteoarchaeological material. Nonetheless, further investigations on human skeletons of known cause of death from documented collections other than the *Terry Collection* are necessary to confirm the trends noted in the current PhD dissertation.

Refinement of macromorphological diagnostic criteria and their application in the palaeopathological practice may open new perspectives in the palaeoepidemiological and evolutionary research of tuberculosis.

Finally, findings of the present PhD dissertation may draw physicians' attention to the rather high prevalence of meningeal involvement in TB patients; and thus, may contribute to further improving the modern medical practice regarding the identification of TBM. According to the modern medical literature (Garg, 1999; Bernaerts *et al*., 2003; Katti, 2004; Gauba & Varma, 2005; Bill, 2006; Myers, 2007; Rock *et al*., 2008; Thwaites *et al*., 2009; Cherian & Thomas, 2011; Christensen *et al*., 2011; Bano *et al*., 2012; Thwaites, 2013; Bini & Hernández Pando, 2014; Daniele, 2014; Taheri *et al*., 2015; Tyagi *et al*., 2016; Chaudhary *et al*., 2017; Vita *et al*., 2017), TBM – the most common form of CNS TB (~70–80%) – occurs in less than 1% of all active TB cases, with children under the age of 5 years representing the most vulnerable group affected by the disease. Although – because of the particular composition of the *Terry Collection* – there were no children among the evaluated skeletons with sectioned skulls **(Suppl. table 1)**, probable TBM-related endocranial alterations and their co-occurrence with each other and/or with likely TB-associated non-endocranial bony changes were observed in a number of adolescent and adult individuals with TB as the cause of death from the *Terry Collection*. It must be noted that the vast majority of the aforementioned specimens were identified to have died of pulmonary TB and only two of them were recorded to have died of TBM **(Suppl. table 1)**.

Nevertheless, results of the current research project fit in with those of recent studies revealing that at autopsy, a large number of individuals died of pulmonary TB without developing neurological signs and symptoms exhibited tubercles in the CNS; and therefore, indicating that involvement of the central nervous system in pulmonary TB is quite common. The above-mentioned findings may incite physicians to check pulmonary TB patients for involvement of the CNS even if they do not display neurological signs and symptoms suggestive of the disease, since early, accurate diagnosis and prompt, adequate treatment are crucial in determining the clinical outcome of TBM that carries a high short-term mortality and a substantial excess morbidity among survivors: approximately one-third of the affected patients die of TBM and up to one-half of the survivors remain with serious neurological sequels, despite the initiation of anti-tuberculosis therapy (Thwaites *et al*., 2002; Gauba & Varma, 2005; Garg, 2010; Christensen *et al*., 2011; Marx & Chan, 2011; Brancusi *et al*., 2012; Bini & Hernández Pando, 2014; Daniele, 2014; Rajashekar *et al*., 2014; Ramirez-Lapausa *et al*., 2015; Vita *et al*., 2017).

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Bácsalmás – Homokbánya, Hungary, 16th–17th century AD, Grave No. 2, *Adultus*, male (photo by *László Paja*).

8 SUMMARY

Tuberculosis (TB) is one of the oldest known infectious diseases that has been plaguing mankind for thousands of years. Using modern medical knowledge, palaeopathologists attempt to establish a retrospective diagnosis of prehistoric and historic TB cases by identifying pathological conditions in bone remains of people lived in the past that may be related to the disease. Nevertheless, on the one hand, probable TB-associated bony changes observed in recent cases may differ from those of detectable in skeletons from archaeological sites, due in part to the introduction of antibiotics in the treatment of TB. On the other hand, in modern clinical cases, bony lesions cannot be directly surveyed with macromorphological methods but with medical imaging techniques only; nonetheless, subtle bony alterations probably related to TB may be impossible to be visualised by the latter ones. Therefore, these bony changes are not relevant to the diagnosis of TB in recent cases and are not described as diagnostic criteria for the disease by physicians in the modern medical literature, even if they could be potentially important elements of TB identification for palaeopathologists. Thus, utilisation of modern diagnostic criteria for TB in the palaeopathological practice may not be appropriate.

Nevertheless, detailed analysis of well-documented collections of pre-antibiotic era skeletons of known cause of death can serve as a unique and important basis for the diagnosis of TB in past human populations, since bone remains of specimens identified to have died of TB and not treated with antibiotics may exhibit similar TB-associated bony lesions to those of observable in skeletons from archaeological sites; they can be directly surveyed with macromorphological methods; and even subtle bony alterations can be recognised in them. Therefore, examination of such collections can contribute to determining the appropriate palaeopathological diagnostic criteria for TB. Since the late 20th century, a number of palaeopathological and palaeomicrobiological studies were performed on osteoarchaeological series and documented skeletal collections that have revealed a correlation between tuberculous meningitis (TBM) and different endocranial alteration types, namely abnormally pronounced digital impressions (APDIs), periosteal appositions (PAs), abnormal blood vessel impressions (ABVIs), and granular impressions (GIs). However, the diagnostic value of the aforementioned lesions has more recently been questioned, as their precise aetiology is still a matter of controversy, and additionally, similar or even the same morphological features can be found in non-TB-related cases.

The main aim of the current PhD dissertation was to expand knowledge and understanding about the development of possible TBM-associated endocranial alterations and to improve their palaeopathological interpretation, as well as to contribute to

strengthening their diagnostic value in the identification of TB in human osteoarchaeological material from the pre-antibiotic era. Thus, review of the modern medical and palaeopathological literature regarding TB was conducted, with special attention to bony changes likely related to the disease. Furthermore, for the first time, a detailed investigation focusing on the macromorphological characteristics and frequencies of the above-mentioned lesions affecting the inner surface of the skull, as well as of their co-occurrence with each other and with non-endocranial bony changes probably associated with TB, was performed on all individuals recorded to have died of different types of TB (TB group) in the *Robert J. Terry Anatomical Skeletal Collection*, and on a control group (non-tuberculous (NTB) group) consisting of randomly selected specimens from the remaining skeletons of the *Terry Collection*, identified to have died of causes other than TB.

The objectives of the present PhD dissertation are the following:

1) To macroscopically evaluate the selected skeletons for the presence of APDIs, PAs, ABVIs, and GIs, as well as for their co-occurrence with each other and with non-endocranial bony changes possibly related to TB;
2) To compare the frequencies of APDIs, PAs, ABVIs, and GIs, as well as of their co-occurrence with each other and with non-endocranial bony changes likely associated with TB, between the TB group and NTB group, considering the sex and age at death of individuals;
3) To macromorphologically characterise APDIs, PAs, ABVIs, and GIs detected in the examined skeletons regarding the prominence (APDIs), as well as the localisation, extent, and number (PAs, ABVIs, and GIs) of lesions in the affected cranial bone(s);
4) To provide example cases showing the most important macromorphological characteristics of APDIs, PAs, ABVIs, and GIs; and
5) To evaluate the diagnostic value of APDIs, PAs, ABVIs, and GIs concerning the palaeopathological identification of TB.

The main results of the current PhD dissertation are the following:

1) As for the presence of APDIs, PAs, ABVIs, and GIs, at least one of them was registered in approximately two-thirds of the selected skeletons from the *Terry Collection*, with APDIs representing the most frequently detected lesion type and with PAs, ABVIs, and GIs occurring in smaller but similar proportions of specimens. In addition, the association of APDIs, PAs, ABVIs, and GIs with each other and/or with probable TB-related non-endocranial bony changes was noted in about one-third of the surveyed individuals.

2) APDIs, PAs, ABVIs, and GIs were registered in both the TB group and NTB group; nonetheless, all of them were recorded more commonly in specimens with TB as the cause of death than in individuals with NTB causes of death. Whereas APDIs and PAs occurred in the TB group about twice as often as in the NTB group, ABVIs and GIs were approximately three and a half times and ten times more frequent in specimens with TB as the cause of death than in individuals with NTB causes of death, respectively. Moreover, the co-occurrence of APDIs, PAs, ABVIs, and GIs with each other was about five times more common in the TB group than in the NTB group; whereas their association with likely TB-related non-endocranial bony changes occurred approximately three times more often in specimens with TB as the cause of death than in individuals with NTB causes of death. The χ^2 comparison of the frequencies of APDIs, PAs, ABVIs, and GIs, as well as of their co-occurrence with each other and with probable TB-associated non-endocranial bony changes, revealed a statistically significant difference between the TB group and NTB group; therefore, similar to the results of previous studies, constituting evidence that there may be a correlation between APDIs, PAs, ABVIs, and GIs and TBM. Thus, they can be used as diagnostic criteria for TBM in the palaeopathological practice.

3) With respect to the macromorphological characteristics of APDIs, PAs, ABVIs, and GIs, in more than two-thirds of the selected skeletons from the *Terry Collection* that showed APDIs, the very slight stage of the aforementioned lesion was detected. As for the localisation of PAs, ABVIs, and GIs, findings of the current PhD dissertation were similar to those of previous studies: PAs and ABVIs were situated particularly in the frontal and parietal bones; whereas GIs were localised predominantly in the occipital and temporal bones, with the pattern and distribution of GIs resembling that of most frequently observed in the affected meninges during the pathogenesis of TBM. Regarding the extent of lesions, whereas the majority of the detected PAs and ABVIs covered less than one-half of the inner surfaces in all cranial bones examined, the extent of the endocranial surface area the observed GIs covered in the affected cranial bones only occasionally exceeded one-fourth of the inner surfaces. Concerning the number of lesions, PAs, ABVIs, and GIs were registered most commonly as multifocal alterations in all cranial bones evaluated.

4) In the present PhD dissertation, a number of example cases were provided that showed the most important macromorphological characteristics of APDIs, PAs, ABVIs, and GIs (*i.e.*, APDIs: prominence; PAs, ABVIs, and GIs: localisation, extent, and number of lesions in the affected cranial bone(s)), as well as of their co-occurrence with each other and/or with likely TB-related non-endocranial bony changes. Therefore, they may give a better insight

into the macromorphological characteristics of the above-mentioned lesions, and may provide palaeopathologists with a stronger basis for establishing a more reliable and accurate diagnosis of TBM in ancient human bone remains that exhibit bony changes resembling those of the example cases presented in the current PhD dissertation.

5) On the basis of the results obtained from the research project performed on selected skeletons from the *Terry Collection*, the diagnostic value of APDIs, PAs, ABVIs, and GIs in the palaeopathological identification of TBM is not equal. PAs may have the weakest diagnostic value. Even if they were detected in the TB group about twice as often as in the NTB group, the χ^2 comparison of the frequencies of PAs revealed a statistically only significant difference between the two groups; thus, suggesting a weaker correlation between PAs and TBM in comparison with APDIs, ABVIs or GIs. APDIs may have a stronger diagnostic value than PAs, since – similar to the PAs – they were registered in the TB group approximately twice as frequently as in the NTB group; but – in contrast to the PAs – the χ^2 comparison of the frequencies of APDIs revealed a statistically not only significant but extremely significant difference; therefore, indicating a stronger correlation between APDIs and TBM than between PAs and TBM. In comparison with PAs and APDIs, ABVIs may have a stronger diagnostic value, as they were about three and a half times more common in the TB group than in the NTB group; and – similar to the APDIs – the χ^2 comparison of the frequencies of ABVIs revealed a statistically extremely significant difference between the two groups; thus, suggesting a stronger correlation between ABVIs and TBM than between PAs or APDIs and TBM. Nevertheless, the findings of the present PhD dissertation fit in with those of previous studies concerning the specificity of PAs, APDIs, and ABVIs for TBM, as more than 10%, 30%, and 6% of the skeletons constituting the NTB group exhibited them on the inner surface of the skull, respectively; therefore, indicating that PAs, APDIs, and ABVIs cannot be considered as specific vestiges of TBM. Nonetheless, in about one-half of the specimens with PAs, APDIs or ABVIs in the NTB group, other probable TBM-related endocranial alterations and/or likely TB-associated non-endocranial bony changes were also noted. Since the disease registered as the cause of death on the morgue record and/or death certificate may not have been the only medical condition present in the surveyed individuals from the *Terry Collection*, specimens identified to have died of causes other than TB could still have suffered from TB at death. Thus, in the aforementioned cases with PAs, APDIs or ABVIs in the NTB group, the tuberculous origin of the recorded endocranial and non-endocranial lesions cannot be excluded. However, it is also possible that in these cases – similar to the other one-half of individuals with PAs, APDIs or ABVIs in the NTB group,

where no signs of other probable TBM-related endocranial alterations or of likely TB-associated non-endocranial bony changes were observed –, medical conditions other than TB might result in the development of the detected lesions.

Among the four evaluated endocranial alteration types, GIs may have the strongest diagnostic value, as they occurred about ten times more often in the TB group than in the NTB group; and – similar to the APDIs and ABVIs – the χ^2 comparison of the frequencies of GIs revealed a statistically extremely significant difference between GIs and TBM; therefore, suggesting a strong correlation between GIs and TBM. Furthermore, the results of the current PhD dissertation may support those of previous studies regarding the specificity of GIs for TBM, as – in contrast to the APDIs, PAs, and ABVIs – GIs affected only the minority of the skeletons composing the NTB group, and in the vast majority of the above-mentioned cases, probable TBM-associated endocranial alterations other than GIs and/or possible TB-related non-endocranial bony changes were also recorded. It must be noted that even if the registered cause of death of the surveyed individuals may not have been TB, specimens could still have suffered from the disease but their death was attributed to another medical condition; thus, it is very likely that in the above-mentioned cases, the observed endocranial and non-endocranial bony changes might result from TB.

In summary, even if PAs, APDIs, and ABVIs cannot be considered as pathognomonic features of TBM, palaeopathologists could still use them – with necessary circumspection – to identify the disease in osteoarchaeological material from the pre-antibiotic era, especially when they simultaneously occur with each other and/or with possible TB-related non-endocranial bony changes. Moreover, the findings of the present PhD dissertation may confirm that GIs can be considered as specific vestiges of TBM; and therefore, the palaeopathological diagnosis of TBM can be established with a high certainty when GIs are present in ancient human bone remains.

Finally, the results of the current PhD dissertation may provide palaeopathologists with a stronger basis for identifying TB in osteoarchaeological material from the pre-antibiotic era and with a more sensitive means of assessing the prevalence of the disease in past human populations. Nevertheless, further investigations on human skeletons of known cause of death from documented collections other than the *Terry Collection* are necessary to confirm the trends noted in the present research project. Refinement of macromorphological diagnostic criteria and their application in the palaeopathological practice may open new perspectives also in the research regarding the evolution of tuberculosis.

9 ÖSSZEFOGLALÓ

A tuberkulózis (tbc) az egyik legősibb fertőző megbetegedés, amely már évezredek óta sújtja az emberiséget és az állatvilágot. A paleopatológusok retrospektív módon, a modern orvosi szakirodalom alapján kísérelik meg a tbc diagnosztizálását a különböző régészeti korokból származó történeti népességekben azáltal, hogy a betegséggel összefüggésbe hozható csontléziókat azonosítanak az egykor élt emberek maradványain. Ugyanakkor a tbc modern diagnosztikai kritériumai nem feltétlenül alkalmazhatók a paleopatológiai gyakorlatban, mivel a recens esetekben megfigyelhető tbc-s eredetű csontelváltozások különbözhetnek a történeti embertani leleteken található lézióktól, többek között azért, mert antituberkulotikus szereket is használnak a tbc kezelésében, amelyek befolyásolhatják a betegség manifesztációját. Emellett a modern klinikai esetekben a csontok nem vizsgálhatók közvetlenül makroszkópos módszerekkel, csak orvosi képalkotó eljárásokkal, amelyek segítségével azonban a nagyon enyhe, kisméretű csontelváltozások sok esetben nem észlelhetők. Ennek következtében a tbc-hez köthető minor csontléziók nem feltétlenül kerülnek említésre a modern orvosi szakirodalomban, mivel nem relevánsak a betegség diagnózisának felállításában.

Mindazonáltal, a preantibiotikus érából származó, ismert halálozási okú egyének csontvázaiból álló, jól dokumentált oszteológiai gyűjtemények felbecsülhetetlen értékkel bírnak a különböző betegségek, így a tbc paleopatológiai gyakorlatban is alkalmazható diagnosztikai kritériumainak meghatározásában, mivel a tbc-ben elhalálozott és antituberkulotikus szerekkel nem kezelt egyének maradványain olyan, a tbc-vel összefüggésbe hozható csontelváltozások azonosíthatók, amelyek a történeti népességekben is megfigyelhetők. Emellett a fent említett gyűjteményekben őrzött csontvázleletek közvetlenül makroszkópos módszerekkel is vizsgálhatók, és a nagyon enyhe, kisméretű csontelváltozások is észlelhetők rajtuk. A múlt század vége óta számos, történeti embertani szériákon és dokumentált oszteológiai gyűjteményeken végzett paleopatológiai és paleomikrobiológiai tanulmány összefüggésbe hozta a tbc-s agyhártyagyulladást különböző, a koponya endocranialis felszínén megfigyelhető csontléziókkal, így a fokozott gödörkézettséggel (*abnormally pronounced digital impression* = APDI), a periostealis újcsontképződményekkel (*periosteal apposition* = PA), a rendellenes érbenyomatokkal (*abnormal blood vessel impression* = ABVI), valamint a granularis benyomatokkal (*granular impression* = GI). Azonban az említett endocranialis elváltozások diagnosztikai értékét a közelmúltban többen megkérdőjelezték, mivel a pontos etiológiájuk jelenleg nem ismert, és a tbc-s meningitis mellett több más megbetegedés is felelős lehet a kialakulásukért.

PhD értekezésem fő célja a paleopatológiai szakirodalomban korábban tbc-s agyhártyagyulladással összefüggésbe hozott endocranialis elváltozásokkal, valamint azok kialakulásával kapcsolatos ismereteink bővítése, továbbá a fent említett léziók mint a tbc paleopatológiai diagnosztizálása során alkalmazható kritériumok diagnosztikai értékének megerősítése.

Dolgozatom első fele a tbc-vel kapcsolatos modern orvosi és paleopatológiai szakirodalmat tekinti át, különös tekintettel a betegséghez köthető csontelváltozásokra. Az értekezés második része a *Robert J. Terry Anatomical Skeletal Collection* csontvázain végzett makromorfológiai és statisztikai elemzések eredményeit mutatja be, amelyek – a fent említett dokumentált oszteológiai gyűjteményen végzett paleopatológiai vizsgálatok közül elsőként – a tbc-s meningitis-hez köthető négyféle endocranialis léziótípus makromorfológiai jellegzetességeire, gyakoriságára, együttes előfordulására, valamint a tbc-vel összefüggésbe hozható nem-endocranialis elváltozásokkal való asszociációjára fókuszáltak. A vizsgálatok során a *Terry Collection*ben található 302 tbc-ben elhalálozott egyén csontváza (tbc-s csoport) mellett 302 véletlenszerűen kiválasztott, nem tbc-ben elhalálozott egyén csontvázát (nem tbc-s csoport) is kiértékeltem.

PhD értekezésem célkitűzései a következők:

1) A *Terry Collection* kiválasztott csontvázainak makromorfológiai elemzése a négyféle tbc-s agyhártyagyulladáshoz köthető endocranialis léziótípus, valamint azok együttes megjelenése és a tbc-vel összefüggésbe hozható nem-endocranialis elváltozásokkal való asszociációja szempontjából;
2) A négyféle vizsgált endocranialis léziótípus, valamint azok együttes megjelenése és a tbc-hez köthető nem-endocranialis elváltozásokkal való asszociációja gyakoriságának összehasonlítása a tbc-s és nem tbc-s csoportban, a kiválasztott egyének nemének és elhalálozási életkorának figyelembevételével;
3) A négyféle vizsgált endocranialis léziótípus makromorfológiai jellegzetességeinek (fokozott gödörkézettség: kifejezettség; periostealis újcsontképződmények, rendellenes érbenyomatok és granularis benyomatok: elhelyezkedés, kiterjedtség és léziók száma az érintett koponyacsontokon) kiértékelése;
4) A négyféle vizsgált endocranialis léziótípus legfontosabb makromorfológiai jellegzetességeit mutató, a *Terry Collection*ből származó példaesetek bemutatása; és
5) A négyféle vizsgált endocranialis léziótípus mint a tbc paleopatológiai diagnosztizálásában alkalmazható kritériumok diagnosztikai értékének elemzése.

PhD dolgozatom eredményei a következő fő pontokban foglalhatók össze:

1) A négyféle tbc-hez köthető endocranialis léziótípus közül legalább egyféle jelenlétét a *Terry Collection*ben vizsgált csontvázak mintegy kétharmadánál figyeltem meg. A leggyakoribb elváltozástípusnak a fokozott gödörkézettség (APDI) bizonyult. Periostealis újcsontképződményeket (PA), rendellenes érbenyomatokat (ABVI) és granularis benyomatokat (GI) a fokozott gödörkézettséghez képest kisebb, de egymáshoz hasonló arányban jegyeztem fel. A négyféle vizsgált endocranialis léziótípus együttes megjelenését, valamint a tbc-hez köthető nem-endocranialis elváltozásokkal való asszociációját a csontvázak mintegy egyharmadánál írtam le.

2) Mind a négy vizsgált endocranialis léziótípus előfordult a tbc-s és a nem tbc-s csoportban is, ugyanakkor valamennyi elváltozástípus gyakoribb volt a tbc-ben elhalálozott egyének körében: az APDI és a PA mintegy kétszer, az ABVI három és félszer, a GI pedig csaknem tízszer gyakrabban fordult elő a tbc-s csoportban, mint a nem tbc-s csoportban. Emellett a négyféle vizsgált endocranialis léziótípus együttes megjelenése és a tbc-hez köthető nem-endocranialis elváltozásokkal való asszociációja is gyakoribb volt a tbc-ben elhalálozott egyének körében: míg az előbbi mintegy ötször, az utóbbi mintegy háromszor gyakrabban fordult elő a tbc-s csoportban, mint a nem tbc-s csoportban. A χ^2-próba alapján a két vizsgálati csoport közötti különbség mind a négy vizsgált endocranialis léziótípus, valamint azok együttes előfordulása és a tbc-hez köthető nem-endocranialis elváltozásokkal való asszociációja tekintetében is szignifikáns volt, ami – a korábbi tanulmányok eredményeihez hasonlóan – arra utal, hogy van összefüggés az APDI, a PA, az ABVI, valamint a GI és a tbc között, így a fent említett elváltozások valóban alkalmazhatók diagnosztikai kritériumokként a tbc paleopatológiai diagnosztizálása során.

3) A négyféle vizsgált endocranialis léziótípus makromorfológiai jellegzetességeit tekintve elmondható, hogy a *Terry Collection*ben vizsgált egyének maradványain feljegyzett APDI kifejezettsége az esetek mintegy kétharmadában nagyon enyhe volt. A PA, az ABVI és a GI lokalizációjára vonatkozó megfigyeléseim alátámasztják a témában megjelent korábbi publikációk eredményeit: a PA és az ABVI a homlokcsonton és a falcsontokon, a GI pedig a nyakszirtcsonton és a halántékcsontokon fordult elő leggyakrabban, és az utóbbi léziótípus eloszlási mintázata nagyfokú hasonlóságot mutatott a tbc-s meningitis patogenezise során az agyhártyákon kialakuló tbc-s gümők eloszlási mintázatával. Míg a megfigyelt PA-k és ABVI-k többsége az érintett koponyacsontok endocranialis felszínének kevesebb, mint felét borította, addig a leírt GI-k által borított terület kiterjedtsége csak ritkán

lépte túl az érintett koponyacsontok endocranialis felszínének egynegyedét. A *Terry Collection* kiválasztott csontvázain talált PA-k, ABVI-k és GI-k többségét multifokális lézióként jegyeztem fel.

4) Doktori értekezésemben számos, a fokozott gödörkézettség (APDI), a periostealis újcsontképződmények (PA), a rendellenes érbenyomatok (ABVI) és a granularis benyomatok (GI) legfontosabb makromorfológiai jellegzetességeit mutató, a *Terry Collection*ből származó példaesetet ismertettem. A példák révén nagyobb betekintést nyerhetünk a négyféle vizsgált endocranialis léziótípus makromorfológiai megjelenési formáiba, emellett nagyobb megbízhatósággal és pontossággal állíthatjuk fel a tbc-s meningitis diagnózisát olyan történeti embertani leleteknél, amelyek a példaesetekben megfigyeltekhez hasonló endocranialis elváltozásokat mutatnak.

5) A *Terry Collection* kiválasztott csontvázain végzett makromorfológiai és statisztikai elemzések eredményei alapján mind a négy vizsgált endocranialis léziótípus alkalmazható diagnosztikai kritériumként a tbc-s agyhártyagyulladás paleopatológiai vizsgálata során, ugyanakkor az egyes elváltozástípusok diagnosztikai értéke különböző.

A legkisebb diagnosztikai értékkel a PA rendelkezik. Bár mintegy kétszeres gyakorisággal fordult elő a tbc-ben elhalálozott egyének körében, a χ^2-próba alapján a PA és a tbc közötti összefüggés gyengébb, mint a másik három endocranialis léziótípus esetén. Az APDI annak ellenére, hogy a PA-hoz hasonlóan mintegy kétszer gyakrabban fordult elő a tbc-s csoportban, mint a nem tbc-s csoportban, a χ^2-próba alapján erősebb összefüggést mutat a tbc-vel, mint a PA. A PA-hoz és az APDI-hoz viszonyítva az ABVI még erősebb diagnosztikai értékkel rendelkezik, mivel három és félszer gyakrabban fordult elő a tbc-ben elhalálozott egyének körében, és a χ^2-próba alapján az APDI-hoz hasonlóan erős összefüggés van a lézió előfordulása és a tbc között.

Mind a három endocranialis léziótípus előfordult a nem tbc-s csoportba tartozó egyének körében is (PA: ~10%, APDI: ~30%, ABVI: ~6%), ugyanakkor ezen esetek mintegy felében a PA, az APDI vagy az ABVI mellett más tbc-vel összefüggésbe hozható endocranialis elváltozástípust és/vagy nem-endocranialis léziót is megfigyeltem a maradványokon. A *Terry Collection* részét képező egyének boncolási jegyzőkönyvén és/vagy halotti bizonyítványán szereplő halálozási ok mellett az egyének más megbetegedésekben, így tbc-ben is szenvedhettek a haláluk idején, emiatt a fent említett esetekben a megfigyelt endocranialis és nem-endocranialis léziók tbc-s eredete sem zárható ki. Azonban az is lehetséges, hogy – azokhoz az esetekhez hasonlóan, ahol a PA-n, APDI-n vagy ABVI-n kívül semmilyen más tbc-vel összefüggésbe hozható endocranialis léziótípust

vagy nem-endocranialis elváltozást sem találtam – nem a tbc, hanem más megbetegedések álltak a leírt PA-k, APDI-k vagy ABVI-k kialakulása hátterében.

A négyféle vizsgált endocranialis léziótípus közül eredményeim alapján a GI bizonyult a legerősebb diagnosztikai értékűnek, mivel ez az elváltozástípus mintegy tízszer gyakrabban fordult elő a tbc-ben elhalálozott egyének körében, és az APDI-hoz és az ABVI-hoz hasonlóan a χ^2-próba is erős összefüggést mutatott a GI és a tbc között. Továbbá a PA-val, az APDI-val és az ABVI-val ellentétben a GI a nem tbc-ben elhalálozott egyének esetében csak elenyésző számban fordult elő, és egy eset kivételével a GI-n kívül más tbc-hez köthető endocranialis léziótípust és/vagy nem-endocranialis elváltozást is megfigyeltem a csontvázakon. Fontos megjegyezni, hogy a nem tbc-s csoportba tartozó egyének – annak ellenére, hogy boncolási jegyzőkönyvükön és/vagy halotti bizonyítványukon nem a tbc-t jelölték meg elhalálozási okként – a halálukat okozó megbetegedés mellett tbc-ben is szenvedhettek. Ebből kifolyólag a fent említett esetekben a megfigyelt endocranialis és nem-endocranialis léziók nagy valószínűséggel tbc-s eredetre vezethetők vissza.

Összegzésként elmondható, hogy a periostealis újcsontképződmények (PA), a fokozott gödörkézettség (APDI) és a rendellenes érbenyomatok (ABVI) nem tekinthetők patognomikus tbc-s csontelváltozásnak. Azonban megfelelő körültekintéssel mindhárom endocranialis léziótípus alkalmazható diagnosztikai kritériumként a tbc paleopatológiai diagnosztizálása során, különösen azokban az esetekben, ahol egymással és/vagy tbc-hez köthető nem-endocranialis elváltozásokkal együtt fordulnak elő a történeti embertani leleteken. A granularis benyomatok (GI) tbc-specifikusságára vonatkozóan értekezésem eredményei fontos bizonyítékot szolgáltatnak. A *Terry Collection* ismert halálozási okú leletein végzett vizsgálatok tanúsága alapján azokban az esetekben, ahol GI figyelhető meg a történeti embertani leleteken, nagy biztonsággal állítható fel a tbc-s meningitis paleopatológiai diagnózisa.

Végezetül, PhD értekezésem eredményei szilárdabb alapot biztosítanak a paleopatológusok számára a tbc diagnosztizálásában és a betegség prevalenciájának becslésében a különböző régészeti korokból származó történeti népességekben. Mindazonáltal, a jövőben további, a preantibiotikus érából származó, ismert halálozási okú egyének csontvázaiból álló, jól dokumentált oszteológiai gyűjtemények vizsgálatára is szükség van ahhoz, hogy megerősítést nyerjenek a *Terry Collection*ben végzett makromorfológiai és statisztikai elemzések során kirajzolódott trendek. A makromorfológiai diagnosztikai kritériumok finomítása és paleopatológiai gyakorlatban való alkalmazása új perspektívákat nyithat meg a tbc evolúciójának a kutatásában is.

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11 LIST OF PUBLICATIONS

MTMT ID: 10043233

1) THE 2 PAPERS PROVIDING BASIS FOR THE DISSERTATION–

Spekker O, Hunt DR, Váradi OA, Berthon W, Molnár E, Pálfi Gy. 2018. Rare manifestations of spinal tuberculosis in the Robert J. Terry Anatomical Skeletal Collection (National Museum of Natural History, Smithsonian Institution, Washington, DC, USA). *International Journal of Osteoarchaeology*, accepted.
IF_{2017}: 1.038

Molnár E, Donoghue HD, Lee OY-C, Wu HHT, Besra GS, Minnikin DE, Bull ID, Llewellyn G, Williams CM, **Spekker O**, Pálfi Gy. 2015. Morphological and biomolecular evidence for tuberculosis in 8th century AD skeletons from Bélmegyer-Csömöki domb, Hungary. *Tuberculosis* **95**(Suppl. 1): S35–S41. DOI: 10.1016/j.tube.2015.02.032 **IF_{2015}: 2.711**

2) PEER-REVIEWED JOURNAL ARTICLES–

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3) PAPERS PUBLISHED IN CONFERENCE PROCEEDINGS–

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APPENDIX

Supplementary table 1: Basic biographic data of specimens in the TB group (N=302).
(MR = morgue record; DC1 = death certificate primary; DC2 = death certificate secondary; DC3 = death certificate tertiary; c. = circa; F = female; M = male; + = included into the evaluation considering TBM-related endocranial alterations; – = excluded from the evaluation considering TBM-related endocranial lesions).

No.	Terry No.	Age at death	Sex	Cause of death				Included or not into the evaluation
				MR	DC1	DC2	DC3	
1	12	c. 61 years	F	TB	Pulmonary TB	–	–	–
2	13R	28 years	M	Pulmonary TB	–	Infection of the right toe	–	+
3	17R	c. 66 years	F	Pulmonary TB	Pneumonia	Pneumonitis	Psychosis, arteriosclerosis	–
4	23R	49 years	F	Pulmonary TB	–	–	–	+
5	30R	26 years	M	TB	–	TB meningitis	–	+
6	35R	60 years	M	Pulmonary TB	–	–	–	+
7	39	22 years	F	TB, pneumonia	Pneumonia	–	–	+
8	54	36 years	M	TB, diarrhoea	Pulmonary TB	–	–	+
9	84	c. 24 years	M	Pulmonary TB	Pulmonary TB	–	–	+
10	87R	73 years	F	Lues	Lues	Suspected TB	–	+
11	89R	c. 32 years	M	TB	–	–	–	+
12	90	18 years	M	–	Ichthyosis	Pulmonary TB	–	+

No.	Terry No.	Age at death	Sex	Cause of death				Included or not into the evaluation
				MR	DC1	DC2	DC3	
13	91R	c. 65 years	F	Pulmonary condition	Pulmonary TB	—	—	+
14	95	c. 35 years	F	Pulmonary TB	—	—	—	+
15	95R	c. 30 years	M	Pulmonary TB	—	—	—	+
16	103R	c. 74 years	F	—	Emphysema	TB	–	+
17	114	43 years	F	TB	—	—	—	+
18	125	31 years	M	Pulmonary TB	—	—	—	—
19	128	21 years	M	TB	Pulmonary TB	—	—	+
20	129	18 years	M	TB spondylitis	—	—	—	+
21	130	58 years	M	Pellagra	Pulmonary TB	—	Inanition	+
22	138	49 years	M	Pulmonary phthisis	Pulmonary TB	—	—	+
23	139	33 years	F	TB	Pulmonary TB	—	—	+
24	145R	31 years	M	Pulmonary TB	—	—	—	+
25	146R	30 years	F	Pulmonary TB	Pulmonary TB	—	Nephritis	+
26	158R	c. 32 years	F	TB	Pulmonary TB	—	—	+

No.	Terry No.	Age at death	Sex	Cause of death				Included or not into the evaluation
				MR	DC1	DC2	DC3	
27	182	43 years	M	Pulmonary TB	Pulmonary TB	–	–	+
28	194	73 years	M	Pulmonary TB	–	–	–	+
29	199R	c. 58 years	F	Pulmonary TB	–	–	–	–
30	204	24 years	M	Pulmonary TB	–	–	–	+
31	205	42 years	M	Pulmonary TB	Pulmonary TB	–	–	+
32	207	45 years	M	Pulmonary TB	–	–	–	+
33	220	c. 56 years	M	Pulmonary TB	–	–	–	+
34	222	20 years	M	Pulmonary TB	Pulmonary TB	–	–	+
35	230	37 years	M	Pulmonary TB	–	–	–	+
36	232R	c. 35 years	F	Pulmonary TB	–	–	–	+
37	235	29 years	M	–	Miliary TB	–	–	+
38	248R	70 years	F	Possible TB	Pneumonia	–	–	+
39	250	52 years	M	Laparotomy, stomach carcinoma	TB peritonitis	–	–	+
40	251	34 years	M	TB	Pulmonary TB	–	–	+

No.	Terry No.	Age at death	Sex	Cause of death				Included or not into the evaluation
				MR	DC1	DC2	DC3	
41	254	21 years	M	Pulmonary TB	—	—	—	+
42	255	22 years	F	Pulmonary TB	—	—	—	+
43	264	c. 67 years	M	TB, pneumonia	—	—	—	+
44	265	32 years	M	TB	—	—	—	+
45	267	c. 42 years	M	Pulmonary TB	—	—	—	+
46	269	20 years	M	TB	—	—	—	+
47	270	55 years	M	TB	—	—	—	+
48	279	34 years	M	Pulmonary TB	—	—	—	+
49	280	24 years	F	TB	—	—	—	+
50	282	57 years	M	Myocarditis	Pulmonary TB	Myocarditis	—	+
51	283R	40 years	M	TB, haemorrhage	Pulmonary TB	—	—	+
52	284	c. 67 years	M	TB	—	—	—	+
53	304	20 years	F	—	Pulmonary TB	—	—	+
54	306	18 years	F	Pulmonary TB	—	—	—	+

No.	Terry No.	Age at death	Sex	Cause of death				Included or not into the evaluation
				MR	DC1	DC2	DC3	
55	309	45 years	M	Pulmonary TB	Pulmonary TB	TB spondylitis	Mastoiditis, sinusitis	+
56	311R	27 years	M	TB	Epilepsy	Pulmonary TB	–	–
57	318	45 years	M	Pulmonary TB, myocarditis	Pulmonary TB	–	–	+
58	328R	65 years	F	Possible TB, pleurisy	Pulmonary carcinoma	Undetermined	–	+
59	329	18 years	M	Pulmonary TB, syphilis	Pulmonary TB	Syphilis	–	+
60	341	38 years	F	Pulmonary TB	–	–	–	+
61	353	c. 37 years	M	–	TB peritonitis	–	–	+
62	358R	c. 36 years	M	Pulmonary TB	–	–	–	+
63	382R	26 years	M	Pulmonary TB	–	–	–	+
64	385	21 years	M	–	Pulmonary TB	–	–	+
65	386R	66 years	M	Pulmonary TB	–	–	–	+
66	395	57 years	M	TB ulcers of the leg	Myocarditis	–	–	–
67	400	c. 44 years	M	TB	–	–	–	+
68	402	c. 50 years	M	TB	–	–	–	+

No.	Terry No.	Age at death	Sex	Cause of death				Included or not into the evaluation
				MR	DC1	DC2	DC3	
69	410R	35 years	M	—	Pulmonary TB	—	—	+
70	413	55 years	M	Pulmonary TB	—	—	—	—
71	414	39 years	M	Pulmonary TB	—	—	—	—
72	423	c. 24 years	M	TB, pericarditis	—	—	—	+
73	424	c. 30 years	M	TB, silicosis	—	—	—	+
74	426R	70 years	M	Cardiorenal disease	Arteriosclerosis	Pulmonary TB	*Diabetes mellitus*	+
75	432	67 years	M	Destructive nasal lesion	TB abscess	Pulmonary TB	—	+
76	434	41 years	M	Pulmonary TB	—	—	—	—
77	444	c. 26 years	M	TB	Pulmonary TB	—	—	+
78	466	31 years	M	Pulmonary TB	—	—	—	+
79	468	23 years	M	Pulmonary TB, TB spondylitis	—	—	—	+
80	490	c. 38 years	M	TB	—	Hepatic cirrhosis	—	+
81	491R	63/71 years	F	Pulmonary TB	Arteriosclerosis	—	—	—
82	504	c. 41 years	M	TB, bronchitis	Pulmonary TB	—	—	+

No.	Terry No.	Age at death	Sex	Cause of death				Included or not into the evaluation
				MR	DC1	DC2	DC3	
83	508	c. 60 years	M	Pulmonary TB	–	–	–	–
84	522	30 years	M	Pulmonary TB	–	–	–	+
85	523	47 years	M	Pulmonary TB	–	–	–	+
86	537	c. 48 years	M	Possible malaria	TB meningitis	–	–	+
87	541	28 years	F	Pulmonary TB	–	–	–	+
88	549	33 years	M	Myocarditis	Pulmonary TB	–	–	+
89	555	56 years	M	Pulmonary TB	–	–	–	+
90	562	17 years	F	Pulmonary TB	–	–	–	+
91	565	c. 32 years	M	Pulmonary TB	–	–	–	+
92	566	40 years	M	Empyema	Empyema	Possible TB	–	+
93	568	28 years	F	Pulmonary TB	–	–	–	+
94	571	31 years	M	TB	–	–	–	+
95	572	60 years	M	Pulmonary TB	–	–	–	+
96	575	c. 47 years	M	Pulmonary TB	–	–	–	+

No.	Terry No.	Age at death	Sex	Cause of death				Included or not into the evaluation
				MR	DC1	DC2	DC3	
97	583	24 years	F	Pulmonary TB	—	—	—	+
98	585	64 years	M	Pulmonary TB	—	—	—	+
99	592	25 years	M	Pulmonary TB	—	—	—	+
100	593	44 or 74 years	M	TB, pneumonia	Pneumonia	—	—	—
101	595	25 years	M	Pulmonary TB	—	—	—	+
102	614	50 years	M	TB	Pulmonary TB	Pneumonia	—	—
103	620	c. 55 years	M	Pulmonary TB	—	Myocarditis	—	+
104	621R	29 years	M	Pulmonary TB	Pulmonary TB	TB emphysema	—	+
105	626R	c. 56 years	F	Pulmonary TB	—	—	—	+
106	632	27 years	F	Pulmonary TB	—	—	—	—
107	645	29 years	M	Pulmonary TB	—	—	—	—
108	656	43 years	M	Bronchitis	Miliary TB	—	—	—
109	660	c. 28 years	M	Pulmonary TB	—	—	—	—
110	663	c. 44 years	M	Syphilis	Aortic aneurysm	Miliary TB	Syphilis	–

No.	Terry No.	Age at death	Sex	Cause of death				Included or not into the evaluation
				MR	DC1	DC2	DC3	
111	664	c. 48 years	M	Pulmonary TB	Pulmonary TB	Pneumonia	—	+
112	669R	72 years	M	Heart disease	Pulmonary TB	Arteriosclerosis	Heart disease	+
113	675	27 years	M	Pulmonary TB	—	—	—	—
114	679	33 years	F	TB	—	—	—	+
115	680	30 years	F	Pulmonary TB	Pulmonary TB	TB peritonitis	—	+
116	706	38 years	F	Pulmonary TB, rectal disease	Syphilis	Lues	–	—
117	707	c. 26 years	M	Pulmonary TB	—	—	—	—
118	711	61 years	M	TB, peritonitis	—	—	—	—
119	725	57 years	M	Pulmonary TB	—	—	—	—
120	728R	76 years	F	Pulmonary TB, senility	—	—	—	+
121	739	40 years	M	TB, *diabetes mellitus*	Pulmonary TB	*Diabetes mellitus*	—	+
122	740R	18 years	M	TB, peritonitis	—	—	—	—
123	745R	c. 34 years	F	TB	—	—	—	—
124	752	71 years	M	TB, pneumonia	Pneumoconiosis	Myocarditis	Arteriosclerosis	+

No.	Terry No.	Age at death	Sex	Cause of death				Included or not into the evaluation
				MR	DC1	DC2	DC3	
125	757	59 years	M	Pulmonary TB	–	–	–	+
126	760	18 years	M	TB spondylitis	–	–	–	–
127	761	c. 81 years	F	Pulmonary TB	Pulmonary TB	Myocarditis	–	+
128	764	c. 58 years	M	Pulmonary TB	–	–	–	–
129	770	65 years	M	Cardiorenal disease	Myocarditis	Pulmonary TB	–	–
130	771	c. 49 years	M	Pulmonary TB	–	–	–	+
131	772	c. 55 years	M	Pulmonary TB, cirrhosis, myocarditis	Myocarditis	–	–	–
132	776	c. 40 years	M	Pulmonary TB	–	–	–	+
133	786	65 years	M	Pulmonary TB	–	–	–	+
134	799	38 years	M	TB	–	–	–	+
135	802	c. 36 years	M	Pulmonary TB	–	–	–	–
136	810	c. 54 years	M	TB	–	–	–	–
137	820R	52 years	M	Pulmonary TB	–	–	–	+
138	821	25 years	M	Pulmonary TB	–	–	–	–

No.	Terry No.	Age at death	Sex	Cause of death				Included or not into the evaluation
				MR	DC1	DC2	DC3	
139	822	16 years	F	Pulmonary TB	–	–	–	+
140	826	38 years	M	Pulmonary TB	–	–	–	–
141	828	46 years	M	TB	–	–	–	+
142	830	28 years	M	TB	–	–	–	–
143	844	26 years	F	Pulmonary TB	–	–	–	+
144	846	48 years	M	Pulmonary TB	–	–	–	+
145	850	23 years	M	Pulmonary TB	–	–	–	–
146	859	c. 23 years	M	Pulmonary TB	–	–	–	–
147	871	c. 56 years	M	Pulmonary TB	–	–	–	–
148	876	c. 22 years	M	Pulmonary TB	–	–	–	+
149	885	26 years	M	Pulmonary TB	–	–	–	–
150	886	c. 23 years	F	Pulmonary TB	–	–	–	–
151	892	c. 59 years	M	Heart disease	Emphysema	Pulmonary TB	–	+
152	895	47 years	M	TB	–	–	–	+

No.	Terry No.	Age at death	Sex	Cause of death				Included or not into the evaluation
				MR	DC1	DC2	DC3	
153	896RR	26 years	F	Pulmonary TB	–	–	–	+
154	897	43 years	M	Pulmonary TB	Pulmonary TB	Myocarditis	–	+
155	902	c. 36 years	M	Pulmonary TB	–	–	–	+
156	905	31 years	M	Pulmonary TB	–	–	–	–
157	907	41 years	F	Pulmonary TB	–	–	–	+
158	914	30 years	M	TB	–	–	–	+
159	915	27 years	M	Pulmonary TB	–	–	–	+
160	918	c. 40 years	M	TB, meningitis	–	–	–	–
161	925	c. 71 years	F	TB	Pulmonary TB	Nephritis	Myocarditis	–
162	929	c. 20 years	F	Pulmonary TB	–	–	–	–
163	932	27 years	M	Pulmonary TB	–	–	–	+
164	933R	40 years	M	Probable TB, ascites	TB peritonitis	–	–	+
165	936	56 years	M	Pulmonary TB	–	–	–	+
166	940	24 years	M	TB	–	–	–	–

No.	Terry No.	Age at death	Sex	Cause of death				Included or not into the evaluation
				MR	DC1	DC2	DC3	
167	950	59 years	M	Pulmonary TB	–	–	–	+
168	952	41 years	F	TB	–	–	–	+
169	955	26 years	M	Pulmonary TB	–	–	–	+
170	957	56 years	F	Chest contusion	Pulmonary TB	–	–	+
171	960	17 years	M	Pulmonary TB	–	–	–	–
172	970	21 years	F	Pulmonary TB	–	–	–	–
173	975	60 years	M	TB, cardiac decompensation	Myocarditis	–	–	+
174	980	63 years	M	Pulmonary TB	–	–	–	–
175	981	31 years	M	TB	–	–	–	–
176	987	23 years	M	Pulmonary TB	–	–	–	+
177	1002	50 years	M	Pulmonary TB	–	–	–	+
178	1005	52 years	M	Pulmonary TB	–	–	–	+
179	1007R	39 years	M	Pulmonary TB	–	–	–	–
180	1013	c. 30 years	M	Pulmonary TB	–	–	–	+

No.	Terry No.	Age at death	Sex	Cause of death				Included or not into the evaluation
				MR	DC1	DC2	DC3	
181	1018	30 years	M	Pulmonary TB	–	–	–	+
182	1020	24 years	M	Pulmonary TB	–	–	–	+
183	1027	c. 41 years	F	Pulmonary TB	–	–	–	+
184	1030	62 years	M	–	Pulmonary TB	–	–	+
185	1031	27 years	M	Pneumonia	Pulmonary TB	–	–	+
186	1033	26 years	M	Pulmonary TB	–	–	–	+
187	1034	48 years	F	Pulmonary TB	TB nephritis	–	–	+
188	1036	38 years	M	Asthma, heart disease	Pulmonary TB	–	–	+
189	1043	46 years	M	Pulmonary TB	–	–	–	+
190	1047	c. 61 years	M	TB	–	–	–	+
191	1048	39 years	M	TB	–	–	–	+
192	1057	35 years	M	Pulmonary TB	–	–	–	+
193	1064	33 years	F	TB, pneumonia	–	–	–	–
194	1072	56 years	M	Pulmonary TB	–	–	–	+

No.	Terry No.	Age at death	Sex	Cause of death				Included or not into the evaluation
				MR	DC1	DC2	DC3	
195	1076	25 years	F	Pulmonary TB	Pulmonary TB	Pulmonary oedema	–	+
196	1086	45 years	M	Pulmonary TB	–	–	–	+
197	1093	29 years	M	Pulmonary TB	–	–	–	+
198	1095	61 years	M	Pulmonary TB	–	–	–	+
199	1096R	40 years	M	Pulmonary TB	–	–	–	+
200	1105	22 years	F	Pulmonary TB	–	–	–	+
201	1106	28 years	M	TB spondylitis, heart disease	TB spondylitis	–	–	+
202	1113	29 years	M	Pulmonary TB	Myocarditis	–	–	+
203	1122	29 years	F	Pulmonary TB	–	–	–	+
204	1124R	49 years	F	Pulmonary TB	–	–	–	+
205	1129	50 years	F	Pulmonary TB	–	–	–	+
206	1132	67 years	M	Pulmonary TB	–	–	–	+
207	1147R	32 years	M	Pleural expansion	Possible TB, pleural effusion	–	–	+
208	1149R	c. 44 years	M	Pulmonary TB	–	–	–	–

No.	Terry No.	Age at death	Sex	Cause of death				Included or not into the evaluation
				MR	DC1	DC2	DC3	
209	1156	c. 56 years	M	Pulmonary TB	–	–	–	+
210	1157	40 years	M	Pulmonary TB	–	–	–	+
211	1159	26 years	M	Pulmonary TB	–	–	–	+
212	1165	c. 26 years	M	Pulmonary TB	–	–	–	+
213	1168	34 years	M	Pulmonary TB	–	–	–	–
214	1169	28 years	M	Pulmonary TB	–	–	–	+
215	1173	38 years	F	Pulmonary TB	–	–	–	+
216	1183	c. 21 years	M	Pneumonia	Pulmonary TB	Pleurisy	–	+
217	1185	33 years	M	Pulmonary TB	Pulmonary haemorrhage	Pulmonary TB	–	+
218	1187	21 years	M	Pulmonary TB	–	–	–	+
219	1190	c. 64 years	M	Pulmonary TB	–	–	–	+
220	1205	38 years	M	Pulmonary TB	–	–	–	+
221	1210	46 years	F	TB	Pulmonary TB	–	–	+
222	1215	25 years	F	Pulmonary TB	Pulmonary TB	Child birth	–	+

No.	Terry No.	Age at death	Sex	Cause of death				Included or not into the evaluation
				MR	DC1	DC2	DC3	
223	1222	28 years	F	Pulmonary TB	—	—	—	+
224	1226	c. 48 years	M	Pulmonary TB	—	—	—	+
225	1230	53 years	M	Cysto-urethro-rectocele with ascites	Pulmonary TB	Pneumothorax	Cirrhosis, myocarditis	+
226	1236	36 years	F	TB	—	—	—	+
227	1247	53 years	M	TB	—	—	—	+
228	1249R	40 years	F	—	Pulmonary TB	—	—	+
229	1255	39 years	M	TB sinusitis	TB of the hips	*Delirium tremens*	—	+
230	1263R	53 years	M	Pulmonary TB	—	—	—	+
231	1264	45 years	M	Pulmonary TB	—	—	—	+
232	1266R	c. 77 years	M	Senility, lues	Pulmonary TB	Syphilis	Parkinson's disease, arteriosclerosis	+
233	1275	c. 59 years	M	Pulmonary TB, myocarditis	Pneumonia	Arteriosclerosis	—	+
234	1276	82 years	M	Pulmonary TB	—	—	—	—
235	1278	45 years	M	Pulmonary TB	—	—	—	+
236	1282	61 years	M	Myocarditis	Pulmonary TB	Myocarditis	—	+

No.	Terry No.	Age at death	Sex	Cause of death				Included or not into the evaluation
				MR	DC1	DC2	DC3	
237	1285	36 years	M	TB	—	—	—	+
238	1287	24 years	F	Pulmonary TB	—	—	—	+
239	1289R	28 years	F	Nephritis	TB nephritis	—	—	—
240	1293	51 years	M	Miliary TB	—	—	—	—
241	1300	28 years	M	TB	—	—	—	+
242	1304R	58 years	M	Pulmonary TB	Pulmonary TB	Pericardial effusion	—	+
243	1306	36 years	F	TB	—	—	—	—
244	1309	36 years	M	Neurological condition	TB spondylitis	Nephritis	Paralysis of the lower extremities	+
245	1313	63 years	M	TB	Syphilis	Pulmonary TB	Myocarditis, arteriosclerosis	+
246	1315	43 years	M	TB	—	—	—	+
247	1316R	c. 95 years	F	Hand & knee TB, senility	Pneumonia	Heart disease, nephritis	—	—
248	1318	43 years	M	Pulmonary TB	—	—	—	+
249	1319	c. 36 years	M	Pulmonary TB	Pulmonary TB	Syphilis	—	+
250	1322	34 years	M	Pulmonary TB	—	—	—	+

No.	Terry No.	Age at death	Sex	Cause of death				Included or not into the evaluation
				MR	DC1	DC2	DC3	
251	1331	41 years	M	Pulmonary TB	–	–	–	+
252	1337RR	35 years	F	Psychosis	Pulmonary TB	Brain syndrome	–	+
253	1346	73 years	M	Lung abscess	Pulmonary TB	–	–	+
254	1351	23 years	F	Pulmonary TB	–	–	–	–
255	1352	28 years	M	Pulmonary TB	–	–	–	+
256	1356	35 years	F	Pulmonary TB	–	–	–	–
257	1359	52 years	M	Bronchitis, alcoholism	Pulmonary TB	–	–	+
258	1361	52 years	M	TB meningitis	–	–	–	–
259	1362	36 years	M	Pulmonary TB	–	–	–	+
260	1363	24 years	F	Pulmonary TB	–	–	–	–
261	1367	32 years	M	Pulmonary TB	–	–	–	+
262	1369	52 years	M	Pulmonary TB	–	–	–	+
263	1377	c. 52 years	F	Haemorrhage	Haemorrhage into the right ventricle	TB meningitis	–	+
264	1379	c. 54 years	M	Myocarditis	Myocarditis	Pulmonary TB	–	+

No.	Terry No.	Age at death	Sex	Cause of death				Included or not into the evaluation
				MR	DC1	DC2	DC3	
265	1388	29 years	M	Pulmonary TB	Pulmonary TB	TB peritonitis	Cardiac decompensation	+
266	1397	35 years	M	TB	—	—	—	+
267	1398	31 years	M	TB, meningitis	—	—	—	+
268	1401	47 years	F	Pulmonary TB	—	—	—	+
269	1406	63 years	F	TB	—	—	—	+
270	1407	44 years	M	TB	—	—	—	+
271	1419	54 years	F	Pulmonary TB	—	—	—	+
272	1422R	c. 35 years	M	Pulmonary TB	—	—	—	+
273	1428R	71 years	M	Pulmonary TB	—	—	—	+
274	1434R	19 years	F	Pulmonary TB	—	—	—	+
275	1451	36 years	M	TB	—	—	—	+
276	1453R	58 years	M	Pulmonary TB	—	—	—	+
277	1455	68 years	M	TB	TB	Pneumonia	—	+
278	1458	37 years	M	Pulmonary TB	—	—	—	+

No.	Terry No.	Age at death	Sex	Cause of death				Included or not into the evaluation
				MR	DC1	DC2	DC3	
279	1468	41 years	F	TB, pneumonia	–	–	–	–
280	1469	42 years	M	TB, *diabetes mellitus*	–	–	–	–
281	1476	51 years	F	Pulmonary TB, TB adenitis	–	–	–	+
282	1486R	51 years	M	*Diabetes mellitus*	Pulmonary TB	*Diabetes mellitus*	–	–
283	1500	24 years	F	Pulmonary phthisis	Pulmonary TB	–	–	–
284	1503	22 years	M	Pulmonary TB	–	–	–	+
285	1506	26 years	M	Pulmonary TB	–	–	–	–
286	1507	23 years	F	Pulmonary TB, heart disease	–	–	–	+
287	1508	55 years	M	Pulmonary TB	–	–	–	–
288	1521	54 years	M	Pulmonary TB	–	–	–	+
289	1529	c. 28 years	M	TB	Pulmonary TB	–	–	–
290	1531	40 years	M	Pulmonary TB	–	–	–	+
291	1533	45 years	M	Pulmonary TB	–	–	–	+
292	1536	71 years	F	Pulmonary TB	–	–	–	+

No.	Terry No.	Age at death	Sex	Cause of death				Included or not into the evaluation
				MR	DC1	DC2	DC3	
293	1539	23 years	M	Pulmonary TB	—	—	—	+
294	1544	c. 24 years	F	TB	Pulmonary TB	—	—	+
295	1551	25 years	F	?	Salpingitis	TB peritonitis	—	+
296	1553	30 years	F	Possible TB, heart disease	Nephritis	–	—	+
297	1555	41 years	F	Pulmonary TB	—	—	—	+
298	1562	46 years	F	Pulmonary TB	—	—	—	+
299	1568	c. 62 years	F	TB	Pulmonary TB	—	—	+
300	1572	c. 44 years	F	Pulmonary TB	—	—	—	+
301	1576	69 years	F	Pulmonary TB	Pulmonary TB	Schizophrenic reaction	—	+
302	1629	80 years	F	Pneumonia	Pulmonary TB	—	—	+

Supplementary table 2: Basic biographic data of specimens in the NTB group (N=302).
(MR = morgue record; DC1 = death certificate primary; DC2 = death certificate secondary; DC3 = death certificate tertiary; c. = circa; F = female; M = male; + = included into the evaluation considering TBM-related endocranial alterations; – = excluded from the evaluation considering TBM-related endocranial lesions).

No.	Terry No.	Age at death	Sex	Cause of death				Included or not into the evaluation
				MR	DC1	DC2	DC3	
1	4R	40 years	M	Antral carcinoma	–	Metastasis of the left orbit	–	+
2	5	67 years	M	Cardiac decompensation	Arteriosclerotic heart disease	Congestive heart failure	–	–
3	12R	46 years	F	Rectal cancer	–	–	–	+
4	15RRR	c. 72 years	F	Myocardial infarction	–	–	–	–
5	19R	c. 69 years	F	Hypertensive heart disease	Hypertensive heart disease	–	–	+
6	25	c. 65 years	F	–	–	–	–	+
7	25R	c. 43 years	F	Alcoholism	Pulmonary oedema	Cerebral oedema	Alcoholism	+
8	31R	c. 38 years	M	Stab wound	Cardiac thrombosis	Septic stab wound in the right arm	–	+
9	44R	c. 72 years	F	Cerebral vascular disease	Cerebral vascular accident	Hypertensive heart disease	–	+
10	46R	c. 67 years	F	Accident	Pneumonia	Subdural haemorrhage from fall	–	+
11	47R	78 years	F	Pneumonia	–	–	–	+
12	53R	c. 60 years	F	Myocarditis	–	Arteriosclerosis	–	–

No.	Terry No.	Age at death	Sex	Cause of death				Included or not into the evaluation
				MR	DC1	DC2	DC3	
13	58R	c. 70 years	F	Cardiorenal disease	Hypertensive heart disease	–	–	+
14	61	c. 74 years	M	Senility, hypertrophic arthritis	Myocarditis	Hypertrophic arthritis	–	–
15	62RR	c. 38 years	M	–	–	–	–	+
16	64R	57 years	F	Cervical cancer	Cancerous cervix with metastasis	–	–	+
17	67R	74 years	F	Arteriosclerotic heart disease	Hypertensive heart disease	–	–	–
18	69	75 years	F	Breast cancer, pneumonia	–	Pneumonia	–	+
19	75R	c. 70 years	F	–	Nephritis	Arteriosclerotic heart disease	–	–
20	76R	c. 62 years	F	Brain oedema	Myocarditis	Pleural effusion	–	+
21	79R	c. 52 years	F	Nephritis	Nephritis	–	–	+
22	86R	71 years	F	Congestive heart disease	Arteriosclerotic heart disease	–	–	–
23	92R	67 years	F	Cerebral thrombosis	–	–	–	–
24	96R	c. 83 years	F	Cerebral arteriosclerosis	–	–	–	–
25	104RR	c. 80 years	F	–	Cerebral vascular accident	Arteriosclerotic heart disease	–	+
26	105R	81 years	F	Heart failure	–	Arteriosclerosis	–	+

No.	Terry No.	Age at death	Sex	Cause of death				Included or not into the evaluation
				MR	DC1	DC2	DC3	
27	112R	c. 59 years	F	Rectal cancer	—	—	—	+
28	117R	81 years	F	Pneumonia	—	Fractured neck & femur	Senile psychosis	—
29	124R	61 years	F	Congestive heart failure	Hypertensive heart disease	Nephritis	—	+
30	127R	c. 72 years	F	Scleroderma	—	—	—	+
31	132R	39 years	F	Heart disease	—	Nephritis	—	+
32	134	53 years	F	Pneumonia	Pneumonia	—	—	+
33	135R	c. 43 years	F	Heart failure	Coronary thrombosis	—	psychosis, *Dementia precox*	+
34	140RR	c. 56 years	F	Pneumonia	—	—	—	+
35	141R	c. 83 years	F	Cerebral accident	Arteriosclerotic heart disease	—	—	+
36	142R	c. 82 years	F	Pneumonia	—	Fractured hip	Senility	+
37	143	58 years	M	Cardiac decompensation	Hypertensive heart disease	—	—	—
38	149R	70 years	F	Nephritis	Uraemia	Arteriosclerosis	Hypertensive heart disease, psychosis	+
39	159R	c. 68 years	F	Pneumonia	—	—	—	—
40	167	77 years	M	Cardiorenal disease	Myocarditis	Lues	—	+

No.	Terry No.	Age at death	Sex	Cause of death				Included or not into the evaluation
				MR	DC1	DC2	DC3	
41	177R	c. 33 years	F	Haemorrhage	Left lung haemorrhage	–	–	+
42	178R	c. 60 years	F	Hypertensive encephalopathy	Cerebral thrombosis	Hypertension	–	+
43	179R	c. 76 years	F	Myocarditis	–	–	–	+
44	197R	60 years	F	Breast carcinoma	–	–	–	+
45	199	c. 70 years	F	Heart failure	Myocarditis	Senility	–	+
46	209	38 years	M	Pneumonia	–	–	–	+
47	213	29 years	M	Nephritis	Nephritis	Urethral fistulae	–	–
48	218	56 years	F	*Diabetes mellitus*, asthma	–	–	–	+
49	221	c. 47 years	M	Intestinal obstruction	–	–	–	+
50	227	57 years	M	Syphilis	–	–	–	+
51	231	c. 60 years	M	Syphilis, senility	Breast carcinoma	Syphilis, senility	–	+
52	237	70 years	M	Hypopyon ulcer of the eye	–	Pneumonia	–	+
53	239R	c. 50 years	F	–	Myocarditis	WMA	–	–
54	243R	c. 74 years	F	*Diabetes mellitus*	Myocardial infarction	*Diabetes mellitus*	–	+

No.	Terry No.	Age at death	Sex	Cause of death				Included or not into the evaluation
				MR	DC1	DC2	DC3	
55	244	c. 66 years	M	Autopsy	Nephritis	–	–	–
56	247R	90 years	F	Myocardial failure	–	–	–	+
57	249R	81 years	F	–	Cardiac dilatation	Myocarditis	–	+
58	259	52 years	M	Pneumonia	–	–	–	+
59	268	62 years	M	Senility	Myocarditis	–	–	+
60	272	49 years	F	Cardiac decompensation, nephritis	–	–	–	+
61	285	54 years	M	Pneumonia	–	–	–	+
62	289R	47 years	F	Nephritis	–	Laennec's cirrhosis	–	–
63	290R	c. 65 years	M	–	–	–	–	–
64	293R	c. 54 years	F	Coronary occlusion	Coronary sclerosis	–	–	+
65	296R	69 years	M	Myocarditis	–	–	–	+
66	298	c. 53 years	M	–	–	–	–	+
67	306R	c. 50 years	F	Hepatic cirrhosis	Brain oedema	Hepatic cirrhosis	–	+
68	312R	64 years	F	Hepatic cirrhosis	–	–	–	–

No.	Terry No.	Age at death	Sex	Cause of death				Included or not into the evaluation
				MR	DC1	DC2	DC3	
69	314	65 years	M	Senility, pneumonia	—	Myocarditis	—	+
70	317	84 years	M	Arteriosclerosis	—	—	—	+
71	338	65 years	M	Pneumonia, myocarditis, senility	—	—	—	+
72	339R	67 years	F	Myocarditis	—	—	—	+
73	344R	52 years	F	Pneumonia	Nephritis	—	—	+
74	347	c. 73 years	M	Syphilis	—	Syphilis	—	+
75	348R	c. 28 years	F	Eclampsia	Nephritis	Pregnancy with eclampsia	—	+
76	349R	c. 50 years	F	Pneumonia	—	—	—	—
77	360	c. 46 years	M	Knee sarcoma with metastasis	—	—	—	—
78	363	c. 65 years	M	Cardiac condition, senility	Myocarditis	Apoplexy, cerebral haemorrhage	—	—
79	369	76 years	M	Fractured skull, senility	—	Myocarditis	Nephritis	—
80	379	58 years	M	Carcinoma of the cervical glands	—	—	—	—
81	391	50 years	M	Gangrenous toes	*Diabetes mellitus*	—	—	—
82	393RR	c. 58 years	F	Accident	Pneumonia	Femur fracture	—	+

No.	Terry No.	Age at death	Sex	Cause of death				Included or not into the evaluation
				MR	DC1	DC2	DC3	
83	397	60 years	M	Uraemia	Syphilis	Myocarditis	Nephritis	+
84	403	52 years	M	Cardiorenal disease	Myocarditis	Nephritis	–	+
85	405R	c. 34 years	F	Hepatic abscess	–	–	–	–
86	408R	74 years	F	Arteriosclerosis	–	–	–	–
87	418R	75 years	F	Congestive heart disease	Hypertensive heart disease	Arteriosclerosis	–	–
88	422	c. 20 years	M	Pneumonia	–	–	–	+
89	431	42 years	M	Cholecystectomy	–	Pneumonia	–	–
90	433	c. 59 years	M	Railroad accident	–	–	–	–
91	437R	c. 44 years	F	Pneumonia	–	–	–	+
92	438	c. 86 years	M	–	–	–	–	+
93	445	66 years	M	Ruptured gastric ulcer, peritonitis	–	–	–	+
94	447	49 years	M	–	Nephritis	–	–	+
95	452	c. 61 years	M	Syphilis, senility	Syphilis	Nephritis	–	+
96	453	c. 42 years	M	Gangrenous bowel	Strangulated inguinal hernia	–	–	+

No.	Terry No.	Age at death	Sex	Cause of death				Included or not into the evaluation
				MR	DC1	DC2	DC3	
97	458	41 years	M	Haemorrhoids	Nephritis	—	—	+
98	463	c. 50 years	M	Myocarditis, rheumatism	—	—	—	+
99	465	25 years	M	Post-operative wound of the chest	Aortic aneurysm	—	—	+
100	470	c. 44 years	M	Cardiorenal disease	—	—	—	+
101	477	22 years	M	Paralysis of the lower extremities	Toxaemia from bed sores	Septicaemia from ulcers of the buttocks	—	+
102	483	44 years	M	Pneumonia	—	—	—	+
103	484R	73 years	F	—	Myocarditis	Arteriosclerosis	—	—
104	487	c. 42 years	F	Toxaemia of pregnancy	Eclampsia	—	—	—
105	488	c. 40 years	F	Hemiplegia	—	—	—	—
106	496	54 years	M	Pellagra	—	—	—	+
107	497	c. 72 years	M	Nephritis	—	—	—	+
108	501	77 years	M	Valvular disease	Arteriosclerosis	—	—	—
109	506	48 years	M	Myocarditis	Asthma	Myocarditis	—	+
110	511	34 years	F	Syphilis	—	—	—	—

No.	Terry No.	Age at death	Sex	Cause of death				Included or not into the evaluation
				MR	DC1	DC2	DC3	
111	512	c. 50 years	F	Mental condition	Myocarditis	Pneumonia	–	+
112	513RR	c. 38 years	F	–	Haemorrhagic pachyonychia	–	–	+
113	520	c. 27 years	F	–	–	–	–	–
114	526R	c. 78 years	F	Arteriosclerotic heart disease	–	–	–	–
115	527	c. 54 years	M	Intestinal carcinoma	Diarrhoea	Enteritis	Myocarditis	+
116	528	c. 64 years	F	Cerebral haemorrhage	Myocarditis	–	–	+
117	534	c. 50 years	M	Stenosis	–	–	–	+
118	536	60 years	M	Cerebral haemorrhage	–	Arteriosclerosis	–	+
119	545	77 years	M	Heart disease	Myocarditis	Arteriosclerosis	–	+
120	552	72 years	M	Myocarditis	Nephritis	Myocarditis	–	+
121	573	59 years	M	Syphilis	–	–	–	+
122	582	c. 49 years	M	Pneumonia	–	–	–	+
123	586	40 years	F	Cardiorenal disease	Nephritis	–	–	+
124	597	c. 61 years	M	Myocarditis	Valvular heart disease	–	–	+

No.	Terry No.	Age at death	Sex	Cause of death				Included or not into the evaluation
				MR	DC1	DC2	DC3	
125	602	49 years	M	Pleurisy	Influenza	Pulmonary infarct & abscess	Pulmonary haemorrhage	+
126	608	45 years	M	Pneumonia, mitral regurgitation	Myocarditis	Nephritis	—	+
127	615	35 years	F	Salpingectomy	Pneumonia	Hysterectomy for fibroid uterus	—	—
128	616R	c. 55 years	F	Possible uraemia	Hypertensive heart disease	—	—	—
129	617	90 years	F	Senility, myocarditis	Myocarditis	—	—	—
130	617R	43 years	F	Pneumonia	—	Encephalic malacia	—	+
131	619	31 years	M	Pneumonia	Pneumonia	—	—	—
132	627R	c. 27 years	F	Poisoning	Arsenical poisoning	Neosalvarsan	—	+
133	629	c. 72 years	M	Pneumonia, senility	—	Hemiplegia	—	+
134	633	78 years	M	Myocraditis	Myocarditis	Arteriosclerosis	—	—
135	636	51 years	M	Cardiac condition	Myocarditis	Bronchitis	—	+
136	643	c. 60 years	M	Cardiorenal disease	Myocarditis	Nephritis	—	—
137	648	c. 63 years	M	Erysipelas, pneumonia, syphilis	Myocarditis	Pneumonia	—	—
138	651	c. 41 years	M	Myocarditis	—	—	—	—

No.	Terry No.	Age at death	Sex	Cause of death				Included or not into the evaluation
				MR	DC1	DC2	DC3	
139	657R	c. 28 years	F	Mitral stenosis	–	–	–	+
140	661	c. 65 years	F	Uraemia	Uraemia	Nephritis	–	–
141	678R	c. 82 years	F	Heat stroke	–	–	–	–
142	685R	c. 95 years	F	Hypertensive heart disease	Hypertensive heart disease	Cerebral thrombosis	–	–
143	686	c. 78 years	F	Myocarditis, senile dementia	–	–	–	+
144	693	57 years	M	Pneumonia	–	–	–	–
145	694	c. 52 years	M	Myocarditis, arteriosclerosis	Myocarditis	Arteriosclerosis	–	+
146	697	71 years	M	Myocarditis	Myocarditis	Nephritis	–	–
147	702R	47 years	M	Myocardial insufficiency	Hypertensive heart disease	Nephritis	–	+
148	704	40 years	M	Nephritis	–	–	–	–
149	712	47 years	M	Cardiorenal disease	Myocarditis	Nephritis	–	–
150	723	22 years	F	Lues	Syphilis	–	–	–
151	726	c. 62 years	M	Myocarditis, syphilis	–	–	–	+
152	727	c. 45 years	M	Gastric carcinoma	–	–	–	+

No.	Terry No.	Age at death	Sex	Cause of death				Included or not into the evaluation
				MR	DC1	DC2	DC3	
153	731	c. 63 years	M	Myocarditis, rheumatic fever	–	–	–	–
154	745	c. 69 years	F	Heart failure, bronchitis, syphilis	Myocarditis	Syphilis	–	–
155	747	45 years	M	Pyelitis	Peritonitis	Ulcerative sigmoiditis	–	–
156	748	85 years	M	Senile dementia	Myocarditis	Arteriosclerosis	–	–
157	759	60 years	M	Cardiorenal disease	Myocarditis	–	–	+
158	762	59 years	M	Syphilis	Myocarditis	Hypertrophied prostate	–	–
159	763	46 years	M	Pneumonia	–	–	–	–
160	766	c. 35 years	F	–	–	–	–	–
161	781	c. 60 years	F	Heart disease	–	–	–	–
162	782	c. 30 years	M	Stab wound	Stabbed in back	–	–	–
163	789	40 years	M	Syphilis	–	–	–	+
164	795	c. 57 years	M	Carcinoma of the cervical glands	–	–	–	+
165	806	78 years	M	Myocarditis, senility	–	–	–	–
166	809R	60 years	M	Hypertensive heart disease	–	–	–	+

No.	Terry No.	Age at death	Sex	Cause of death				Included or not into the evaluation
				MR	DC1	DC2	DC3	
167	812	c. 56 years	M	Myocarditis, arteriosclerosis	–	–	–	–
168	813	60 years	M	Myocarditis, arteriosclerosis, gangrenous leg	–	–	–	–
169	815	c. 32 years	F	Homicide by firearms	–	–	–	–
170	823	c. 60 years	M	Cerebral apoplexy	–	–	–	+
171	833R	47 years	M	Blastomycosis	–	–	–	+
172	834R	87 years	F	Degenerative heart disease	Arteriosclerosis	–	–	+
173	863	73 years	M	Senility	Cardiorenal disease	Pneumonia	–	+
174	868	60 years	M	Myocarditis	–	–	–	–
175	870	60 years	M	Parkinson's disease	Myocarditis	Parkinson's disease	–	–
176	872	48 years	M	Pneumonia	Lead poisoning	–	–	–
177	875	c. 50 years	M	Intestinal obstruction	Erysipelas	–	–	–
178	878	72 years	M	Gastric carcinoma	–	–	–	–
179	879	50 years	M	Myocarditis	–	–	–	–
180	880	c. 27 years	F	Nephritis	Myocarditis	Arthritis	–	–

No.	Terry No.	Age at death	Sex	Cause of death				Included or not into the evaluation
				MR	DC1	DC2	DC3	
181	881	c. 24 years	M	Chancroid ulcers	Nephritis	—	—	—
182	891	39 years	F	Pneumonia	–	—	—	+
183	903R	c. 51 years	F	—	Subdural brain haemorrhage from fall	—	—	+
184	904R	52 years	F	Degenerative heart disease	Degenerative heart disease	Arteriosclerosis	*Diabetes mellitus*	—
185	908	c. 52 years	M	Lip cancer	—	—	—	—
186	919	c. 55 years	M	Myocarditis	—	—	—	+
187	930R	c. 80 years	F	Cerebral apoplexy	—	—	—	+
188	934	62 years	F	Myocarditis, heart failure	—	—	—	+
189	938	73 years	M	Myocarditis, sigmoid cancer	Pneumonia	Myocarditis	—	+
190	941	59 years	M	Cardiac condition	Myocarditis	—	—	+
191	942	49 years	M	Rheumatism?	Pellagra	—	—	—
192	946	48 years	M	Pneumonia	—	—	—	+
193	948	39 years	F	Heart disease	Myocarditis	—	—	+
194	949	24 years	F	Nephritis	—	—	—	—

No.	Terry No.	Age at death	Sex	Cause of death				Included or not into the evaluation
				MR	DC1	DC2	DC3	
195	951R	c. 62 years	F	Incarcerated umbilical hernia	–	–	–	–
196	957R	76 years	F	Femur fracture	–	–	–	+
197	963	71 years	M	Cardiac decompensation	Myocarditis	–	–	–
198	964	49 years	M	Cerebral apoplexy	Cerebral haemorrhage	–	–	+
199	968	48 years	M	Neurological condition	Lues	–	–	+
200	973	66 years	M	Pneumonia	Myocarditis	Pneumonia	–	+
201	974	77 years	M	Influenza	Myocarditis	Arteriosclerosis	–	–
202	979	85 years	M	Myocarditis, hypertension, senility	–	–	–	–
203	997	c. 88 years	F	Myocarditis, senility	–	–	–	–
204	1023	c. 20 years	M	Car accident	–	–	–	+
205	1029R	30 years	M	Parkinson's disease	–	–	–	+
206	1040	69 years	M	Penile cancer with metastasis	–	–	–	–
207	1045	c. 41 years	M	Nephritis	Pulmonary embolism	Myocarditis	Nephritis	+
208	1046	c. 60 years	M	–	Hypertensive heart disease	–	–	+

No.	Terry No.	Age at death	Sex	Cause of death				Included or not into the evaluation
				MR	DC1	DC2	DC3	
209	1050	64 years	M	Intestinal stasis	Intestinal obstruction	Peritonitis	–	+
210	1051	74 years	M	Gastrointestinal carcinoma	Gastroenteritis	–	–	–
211	1058	68 years	F	Myocarditis	Cerebral apoplexy	Cerebral haemorrhage	Myocarditis	+
212	1060	c. 65 years	M	Asthma, myocarditis	–	–	–	+
213	1066R	62 years	M	Pneumonia	Degenerative heart disease	Arteriosclerosis	–	+
214	1070	c. 51 years	M	Nephritis	Myocarditis	Nephritis	–	+
215	1071R	c. 70 years	F	Accident	Endocarditis	Stenosis, hip fracture	–	+
216	1081	50 years	M	Cardiorenal disease	Myocarditis	–	–	–
217	1098	c. 60 years	M	Cerebral haemorrhage	Cerebral haemorrhage	Arteriosclerosis	–	+
218	1100RR	c. 76 years	F	Brain syndrome	Arteriosclerotic heart disease	Brain syndrome	–	+
219	1102R	c. 76 years	F	Coronary thrombosis	Coronary thrombosis	Arteriosclerotic heart disease	–	+
220	1107	78 years	M	Myocarditis, senility	–	–	–	+
221	1116	80 years	M	–	Myocarditis	Nephritis	Hypertrophied prostate	–
222	1130R	79 years	M	Convulsions	Cerebral haemorrhage	Arteriosclerosis	–	+

No.	Terry No.	Age at death	Sex	Cause of death				Included or not into the evaluation
				MR	DC1	DC2	DC3	
223	1133RR	c. 80 years	F	Arteriosclerosis, avitaminosis, dehydration	Malnutrition	Senility	–	+
224	1134R	70 years	F	Hyperarthritis	Arteriosclerosis	Senile psychosis	Hyperarthritis	+
225	1135	c. 62 years	F	Pneumonia	–	–	–	–
226	1137R	c. 78 years	F	Pneumonia	Degenerative heart disease	Pneumonia	Arteriosclerosis	+
227	1138R	37 years	M	Pneumonia	Pneumonia	Pleural effusion	–	+
228	1140	46 years	M	Cardiac decompensation	Myocarditis	–	–	+
229	1161RR	c. 56 years	F	Hernia	Intestinal obstruction	Incisional hernia	–	–
230	1163	41 years	F	Pellagra	–	–	–	+
231	1182R	c. 48 years	F	Pneumonia	Aortitis	–	–	+
232	1186	c. 44 years	F	Lung abscess	Lung abscess	Pneumonia	–	+
233	1192	58 years	M	Pneumonia	–	–	–	+
234	1198	c. 42 years	F	Hypertension	Myocarditis	–	–	–
235	1204R	74 years	M	Heart disease	Arteriosclerotic heart disease	–	–	+
236	1219	79 years	M	Myocarditis, nephritis	Myocarditis	Senility	–	+

No.	Terry No.	Age at death	Sex	Cause of death				Included or not into the evaluation
				MR	DC1	DC2	DC3	
237	1224	60 years	M	Mediastinal tumour	Aortic aneurysm	–	–	+
238	1228	79 years	M	Nephritis, pneumonia	Myocarditis	Pneumonia	–	+
239	1229	c. 73 years	M	Gangrenous foot	Gangrenous foot	Arteriosclerosis	Myocarditis	+
240	1232	57 years	M	Pneumonia, myocarditis, arteriosclerosis	–	–	–	+
241	1243R	c. 49 years	F	Myocarditis	–	–	–	+
242	1252	50 years	F	Uterine fibroid	Nephritis	Uraemia	–	+
243	1267	c. 78 years	M	Myocarditis, senility	–	–	–	+
244	1271	58 years	M	Lues	Lues	Myocarditic	Cardiac decompensation	+
245	1277	c. 59 years	M	Heat stroke	Epilepsy	–	–	+
246	1281	c. 53 years	M	Hepatic carcinoma	Hepatic carcinoma	Ascites	–	–
247	1288R	c. 58 years	F	Nephritis	Nephritis	Arteriosclerosis	–	–
248	1290	59 years	F	Myocarditis	Myocarditis	Nephritis	–	–
249	1291	c. 52 years	M	Cardiac decompensation	Hypertensive heart disease	–	–	+
250	1299R	52 years	M	Gastric ulcer	Gastric ulcer	Lues	–	+

No.	Terry No.	Age at death	Sex	Cause of death				Included or not into the evaluation
				MR	DC1	DC2	DC3	
251	1310	c. 85 years	M	Cardiovascular reactivity	Arteriosclerotic heart disease	Auricular fibrillation	–	+
252	1314	c. 61 years	F	Myocarditis, nephritis, senility	–	–	–	–
253	1323	50 years	M	Myocarditis	–	–	–	–
254	1336	68 years	M	Pneumonia	–	–	–	–
255	1342	c. 74 years	M	Hypertensive heart disease	–	–	–	+
256	1343	c. 73 years	F	Heart failure, nephritis	Myocarditis	Nephritis	Hypertension	+
257	1347R	38 years	F	Cardiorenal disease	Hypertensive heart disease	–	–	+
258	1349	86 years	M	Cerebral accident, haemorrhage	Cerebral haemorrhage	Senility	Old cerebral haemorrhage	–
259	1353R	c. 50 years	F	Pneumonia	–	–	–	+
260	1355R	73 years	F	Asthma	Arteriosclerotic heart disease	–	–	–
261	1368	37 years	M	Appendicitis	Gangrenous appendix	Pneumonia	–	+
262	1375R	c. 38 years	M	Pneumonia	–	–	–	+
263	1376	46 years	M	Pneumonia	Pneumonia	Myocarditis	–	+
264	1378	54 years	M	Peritonitis	–	–	–	+

No.	Terry No.	Age at death	Sex	Cause of death				Included or not into the evaluation
				MR	DC1	DC2	DC3	
265	1387	40 years	M	Lues	–	–	–	+
266	1391R	c. 65 years	F	Myocarditis	–	–	–	–
267	1399	c. 37 years	M	Brain abscess	–	–	–	–
268	1405	75 years	F	Myocarditis	–	–	–	+
269	1411R	65 years	M	–	Nephritis, uraemia	Hypertrophied prostate	–	+
270	1416	c. 70 years	F	Hypertensive heart disease	Arteriosclerotic heart disease	Senile psychosis	–	+
271	1417R	37 years	F	Dysentery	Perianal & ischiorectal abscesses	Staphylococcosis	Secondary anaemia	+
272	1435	66 years	F	Myocarditis, arteriosclerosis	–	–	–	+
273	1439R	56 years	M	Epilepsy, hypertension	Pneumonia	Arteriosclerotic dementia	–	+
274	1444	59 years	M	Heart disease	Arteriosclerotic heart disease	–	–	+
275	1460R	58 years	M	Hypertrophied prostate	Hypertrophied prostate	Nephritis	–	–
276	1462	c. 54 years	F	Myocarditis	Myocarditis	Syphilis	–	–
277	1467	73 years	M	Gastric malignancy	Arteriosclerotic heart disease	Cardiac decompensation	–	+
278	1492	65 years	M	Myocarditis, pneumonia	–	–	–	–

No.	Terry No.	Age at death	Sex	Cause of death				Included or not into the evaluation
				MR	DC1	DC2	DC3	
279	1495	89 years	M	Myocarditis	Myocarditis	Pneumonia	–	+
280	1502R	c. 82 years	F	Arteriosclerosis	Arteriosclerosis	Senility	–	+
281	1505R	41 years	F	Hemiplegia	Hypertension	Cerebral haemorrhage	–	+
282	1514	c. 70 years	M	Hemiplegia, strictures	–	–	–	+
283	1515	43 years	F	Hypertensive heart disease	Cerebral haemorrhage	Hypertensive heart disease	–	–
284	1519	71 years	M	Myocarditis	Myocarditis, cardiac decompensation	–	–	+
285	1534	44 years	M	Urinary bladder calculi	Pyelonephritis, catarrhal cystitis	Bladder & urethral calculi	–	+
286	1541R	c. 57 years	F	?	Coronary occlusion	Arteriosclerotic heart disease	–	–
287	1543	c. 70 years	M	Thrombosis	–	–	–	+
288	1549	c. 40 years	F	Cerebral apoplexy	–	–	–	+
289	1552	84 years	F	Hypertension, senility	Cardiac decompensation	Arteriosclerotic vascular disease	–	+
290	1554	c. 56 years	F	Hypertensive heart disease	–	–	–	+
291	1567	c. 69 years	F	Stroke, heart failure	–	–	–	+
292	1581	64 years	F	Arteriosclerotic heart disease	–	–	–	+

No.	Terry No.	Age at death	Sex	Cause of death				Included or not into the evaluation
				MR	DC1	DC2	DC3	
293	1587	c. 76 years	F	Coronary vessel disease	Coronary vessel disease	Pneumonia	–	–
294	1592	53 years	F	Arteriosclerotic heart disease	–	–	–	+
295	1599	c. 41 years	F	Suicide	–	–	–	+
296	1600	26 years	F	Alcoholism, epilepsy	Pneumonia	–	–	–
297	1604	50 years	F	Cerebral haemorrhage	Cerebral haemorrhage	Hypertensive vascular disease	–	+
298	1614	38 years	F	–	Congestive heart failure	Rheumatic mitral valve disease	Mental deficiency	+
299	1627	c. 90 years	F	Hypertensive heart disease, failure	Arteriosclerotic heart disease	–	–	+
300	1631	83 years	F	Arteriosclerotic heart disease	–	–	–	–
301	1633	80 years	F	Coronary occlusion	Coronary occlusion	Coronary stenosis	–	–
302	1634	63 years	F	Coronary thrombosis	Coronary thrombosis	Arteriosclerosis	–	–

Supplementary table 3: Individual data regarding TBM-related endocranial alterations in the TB group (+ = present; − = not present).

No.	Terry No.	APDIs	ABVIs	PAs	GIs
1	13R	+	+	−	−
2	23R	−	+	−	−
3	30R	+	−	−	+
4	35R	−	−	−	−
5	39	−	−	−	−
6	54	+	−	−	−
7	84	+	+	−	+
8	87R	−	−	−	+
9	89R	+	−	−	−
10	90	+	−	−	−
11	91R	−	−	−	−
12	95	+	+	−	+
13	95R	+	−	−	−
14	103R	−	−	−	−
15	114	−	−	−	−
16	128	+	+	+	−
17	129	+	−	−	+
18	130	−	−	−	−
19	138	+	−	−	+
20	139	+	−	−	+
21	145R	−	+	−	+
22	146R	+	−	−	−
23	158R	−	+	−	+
24	182	+	−	−	+
25	194	+	−	−	−
26	204	+	+	+	−
27	205	+	−	−	+
28	207	+	−	−	−
29	220	+	+	−	+
30	222	+	−	−	+
31	230	+	−	−	+
32	232R	−	−	−	+
33	235	+	+	−	−
34	248R	−	−	−	−
35	250	−	−	−	−
36	251	+	−	−	−
37	254	+	+	+	−
38	255	+	+	−	+

No.	Terry No.	APDIs	ABVIs	PAs	GIs
39	264	–	–	–	–
40	265	+	+	–	–
41	267	+	–	–	–
42	269	+	–	–	+
43	270	+	–	–	+
44	279	+	+	–	+
45	280	+	+	+	+
46	282	–	–	–	–
47	283R	+	–	–	–
48	284	–	–	–	–
49	304	+	+	+	–
50	306	+	+	+	–
51	309	–	–	–	–
52	318	–	–	–	–
53	328R	–	–	–	–
54	329	–	+	–	+
55	341	+	–	–	+
56	353	–	+	–	–
57	358R	–	+	–	–
58	382R	+	–	–	–
59	385	+	–	+	–
60	386R	–	–	–	–
61	400	+	–	–	–
62	402	–	–	–	–
63	410R	–	–	–	–
64	423	+	–	+	–
65	424	–	–	–	–
66	426R	–	–	–	–
67	432	–	–	–	+
68	444	–	–	–	+
69	466	+	–	–	–
70	468	+	–	–	–
71	490	–	–	–	–
72	504	–	–	–	+
73	522	+	+	+	+
74	523	–	–	–	–
75	537	–	–	–	–
76	541	–	–	–	+
77	549	–	–	–	–
78	555	–	–	–	–

No.	Terry No.	APDIs	ABVIs	PAs	GIs
79	562	+	−	−	+
80	565	+	−	−	−
81	566	−	−	−	+
82	568	−	+	+	+
83	571	−	+	−	−
84	572	+	−	−	−
85	575	−	−	−	+
86	583	+	−	−	−
87	585	+	−	−	−
88	592	+	−	−	−
89	595	+	−	−	+
90	620	−	−	−	+
91	621R	+	+	+	−
92	626R	−	−	−	−
93	664	+	−	−	+
94	669R	−	−	−	−
95	679	−	−	−	−
96	680	−	−	−	+
97	728R	+	−	−	−
98	739	−	+	−	+
99	752	+	−	−	+
100	757	+	−	−	−
101	761	−	−	−	−
102	771	+	−	−	−
103	776	+	−	−	−
104	786	+	−	−	−
105	799	+	−	−	−
106	820R	+	−	−	−
107	822	+	+	−	+
108	828	+	−	−	+
109	844	+	−	−	−
110	846	+	−	+	−
111	876	+	−	−	+
112	892	+	−	−	−
113	895	−	−	−	−
114	896RR	+	+	−	+
115	897	+	−	+	−
116	902	−	+	−	−
117	907	+	−	−	−
118	914	+	−	−	+

No.	Terry No.	APDIs	ABVIs	PAs	GIs
119	915	+	−	+	−
120	932	+	+	+	−
121	933R	+	+	−	+
122	936	+	−	−	−
123	950	+	−	−	−
124	952	−	−	−	+
125	955	+	+	+	−
126	957	−	−	−	−
127	975	−	−	−	+
128	987	+	+	+	+
129	1002	+	−	−	−
130	1005	+	−	−	−
131	1013	+	−	−	−
132	1018	+	−	−	+
133	1020	+	+	−	+
134	1027	−	+	+	+
135	1030	−	+	−	−
136	1031	+	−	−	−
137	1033	+	+	+	−
138	1034	+	−	+	−
139	1036	+	−	−	−
140	1043	−	−	−	−
141	1047	+	−	−	−
142	1048	+	−	−	−
143	1057	+	−	+	+
144	1072	+	−	−	−
145	1076	+	+	−	+
146	1086	−	−	−	−
147	1093	+	−	−	−
148	1095	+	−	−	−
149	1096R	+	−	−	+
150	1105	+	+	+	−
151	1106	+	−	−	+
152	1113	+	−	+	−
153	1122	+	+	+	−
154	1124R	−	−	−	−
155	1129	+	−	−	−
156	1132	+	−	−	−
157	1147R	−	−	−	−
158	1156	+	−	−	−

No.	Terry No.	APDIs	ABVIs	PAs	GIs
159	1157	+	−	−	−
160	1159	+	−	+	+
161	1165	+	+	+	−
162	1169	+	+	+	−
163	1173	+	−	−	−
164	1183	+	−	−	−
165	1185	+	−	−	−
166	1187	+	−	−	−
167	1190	+	−	+	−
168	1205	+	−	−	−
169	1210	+	−	−	−
170	1215	+	−	−	−
171	1222	+	+	+	+
172	1226	−	−	−	−
173	1230	+	−	−	−
174	1236	+	−	+	−
175	1247	−	−	−	−
176	1249R	+	−	−	+
177	1255	+	−	+	−
178	1263R	+	−	−	+
179	1264	+	−	−	+
180	1266R	−	−	−	−
181	1275	+	−	−	−
182	1278	+	−	−	−
183	1282	−	−	−	−
184	1285	+	−	+	−
185	1287	+	−	+	−
186	1300	+	−	+	−
187	1304R	+	−	−	+
188	1309	+	−	−	+
189	1313	+	−	+	−
190	1315	+	−	−	−
191	1318	+	−	+	+
192	1319	+	−	+	+
193	1322	+	+	+	−
194	1331	−	−	−	+
195	1337RR	−	−	−	−
196	1346	−	−	−	−
197	1352	−	−	−	−
198	1359	+	−	+	−

No.	Terry No.	APDIs	ABVIs	PAs	GIs
199	1362	+	−	−	−
200	1367	+	−	−	−
201	1369	+	+	+	−
202	1377	−	+	+	−
203	1379	−	−	−	−
204	1388	+	−	+	+
205	1397	+	−	−	−
206	1398	+	−	+	−
207	1401	−	−	−	−
208	1406	−	−	−	−
209	1407	+	−	−	−
210	1419	−	−	−	−
211	1422R	+	−	−	−
212	1428R	+	−	−	−
213	1434R	+	−	−	−
214	1451	−	−	−	−
215	1453R	−	−	−	−
216	1455	+	−	−	−
217	1458	+	−	+	+
218	1476	−	−	−	−
219	1503	+	−	−	+
220	1507	+	−	−	−
221	1521	+	+	−	−
222	1531	−	−	−	−
223	1533	+	−	−	+
224	1536	−	−	−	−
225	1539	+	−	−	−
226	1544	−	+	+	−
227	1551	+	+	−	−
228	1553	+	−	+	−
229	1555	+	+	−	−
230	1562	+	+	+	−
231	1568	−	−	−	−
232	1572	+	−	−	+
233	1576	−	−	−	−
234	1629	−	−	−	−

Supplementary table 4: Individual data regarding TBM-related endocranial alterations in the NTB group (+ = present; − = not present).

No.	Terry No.	APDIs	ABVIs	PAs	GIs
1	4R	−	−	−	+
2	12R	−	+	+	−
3	19R	+	−	−	−
4	25	−	−	−	−
5	25R	−	+	−	−
6	31R	−	−	−	−
7	44R	−	−	−	−
8	46R	−	−	−	−
9	47R	−	−	−	−
10	58R	+	−	+	−
11	62RR	+	−	−	−
12	64R	+	−	−	−
13	69	−	−	−	−
14	76R	−	−	−	−
15	79R	−	−	−	−
16	104RR	−	−	−	−
17	105R	−	−	−	−
18	112R	+	−	−	−
19	124R	−	−	−	−
20	127R	+	+	−	−
21	132R	−	−	−	−
22	134	−	−	−	−
23	135R	+	−	−	−
24	140RR	−	+	−	−
25	141R	−	−	−	−
26	142R	−	−	−	−
27	149R	−	−	−	−
28	167	+	−	−	−
29	177R	−	−	−	−
30	178R	−	−	+	−
31	179R	−	−	−	−
32	197R	+	−	−	+
33	199	−	−	−	−
34	209	+	−	−	−
35	218	+	−	−	−
36	221	−	−	−	−
37	227	+	−	−	−
38	231	+	+	−	−

No.	Terry No.	APDIs	ABVIs	PAs	GIs
39	237	–	–	–	–
40	243R	–	–	–	–
41	247R	–	–	–	–
42	249R	–	–	–	–
43	259	+	–	–	–
44	268	+	–	–	–
45	272	+	–	+	+
46	285	–	–	–	–
47	293R	–	–	–	–
48	296R	+	–	–	–
49	298	–	–	–	–
50	306R	–	–	–	–
51	314	+	–	–	–
52	317	–	–	–	–
53	338	–	–	–	–
54	339R	+	–	–	–
55	344R	–	–	–	–
56	347	–	–	–	–
57	348R	+	–	–	–
58	393RR	–	–	–	–
59	397	–	–	–	–
60	403	+	–	–	–
61	422	+	–	–	–
62	437R	+	–	–	–
63	438	–	–	–	–
64	445	+	–	–	–
65	447	+	–	–	–
66	452	–	–	–	–
67	453	+	–	–	–
68	458	–	–	–	–
69	463	+	–	–	–
70	465	+	–	–	+
71	470	+	–	+	–
72	477	–	+	–	–
73	483	+	–	–	–
74	496	+	–	–	–
75	497	–	–	–	–
76	506	+	–	–	+
77	512	+	+	–	–
78	513RR	–	–	–	–

No.	Terry No.	APDIs	ABVIs	PAs	GIs
79	527	–	–	–	–
80	528	–	–	–	–
81	534	–	+	–	–
82	536	+	–	+	–
83	545	+	–	–	–
84	552	–	–	–	–
85	573	+	–	–	–
86	582	–	–	–	–
87	586	–	–	–	–
88	597	+	–	–	–
89	602	–	–	–	–
90	608	–	–	–	–
91	617R	–	–	+	–
92	627R	–	–	–	–
93	629	–	–	+	–
94	636	+	–	–	–
95	657R	+	–	–	–
96	686	–	–	+	–
97	694	+	–	–	–
98	702R	–	–	–	–
99	726	–	–	–	–
100	727	–	–	–	–
101	759	+	–	+	–
102	789	–	–	–	–
103	795	+	–	–	–
104	809R	–	–	–	–
105	823	+	–	–	–
106	833R	+	–	–	–
107	834R	–	–	–	–
108	863	–	–	–	–
109	891	–	–	–	–
110	903R	–	–	–	–
111	919	–	–	–	–
112	930R	–	–	–	–
113	934	–	–	–	–
114	938	–	–	–	–
115	941	–	–	+	–
116	946	+	–	+	–
117	948	–	–	+	–
118	957R	–	–	–	–

No.	Terry No.	APDIs	ABVIs	PAs	GIs
119	964	–	–	+	–
120	968	–	–	–	–
121	973	+	–	–	–
122	1023	+	–	–	–
123	1029R	–	–	–	–
124	1045	–	–	–	–
125	1046	+	–	–	–
126	1050	–	–	–	–
127	1058	–	–	–	–
128	1060	–	–	–	–
129	1066R	–	+	–	–
130	1070	–	–	–	–
131	1071	–	–	–	–
132	1098	–	–	–	–
133	1100RR	–	–	–	–
134	1102R	–	–	–	–
135	1107	–	–	–	–
136	1130R	+	–	–	–
137	1133RR	–	–	–	–
138	1134R	–	–	–	–
139	1137R	–	–	–	–
140	1138R	+	–	–	–
141	1140	+	–	–	–
142	1163	–	–	–	–
143	1182R	–	–	–	–
144	1186	+	–	–	–
145	1192	+	–	–	–
146	1204R	–	+	–	–
147	1219	–	–	–	–
148	1224	+	–	+	–
149	1228	+	–	–	–
150	1229	+	–	–	–
151	1232	–	–	–	–
152	1243R	–	+	+	–
153	1252	–	–	–	–
154	1267	–	–	–	–
155	1271	–	+	–	–
156	1277	–	–	–	–
157	1291	+	–	–	–
158	1299R	–	–	–	–

No.	Terry No.	APDIs	ABVIs	PAs	GIs
159	1310	–	–	–	–
160	1342	+	–	–	–
161	1343	–	–	–	–
162	1347R	–	–	–	–
163	1353R	–	–	–	–
164	1368	–	–	+	–
165	1375R	–	–	–	–
166	1376	–	–	–	–
167	1378	–	–	–	+
168	1387	–	–	+	–
169	1405	–	–	–	–
170	1411R	–	–	–	–
171	1416	–	–	–	–
172	1417R	+	–	–	–
173	1435	–	–	–	–
174	1439R	–	–	–	–
175	1444	–	–	–	–
176	1467	–	–	–	–
177	1495	–	–	–	–
178	1502R	–	–	–	–
179	1505R	+	–	–	–
180	1514	–	–	–	–
181	1519	–	–	+	–
182	1534	–	–	–	–
183	1543	–	–	–	–
184	1549	–	–	–	–
185	1552	–	–	–	–
186	1554	–	–	–	–
187	1567	–	–	–	–
188	1581	–	–	–	–
189	1592	–	–	–	–
190	1599	+	–	–	–
191	1604	–	–	+	–
192	1614	+	–	–	–
193	1627	–	–	–	–

Supplementary table 5: Individual data of specimens exhibiting at least one type of probable TBM-associated endocranial alterations regarding possible TB-related non-endocranial bony changes in the TB group (Σ=181) (+ = present; − = not present).

No.	Terry No.	PNBFs on the visceral costal surfaces	HPO	Extra-spinal osteomyelitis	Extra-spinal arthritis	Vertebral hypervascularisation	Vertebral lytic lesions and/or arthritis	Reactive new bone formations indicative of a cold abscess
1	13R	+	−	−	−	+	−	−
2	23R	+	−	−	−	−	−	−
3	30R	−	−	−	−	+	−	−
4	54	−	−	−	−	−	−	+
5	84	−	−	−	−	−	+	+
6	87R	−	−	−	−	−	−	−
7	89R	+	−	−	−	+	+	+
8	90	+	−	−	−	+	−	−
9	95	−	+	−	−	−	+	+
10	95R	+	−	−	−	+	−	−
11	128	+	−	−	−	+	−	−
12	129	+	−	+	−	+	+	+

No.	Terry No.	PNBFs on the visceral costal surfaces	HPO	Extra-spinal osteomyelitis	Extra-spinal arthritis	Vertebral hypervascularisation	Vertebral lytic lesions and/or arthritis	Reactive new bone formations indicative of a cold abscess
13	138	+	–	–	–	–	–	+
14	139	–	–	–	–	+	–	–
15	145R	+	–	–	–	+	–	–
16	146R	–	–	–	–	–	–	–
17	158R	+	+	–	–	–	–	–
18	182	+	–	–	–	+	–	+
19	194	–	–	–	–	–	–	–
20	204	+	–	–	+	+	–	–
21	205	–	–	–	+	+	–	–
22	207	+	–	–	+	–	–	–
23	220	–	–	–	–	–	–	–
24	222	+	–	–	–	+	–	–
25	230	+	–	–	–	–	–	–
26	232R	–	–	–	–	–	–	–

No.	Terry No.	PNBFs on the visceral costal surfaces	HPO	Extra-spinal osteomyelitis	Extra-spinal arthritis	Vertebral hypervascularisation	Vertebral lytic lesions and/or arthritis	Reactive new bone formations indicative of a cold abscess
27	235	–	–	–	–	+	–	+
28	251	+	–	–	–	–	–	–
29	254	+	+	–	–	–	–	–
30	255	+	–	–	–	+	–	–
31	265	+	–	–	–	+	+	+
32	267	–	–	+	–	+	–	–
33	269	+	–	–	–	+	–	+
34	270	–	–	–	–	+	–	–
35	279	+	–	–	–	+	+	–
36	280	–	–	–	–	+	–	–
37	283R	–	–	–	–	+	–	–
38	304	–	–	–	–	+	–	–
39	306	+	+	–	–	+	–	–
40	329	+	–	+	–	–	+	+

No.	Terry No.	PNBFs on the visceral costal surfaces	HPO	Extra-spinal osteomyelitis	Extra-spinal arthritis	Vertebral hypervascularisation	Vertebral lytic lesions and/or arthritis	Reactive new bone formations indicative of a cold abscess
41	341	–	–	–	–	–	–	–
42	353	–	–	–	–	+	–	+
43	358R	+	–	–	–	+	–	–
44	382R	+	–	–	–	+	–	–
45	385	–	–	–	–	+	–	–
46	400	+	–	–	–	+	–	–
47	423	+	–	–	–	+	–	–
48	432	+	–	+	–	+	+	+
49	444	+	–	–	–	+	–	–
50	466	+	–	–	–	+	+	–
51	468	+	–	+	+	+	+	+
52	504	+	–	–	–	+	–	–
53	522	+	–	–	–	–	–	–
54	541	+	–	–	–	+	–	–

No.	Terry No.	PNBFs on the visceral costal surfaces	HPO	Extra-spinal osteomyelitis	Extra-spinal arthritis	Vertebral hypervascularisation	Vertebral lytic lesions and/or arthritis	Reactive new bone formations indicative of a cold abscess
55	562	+	–	–	–	+	–	–
56	565	+	–	–	–	+	–	–
57	566	+	–	–	–	–	–	–
58	568	+	–	–	–	+	–	–
59	571	–	–	–	–	+	–	–
60	572	+	–	–	–	–	–	–
61	575	+	–	–	–	+	–	–
62	583	–	–	–	–	+	–	–
63	585	–	–	–	–	–	–	–
64	592	+	+	+	–	+	–	–
65	595	–	–	–	–	+	–	–
66	620	–	–	–	–	–	+	–
67	621R	+	–	–	–	+	–	–
68	664	+	–	–	–	+	–	–

No.	Terry No.	PNBFs on the visceral costal surfaces	HPO	Extra-spinal osteomyelitis	Extra-spinal arthritis	Vertebral hypervascularisation	Vertebral lytic lesions and/or arthritis	Reactive new bone formations indicative of a cold abscess
69	680	–	–	–	–	–	–	–
70	728R	–	–	–	–	+	–	–
71	739	–	–	–	–	+	–	–
72	752	–	–	–	–	–	–	–
73	757	–	–	–	–	–	–	–
74	771	–	–	–	–	–	–	–
75	776	–	–	–	+	+	–	–
76	786	–	–	–	–	+	–	–
77	799	+	–	–	–	+	–	–
78	820R	+	–	–	–	–	–	–
79	822	+	–	–	–	+	–	–
80	828	+	+	–	–	–	–	–
81	844	–	–	–	–	–	–	–
82	846	+	–	–	–	+	–	–

No.	Terry No.	PNBFs on the visceral costal surfaces	HPO	Extra-spinal osteomyelitis	Extra-spinal arthritis	Vertebral hypervascularisation	Vertebral lytic lesions and/or arthritis	Reactive new bone formations indicative of a cold abscess
83	876	+	–	–	–	+	–	–
84	892	+	–	–	–	+	–	–
85	896RR	+	–	–	+	+	–	–
86	897	+	–	–	–	+	+	–
87	902	+	+	+	+	+	+	+
88	907	–	–	–	–	–	–	–
89	914	–	–	–	–	–	–	–
90	915	+	–	–	–	+	–	–
91	932	–	–	–	–	–	–	–
92	933R	+	–	–	–	+	–	–
93	936	–	–	–	–	+	–	–
94	950	+	–	–	–	–	–	–
95	952	–	–	–	–	–	–	–
96	955	+	+	–	–	+	–	–

No.	Terry No.	PNBFs on the visceral costal surfaces	HPO	Extra-spinal osteomyelitis	Extra-spinal arthritis	Vertebral hypervascularisation	Vertebral lytic lesions and/or arthritis	Reactive new bone formations indicative of a cold abscess
97	975	+	+	–	–	–	–	–
98	987	+	+	–	–	–	–	–
99	1002	–	–	–	–	–	–	–
100	1005	–	–	–	–	–	–	–
101	1013	+	–	–	–	+	–	–
102	1018	+	–	+	–	+	+	+
103	1020	+	+	–	–	+	–	–
104	1027	–	–	–	–	–	–	–
105	1030	–	–	–	–	–	–	–
106	1031	–	–	–	–	+	–	–
107	1033	+	–	–	–	+	–	–
108	1034	–	–	–	–	–	–	–
109	1036	–	–	–	–	+	–	–
110	1047	+	–	–	–	–	–	–

No.	Terry No.	PNBFs on the visceral costal surfaces	HPO	Extra-spinal osteomyelitis	Extra-spinal arthritis	Vertebral hypervascularisation	Vertebral lytic lesions and/or arthritis	Reactive new bone formations indicative of a cold abscess
111	1048	–	–	–	–	–	–	–
112	1057	+	–	–	–	–	–	–
113	1072	–	–	–	–	–	–	–
114	1076	+	–	–	–	+	–	–
115	1093	+	–	–	–	+	+	+
116	1095	–	–	–	–	–	–	–
117	1096R	+	+	–	–	+	–	–
118	1105	+	+	–	–	+	–	–
119	1106	+	–	+	+	–	+	+
120	1113	–	–	–	–	–	–	–
121	1122	+	+	–	–	–	–	–
122	1129	+	–	–	–	–	–	–
123	1132	–	–	–	–	–	–	–
124	1156	+	+	–	–	–	–	–

No.	Terry No.	PNBFs on the visceral costal surfaces	HPO	Extra-spinal osteomyelitis	Extra-spinal arthritis	Vertebral hypervascularisation	Vertebral lytic lesions and/or arthritis	Reactive new bone formations indicative of a cold abscess
125	1157	–	–	–	–	+	–	–
126	1159	+	+	–	–	+	–	–
127	1165	–	–	–	–	+	–	–
128	1169	+	–	–	–	+	–	–
129	1173	–	–	–	–	+	–	–
130	1183	+	–	–	–	+	–	–
131	1185	+	+	+	+	+	–	+
132	1187	+	–	–	–	+	–	–
133	1190	+	–	–	–	–	–	–
134	1205	+	–	–	+	–	–	–
135	1210	+	–	–	–	+	–	–
136	1215	+	–	–	–	+	–	+
137	1222	–	–	–	–	–	–	–
138	1230	+	–	–	–	–	–	–

No.	Terry No.	PNBFs on the visceral costal surfaces	HPO	Extra-spinal osteomyelitis	Extra-spinal arthritis	Vertebral hypervascularisation	Vertebral lytic lesions and/or arthritis	Reactive new bone formations indicative of a cold abscess
139	1236	–	–	–	–	+	–	–
140	1249R	–	–	–	–	–	–	–
141	1255	–	–	–	–	–	+	+
142	1263R	+	–	–	–	–	–	–
143	1264	–	–	–	–	–	–	–
144	1275	+	–	–	–	–	–	–
145	1278	–	–	–	–	–	–	–
146	1285	–	–	+	+	–	+	–
147	1287	+	–	–	–	+	+	+
148	1300	+	–	–	–	+	–	–
149	1304R	–	–	–	–	–	–	–
150	1309	+	–	+	–	–	+	+
151	1313	–	–	–	–	–	–	–
152	1315	+	+	–	–	+	+	–

No.	Terry No.	PNBFs on the visceral costal surfaces	HPO	Extra-spinal osteomyelitis	Extra-spinal arthritis	Vertebral hypervascularisation	Vertebral lytic lesions and/or arthritis	Reactive new bone formations indicative of a cold abscess
153	1318	+	–	–	–	–	–	–
154	1319	+	–	–	–	+	–	–
155	1322	+	–	–	–	+	–	–
156	1331	+	–	–	–	+	–	–
157	1359	–	–	–	–	–	–	–
158	1362	+	–	–	–	+	–	–
159	1367	–	–	–	–	–	–	–
160	1369	+	–	–	–	+	–	–
161	1377	–	–	–	–	+	–	–
162	1388	+	–	–	–	+	–	–
163	1397	+	–	–	–	–	–	–
164	1398	+	–	–	–	+	–	–
165	1407	+	–	+	–	+	+	+
166	1422R	+	–	–	–	–	–	+

No.	Terry No.	PNBFs on the visceral costal surfaces	HPO	Extra-spinal osteomyelitis	Extra-spinal arthritis	Vertebral hypervascularisation	Vertebral lytic lesions and/or arthritis	Reactive new bone formations indicative of a cold abscess
167	1428R	+	–	–	–	+	–	–
168	1434R	+	–	–	–	+	–	–
169	1455	–	–	–	–	–	–	–
170	1458	+	–	–	–	–	–	–
171	1503	+	–	–	–	+	–	–
172	1507	+	–	–	–	+	–	–
173	1521	+	–	–	–	–	–	–
174	1533	+	–	–	–	–	–	–
175	1539	+	–	–	–	–	–	–
176	1544	+	–	–	–	+	–	–
177	1551	–	–	–	–	+	–	–
178	1553	–	–	–	–	+	–	–
179	1555	+	+	–	–	–	–	–

No.	Terry No.	PNBFs on the visceral costal surfaces	HPO	Extra-spinal osteomyelitis	Extra-spinal arthritis	Vertebral hypervascularisation	Vertebral lytic lesions and/or arthritis	Reactive new bone formations indicative of a cold abscess
180	**1562**	–	–	–	–	–	–	–
181	**1572**	+	–	–	–	–	–	–

Supplementary table 6: Individual data of specimens exhibiting at least one type of probable TBM-associated endocranial alterations regarding possible TB-related non-endocranial bony changes in the NTB group (Σ=84) (+ = present; − = not present).

No.	Terry No.	PNBFs on the visceral costal surfaces	HPO	Extra-spinal osteomyelitis	Extra-spinal arthritis	Vertebral hypervascularisation	Vertebral lytic lesions and/or arthritis	Reactive new bone formations indicative of a cold abscess
1	4R	−	−	−	−	−	−	−
2	12R	−	−	−	−	−	−	−
3	19R	−	−	−	−	+	+	−
4	25R	−	−	−	−	−	−	−
5	58R	−	−	−	−	−	−	−
6	62RR	−	−	−	−	+	−	−
7	64R	−	−	−	−	−	−	−
8	112R	−	+	−	−	−	−	+
9	127R	−	−	−	−	−	−	−
10	135R	−	−	−	−	−	−	−
11	140RR	−	−	−	−	−	−	−
12	167	−	−	−	−	−	−	−

No.	Terry No.	PNBFs on the visceral costal surfaces	HPO	Extra-spinal osteomyelitis	Extra-spinal arthritis	Vertebral hypervascularisation	Vertebral lytic lesions and/or arthritis	Reactive new bone formations indicative of a cold abscess
13	178R	–	–	–	–	–	–	–
14	197R	–	–	–	–	–	–	–
15	209	–	–	–	–	+	–	–
16	218	+	–	–	–	+	–	–
17	227	–	–	–	–	–	–	–
18	231	–	–	–	–	–	–	–
19	259	–	–	–	–	+	–	–
20	268	–	–	–	–	–	–	–
21	272	–	–	–	–	–	–	–
22	296R	–	–	–	–	–	–	–
23	314	–	–	–	–	–	–	–
24	339R	–	+	–	–	–	–	–
25	348R	–	–	–	–	–	–	–
26	403	–	–	–	–	–	–	–

No.	Terry No.	PNBFs on the visceral costal surfaces	HPO	Extra-spinal osteomyelitis	Extra-spinal arthritis	Vertebral hypervascularisation	Vertebral lytic lesions and/or arthritis	Reactive new bone formations indicative of a cold abscess
27	422	–	–	–	–	–	–	–
28	437R	–	–	–	–	–	–	–
29	445	–	–	–	–	–	–	–
30	447	–	–	–	–	–	–	–
31	453	–	–	–	–	–	–	–
32	463	–	–	–	–	–	–	–
33	465	+	–	+	–	+	–	–
34	470	–	–	–	–	–	–	–
35	477	+	–	+	–	–	+	+
36	483	–	–	–	–	–	–	–
37	496	–	–	–	–	–	–	–
38	506	+	+	+	–	–	–	–
39	512	–	–	–	–	–	–	–
40	534	–	+	–	–	–	–	–

No.	Terry No.	PNBFs on the visceral costal surfaces	HPO	Extra-spinal osteomyelitis	Extra-spinal arthritis	Vertebral hypervascularisation	Vertebral lytic lesions and/or arthritis	Reactive new bone formations indicative of a cold abscess
41	536	–	–	–	–	–	–	–
42	545	–	–	–	–	–	–	–
43	573	–	–	–	–	+	–	–
44	597	–	–	–	–	–	–	–
45	617R	–	–	–	–	–	–	–
46	629	–	–	–	–	–	–	–
47	636	–	–	–	–	–	–	–
48	657R	–	–	–	–	+	–	–
49	686	–	–	–	–	–	–	–
50	694	–	–	–	–	–	–	–
51	759	–	–	–	–	–	–	–
52	795	–	–	–	–	+	–	–
53	823	–	–	–	–	–	+	–
54	833R	+	+	+	–	–	+	–

No.	Terry No.	PNBFs on the visceral costal surfaces	HPO	Extra-spinal osteomyelitis	Extra-spinal arthritis	Vertebral hypervascularisation	Vertebral lytic lesions and/or arthritis	Reactive new bone formations indicative of a cold abscess
55	941	–	–	–	–	–	–	–
56	946	–	–	–	–	+	–	–
57	948	+	–	–	–	–	–	–
58	964	–	–	–	–	–	–	–
59	973	–	–	–	–	–	–	–
60	1023	–	–	–	–	+	–	–
61	1046	–	–	–	–	–	–	–
62	1066R	–	–	–	–	–	–	–
63	1130R	–	–	–	–	–	–	–
64	1138R	–	–	–	–	–	–	–
65	1140	–	–	–	–	–	–	–
66	1186	–	–	–	–	–	–	–
67	1192	–	–	–	–	–	–	–
68	1204R	–	–	–	–	–	–	–

No.	Terry No.	PNBFs on the visceral costal surfaces	HPO	Extra-spinal osteomyelitis	Extra-spinal arthritis	Vertebral hypervascularisation	Vertebral lytic lesions and/or arthritis	Reactive new bone formations indicative of a cold abscess
69	**1224**	–	–	–	–	–	–	–
70	**1228**	–	–	–	–	–	–	–
71	**1229**	–	–	–	–	–	–	–
72	**1243R**	–	–	–	–	–	–	–
73	**1271**	–	–	–	–	–	–	–
74	**1291**	–	–	–	–	–	–	–
75	**1342**	–	–	–	–	–	–	–
76	**1368**	–	–	–	–	–	–	–
77	**1378**	–	–	–	–	+	–	–
78	**1387**	–	–	–	–	–	–	–
79	**1417R**	–	+	–	–	–	–	–
80	**1505R**	–	–	–	–	–	–	–
81	**1519**	–	–	–	–	–	–	–
82	**1599**	–	–	–	–	–	–	–

No.	Terry No.	PNBFs on the visceral costal surfaces	HPO	Extra-spinal osteomyelitis	Extra-spinal arthritis	Vertebral hypervascularisation	Vertebral lytic lesions and/or arthritis	Reactive new bone formations indicative of a cold abscess
83	**1604**	–	–	–	–	–	–	–
84	**1614**	–	–	–	–	+	–	+