SKELETAL MANIFESTATION OF TUBERCULOSIS IN THE MEDIEVAL POPULATION OF BOROVCE (8th–12th CENTURY AD, SLOVAKIA) IN RELATIONSHIP TO THE OCCURRENCE OF LONG BONE CHANGES AND CRIBRA ORBITALIA

Prejavy tuberkulózy na kostrových pozostatkoch v stredovekej populácii z Boroviec (8. –12. stor. n. l.) vo vzťahu k patologickým zmenám dlhých kostí a cribra orbitalia

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Abstract

Numerous studies describe a variety of human susceptibility factors to TB and discuss the diagnostic value of lesions attributable to this infectious disease. Regarding the differential diagnosis in skeletal populations a variety of specific and non-specific alterations is evaluated when relying on a macroscopic analysis only. The here presented results of a macroscopic investigation of 439 specimen from the medieval site Borovce (Slovakia) confirm the presence of one case of late skeletal tuberculosis and 15 cases of atypical alterations such as hypervascularisation of vertebral bodies, periosteal depositions on ribs and endocranial lesions. Tuberculosis affected primarily younger individuals in this population (most frequently juveniles and adults up to 39 years). In three cases atypical endocranial structures were indicative of tuberculous meningitis, occurring only in immatures. Further a co-occurrence of unspecific stress features and tuberculous lesions was observed. Seven out of the 16 TB affected skeletons revealed *cribra orbitalia* and 7 cases of long bone changes were identified. Despite of the frequent occurrence of these unspecific stress markers in individuals suggestive of TB, alterations such as *cribra orbitalia*, periostitis, hypertrophy or osteomyelitis of long bones can´t be linked with TB directly unless a biomolecular analysis will confirm a TB infection in the observed specimen. Therefore the here presented conclusions will be additionally confirmed by biomolecular analysis.

Key words: *Pott's disease, Mycobacterium tuberculosis, cribra orbitalia, osteomyelitis, Middle Ages*

Introduction

The analyzed skeletal collection comes from the Early Medieval Slavic cemetery at Borovce (dated to the 8th to the beginning of the 12th century AD), which is situated 80 km North-East from Bratislava. This burial site is from an archaeological perspective special due to the greatest concentration of niche graves of the so called "podmola" type found in Central Europe, and also for the northernmost occurrence of niche graves of the "tunnel" type in Central Europe (Staššíková-Štukovská, 2001). Niche graves were often found at nomadic cemeteries and were therefore often considered to be of Avar origin, or linked with the Avar settlement of the present-day Slovak territory (Štefanovičová, 2002). The grave goods and jewelry indicate the presence of a Slavic social upper class at the site Borovce (Staššíková-Štukovská, 1997).

The sex estimation of the investigated individuals was conducted according to several methodologies (Acsádi & Nemeskéri, 1970; Ferembach, Schwidetzky, & Stloukal, 1979; Houët, Brůžek & Murail, 1999; Knussmann, 1988) in 2006 by Domonkošová Tibenská, Thurzo and Šefčáková. Age estimation followed the complex methodology by Acsádi and Nemeskéri (1970). This Medieval Slavic population was due to its good preservation also analyzed for the presence of skeletal and dental pathology (Staššíková-Štukovská, Thurzo, Šefčáková, Kuželka, & Spišiak, 2005; Šefčáková, 2003; Šefčáková, Strouhal, Němečková, Thurzo, &, Staššíková-Štukovská, 2001), but mainly for the presence of lesions indicating environmental and nutritional stress like *cribra orbitalia* (Beňuš, Obertová & Masnicová, 2010; Obertová, 2005; Obertová & Thurzo, 2004; Obertová & Thurzo, 2008). According to the study of Beňuš et al. (2010) *cribra orbitalia* was found in 48.8% in the Borovce series. Iron deficiency anemia is still accepted as the most frequent cause of *cribra orbitalia* (or CO), with multifactorial etiology including also infectious disease (TB respectively), disease pattern and the host's immune response to it (Kent, Weinberg & Stuart-Macadam, 1994; Stuart-Macadam, 1992). According to Weiss and Goodnough (2005) is iron deficiency anemia in chronic disease linked with decreased plasma iron levels and inflammatory reactions. This might support the hypothesis of a tuberculous origin of anemia or a higher susceptibility to TB due to already persisting anemia and it's manifestation through the co-occurrence of tuberculous and cribrotic lesions.

According to Roberts and Buikstra (2003) only 3–5% of untreated people infected with TB develop bone damage in the skeleton. The pathogen (most frequently *Mycobacterium tuberculosis*) is spread via haematogenous and lymphatic route from a primary focus in the lungs or gastrointestinal tract, most often it is the spine that is involved. When dealing with skeletal remains, the macroscopic diagnostics of TB becomes difficult when only early-stage bone changes are present. A number of studies based on the examination of skeletal collections with known causes of death, focused on searching for atypical or early-stage lesions. These studies enabled to broaden the diagnostic criteria for TB in adding three types of alterations: rib lesions, superficial vertebral changes including hypervascularisation and endocranial alterations (Baker, 1999; Schultz, 2001; Hershkovitz et al., 2002). The presence of these changes was investigated in this analysis. Further we investigated the co-occurrence of *cribra orbitalia* and long bone changes (periostitis, hypertrophy and osteomyelitis) and tuberculous lesions. Cribrotic changes and periostitis are considered stress factors and usually occur in individuals with a weakened immunity due to a series of factors; among them chronic infectious disease. Recently a study by Molnár et al. (2015) reported that atypical or early-TB changes were accompanied by stress factors in a number of cases – *cribra orbitalia* was observed in seven cases, while long bone periostitis occurred in six cases.

The bone changes caused by a tuberculosis infection may be specific or non-specific, meaning they could be related to

TB, but also to a number of other diseases. The differential diagnosis of the tuberculous spine includes: spinal infections (of pyogenic, Brucella or fungal origin), neoplastic (commonly lymphoma, metastasis or malignant bone tumors) and also degenerative age related changes (Kelley & El-Najjar, 1980). However, in case of pyogenic spondylitis there is no active pulmonary tuberculosis, therefore no rib lesions are present in individuals that suffered from pyogenic spondylitis. Active pulmonary TB is present in 60% of all TB infections, therefore in our investigated skeletal collection individuals with both vertebral lesions and rib lesions are very likely to have suffered from tuberculosis rather than from any other illness with spine involvement. Other diseases that can produce similar rib lesions are respiratory infections caused by anaerobic bacteria or mycoses, where a severe pleural infection was present. The incidence and characteristics of rib lesions vary according to the causative organism and chronicity of the infection (Molto, 1990). Actynomycolic infections cause osteolytic and/or osteoblastyc lesions with bone thickening. The lesions found in the skeletal collection from Borovce were classified as periosteal depositions without inflammatory changes. Periosteal depositions on ribs were reported in tuberculous patients with well documented health records as well as in the Terry anatomical collection (Pálfi, Bereczki, Ortner, & Dutour, 2012). This collection provides evidence that endocranial lesions, vertebral hypervascularization, rib periostitis, diffuse periostitis of long bones and especially their association have diagnostic value in the identification of tuberculosis (Pálfi et al., 2012). Therefore in this study we focused mainly on the presence of the combination of certain TB attributable skeletal lesions (and additionally CO and long bone changes) as they may be useful in the diagnosis of TB in dry bone material (Kelley & El-Najjar, 1980).

Aim

This paper aims to present the data on the macroscopic analysis of signs of skeletal manifestation of tuberculosis found in the medieval (8th – 12th century AD) population of Borovce (Slovakia). It will also review the diagnostic criteria used in paleopathology to identify TB and discuss the limitations regarding a macroscopic analysis as well as the distribution of different lesions linked with TB. In addition, it will point out the co-occurrence of tuberculous lesions and *cribra orbitalia* as well as long bone perioste-al changes. These data will contribute to a paleoepidemiological study of TB in past populations living on the present-day Slo vak territory.

Methodology

The skeletal material was analyzed macroscopically. Pathognomic changes related to TB were observed. They can be found in destructive lesions, with little or no new bone formation. A typical location of these changes is the lower thoracic and lumbar spine, also the hip and knee joints, but potentially any bone may be affected (Roberts & Buikstra, 2003). The non-specific changes linked with TB may include bone formation on the visceral surface of ribs, destructive lesions of the bone underlying the skin lesions, bone formation particularly on long bones, tuberculous dactylitis of the hand and foot bones. Another group of unspecific possibly TB induced changes includes endocranial changes due to tuberculous meningitis and changes on pelvic bones due to gastrointestinal tuberculous involvement (Roberts & Buikstra, 2003). Both specific and TB non-specific skeletal changes were present in this collection and put into relationship to location on the skeleton, as well as age of the infected individual and sex. Fisher`s exact test was used to attest intersexual differences in the distribution of TB lesions.

Further, the occurrence of *cribra orbitalia* and long bone lesions in relationship to tuberculous lesions were observed, as they are often connected with high pathogen load and frequent occurrence of infectious diseases (Blom et al., 2005; Buzon, 2006; Stuart-Macadam, 1992).

The morphological analysis of the skeletal series was conducted on a total of 439 individuals (251 adults and 188 subadults). The group of adults consisted of 77 males, 93 females and of 31 individuals which were determined as probably male and 34 as probably female. It was not possible to determine sex in 16 adult skeletons. Among the adult individuals there were mainly mature ones from 40 to 60 (n = 134) then adults aged 20 to 39 (n = 95) and 21 senile individuals older than 60. The group of subadults consisted of 100 children aged 6 months to 6.9 years, of 35 children aged 7 to 13.9 years, of 18 juveniles (14–18 years) and of 35 circumnates.

Results

During the macromorphological analysis of the skeletal material of the medieval site Borovce, only 1 case of TB specific bone changes was detected, and 15 cases of non-specific changes possibly indicating an early skeletal form were detected. These classical TB changes (*Malum Potti*) were observed in an adult (30–40 years) female who suffered from cold abscess, collapsed vertebral bodies with synostosis of the 8th to 12th thoracic vertebrae and thus developed a serious deformation limiting the flexibility of the vertebral column (Staššíková-Štukovská, Thurzo, Šefčáková, & Lietava, 2006). This case from grave No. 22/86 has been previously described in 2006 (Staššíková-Štukovská et al., 2006) and reanalyzed during this study. Besides the above described tuberculous changes of the spine and deformed costovertebral articulations, no other lesions related to an infectious disease could be found, nor on the ribs, or any other bone.

Atypical or early-stage TB lesions were observed in 15 cases: in 6 (2.39%) out of 251 adult individuals and in 9 (4.79%) out of 188 subadults. Including the above described female a total of 2.79% of the adults suffered from TB. Regarding the 9 affected subadult individuals, 5 belonged to the age category of juveniles (14 – 18 years), 3 were classified as Infans I (6 months – 6.9 years) and 1 was aged 7 to 13.9 years. There was a relatively high prevalence of juveniles with TB lesions (27.78%) which was rather due to the small number of individuals in this age category (only 18, out of which 5 were affected).

Regarding the distribution of TB changes in adult individuals of different sex, the results were as following: out of the 7 infected adults 4 were female, but it was not possible to estimate the sex in 3 other individuals (2 were determined as more likely to be male and one as more likely to be female). Considering this age estimation (Domonkošová Tibenská et al., 2006) there were more female adult individuals with TB lesions than male ones. After applying Fisher´s exact test to attest intersexual differences in the frequency of TB lesions, no statistically significant differences could be found in the group of adult individuals ($p = 0.4570$). The distribution of lesions in the group of juvenile individuals looks similar, out of 5 affected were 2 classified as females, 1 as likely to be female, 1 likely to be male and 1 case where sex estimation was not possible (Table 1, Table 2). Again, there were no statistically significant intersexual differences in the distribution of TB lesions ($p = 0.2941$).

Except for 1 senile and 2 mature individuals, the affected individuals represent younger age groups (Table 1, Table 2): 4 adults aged 20 to 39 years and 5 juveniles from 14 to 18 years, as well as children from 6 months to 6.9 years (3 cases) and from 7 to 13.9 years (1 case).

The most frequent lesions were abnormal vertebral vascularization and pitting (Figure 1) with lytic lesions or even with cystic appearance (Figure 2). Vertebral changes only with no other bone affected were found in 2 out of 6 individuals with

Table 1. *Adult individuals with tuberculous lesions*

Sex		Age				
		Not determined	**Adultus** (20–39 years)	**Maturus** (40–59 years)	**Senilis** (60+ years)	**Total**
Not determined	n	–	–	–	–	–
	%	0	0	0	0	0
Males with TB	n	–	–	–	–	–
	%	–	0	0	0	0
Males (?) with TB	n	–	–	1	1	2
	%	–	0	5.26	33.33	6.45
Females with TB	n	–	4	–	–	4
	%	–	9.09	0	0	4.30
Females (?) with TB	n	–	–	1	–	1
	%	–	0	6.67	0	2.94
Total	n	–	4	2	1	7
	%	0	4.21	1.49	4.76	2.79

Table 2. *Subadults with tuberculous lesions*

Sex		Age				
		Circumnatale 5 months intrauterine – 6 months postnatal	**Infans I** 6 months – 6.9 years	**Infans II** 7–13.9 years	**Juvenis** 14–18 years	**Total**
Not determined	n	–	3	–	1	4
	%	0	3	0	100	2.41
Males with TB	n	–	–	–	–	–
	%	–	–	–	0	0
Males (?) with TB	n	–	–	1	1	2
	%	–	–	100	20	33.33
Females with TB	n	–	–	–	2	2
	%	–	–	0	40	33.33
Females (?) with TB	n	–	–	–	1	1
	%	–	–	0	33.33	16.67
Total	n	–	3	1	5	9
	%	0	3	2.86	27.78	4.79

affected vertebral column (including the female from grave No. 22/86). Then there were 3 individuals with affected vertebrae and periosteal reactions on the visceral rib surface (Figure 3) and 1 individual with affected vertebrae and periostitis of the femur. Periosteal depositions were the most frequently found TB non-specific lesion. In 6 cases these depositions appeared on the visceral rib surface where they can be indicative of pulmonary TB, in 3 out of these 6 cases the individuals had also abnormal skeletal changes on vertebral bodies and 2 other individuals had besides affected ribs also atypical endocranial alterations possibly due to tuberculous meningitis (Figure 4).

An association of different alterations could be detected: atypical or early TB changes were accompanied by stress factors in a number of cases. Long bone periostitis was observed in one individual (affecting both left tibia and fibula), abnormal thickening (probably hypertrophy) and/or retroflexion of long bones was observed in 7 individuals. In 3 out of these 7 cases osteomyelitic bone changes were present; in the other 4 cases these changes were classified as thickening of diaphysis of unknown origin (hypertrophy due to a healed fracture was excluded). Long bone changes occurred regardless of age in 7 individuals: 1 infant, 1 juvenile, 2 adults, 2 mature individuals and one individual over 60 (Table 3).

In 7 (43.75%) out of the 16 skeletons suggestive of tuberculosis the above described TB lesions were accompanied by *cribra orbitalia* (mainly the porotic form). Cribrotic changes were found in the orbits of 5 subadults (2 infants younger than 4 years, 1child between 12 and 15 and 2 juveniles aged approximately 15 to19). The 2 adults with cribrotic changes belonged to the age category Maturus II (50–60 years) and Senilis (60+ years), both were estimated as probably male. Surprisingly none of the children with *cribra orbitalia* had additional long bone changes, these occurred only in the two adults with CO (*cribra orbitalia*) and were classified as hypertrophy or thickening of the diaphysis of the tibia. In three of the children with CO, cribrotic changes occurred also on the lamina interna, these endocranial changes could be diagnosed as atypical blood vessel impressions due to tuberculous meningitis. These changes were present only in children under 15, excluding the two juveniles (Table 3).

Discussion

The results clearly show that atypical changes indicative of TB occurred significantly more often (15 cases) than the classical alterations represented by one single case. The one female individual from grave No. 22/86 developed alterations typical

for skeletal tuberculosis. These changes diagnosed as Pott´s disease usually appear as post-primary, late manifestation of tuberculous reinfection in adulthood.

Early TB or non-specific changes were present in 15 individuals, mainly in younger age groups (most of them were juveniles and adults up to 39 years) and then in children of the age categories Infans I and II. Younger adults and children are in general more susceptible to this disease due to a greater degree of vascularity in juvenile bone and a large amount of haematopoetic marrow (Ortner & Putschar, 1985). The clinical presentation depends on the individual´s response to the presence of the pathogen, therefore small children with weak immunity (in the age categories of infants) might have died as a direct cause of a TB infection and therefore no developed or TB typical skeletal changes could be found in these skeletons. The co-occurrence of *cribra orbitalia* and endocranial changes related to *Meningitis tuberculosa* in 3 immatures might support this argument. The co-occurrence of these changes leads to the conclusion that these children suffered from iron deficiency as a direct cause of *Meningitis tuberculosa.* Endocranial changes are caused by an inflammatory meningeal reaction, which leads to fibrous exudates around basal cisterns and the brain stem, and a wide scale of destructions of the internal skull base (Hershkovitz et al., 2002; Kolbinger, Heindel, Pawlik, & Schröder, 1994; Lewis, 2004). The endocranial features found in the three immature skeletons were of proliferative character, with small often conflating grooves, with the greatest concentration at the cranial vault and base. In one case the bone appeared thicker almost hypertrophic. Recent epidemiological studies show that 26–35 % of infected immatures develop meningitis (Teschler-Nicola et al., 2015). No features indicative of a meningeal infection were found in adult individuals from this site. One of the subadults with macroscopic evidence for CO and meningeal tuberculosis revealed also periosteal depositions on the ventral surface of five ribs. Lesions at the visceral surface of ribs are considered unspecific manifestations of TB (Kelley & Micozzi, 1984). Two other (juvenile) individuals with CO had hypervascularized vertebral bodies, only thoracic vertebrae were affected in these cases (as a typical location). In the given context *cribra orbitalia* was frequently linked with atypical or non-specific tuberculous changes in subadult individuals. However these macroscopic observations need to be proved by a biomolecular analysis aimed on confirming the presence of a TB causing bacteria, only then a correlation between cribrotic changes of the orbita and tuberculous changes can be established.

Figure 1. *Abnormal vascularization of the vertebral body of a thoracic vertebra*

Figure 2. *Lytic lesions on vertebral bodies (cystic appearance)*

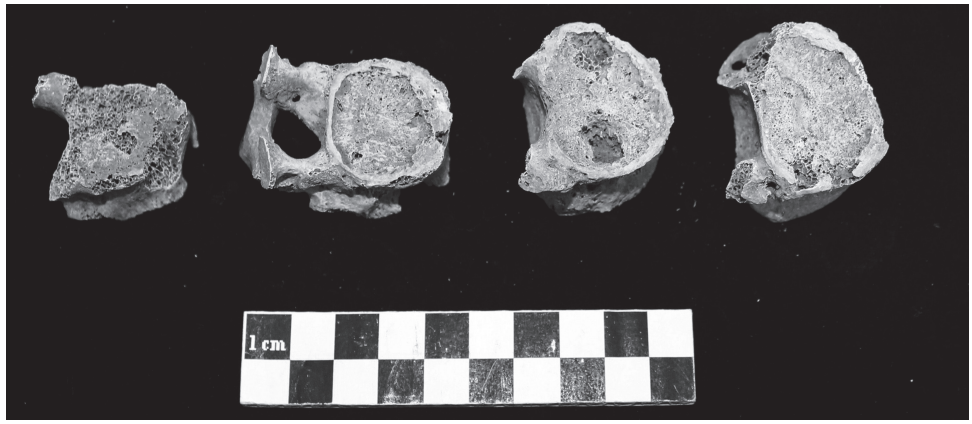

Figure 3. *Periosteal deposition on ventral rib surface*

Figure 4. *Endocranial lesions – probably atypical blood vessel impressions*

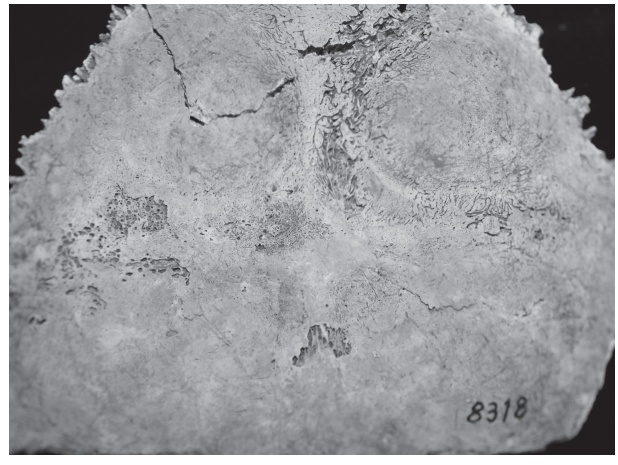

Table 3. *Individuals with TB-specific and TB-nonspecific skeletal changes*

Grave No.	Bone	Macroscopic finding	CO
402/99	Left tibia Right fibula	Thickening of diaphysis, osteomyelitis Thickening of diaphysis, osteomyelitis	–
120/88	Left tibia	Thickening, retroflexion, osteomyelitis	–
337/94	Both femurs Both pelvic bones	Thickening, osteomyelitis osteomyelitis	–
316/94	Thoracic vertebrae Left femur	Hypervascularization, cavitation Thickening, retroflexion	–
220A/92	Thoracic vertebrae ribs Left tibia	Hypervascularization, periostitis periostitis Thickening, retroflexion	+
308/94	Parietal bone	Cribrotic changes, atypical blood vessel impressions	+
179/89	Left temporal bone ribs	Cribrotic changes, atypical blood vessel impressions periostitis	+
22/86	Thoracic vertebrae Lumbar vertebrae	Mallum Potti	–
321/94	Thoracic vertebrae	hypervascularization	+
141/88	Thoracic vertebrae	hypervascularization	+
228/92	Parietal bone	Hypertrophy, atypical blood vessel impressions	+
144/88	Left tibia Left fibula	Thickening, periostitis Thickening, periostitis	–
208A/92	Thoracic vertebrae	hypervascularization	–
154/88	Left tibia Left clavicle	Thickening, hypertrophy thickening	+
145/88	Parietal bone	Atypical blood vessel impressions	–
187/89	ribs	periostitis	–

Through morphological inspection we observed 7 cases of long bone changes (1 infant, 1 juvenile, 2 adults, 2 mature individuals and 1 senile). Only bones of the lower extremities were affected, most frequently by atypical thickening of the cortical bone of the diaphysis and retroflexion, in some cases severe osteomyelitis was observed and some individuals had periosteal depositions. The most frequently affected bone was the tibia. In one juvenile individual with both femurs affected by severe osteomyelitis of the proximal epiphyses and acetabuli of both coxae, and a severe destruction of the articular surface, the infection was diagnosed as tuberculosis of joints. The hip joint is affected in 25% of skeletal tuberculosis cases. Despite of this rather typical location of TB lesions no other bones of this individual were affected. In the other cases of atypical long bone changes, these alterations were linked with hypervascularisation of vertebral bodies or periostitis of ribs. Despite the co-occurrence of these TB indicating features, long bone changes can´t be classified as a skeletal feature attributable to tuberculosis infection yet. These non-specific changes often linked with TB should never be used alone to diagnose TB, and neither can they be proved to be caused by TB based on biomolecular analysis, as they can be caused by many other diseases potentially present in a TB affected skeleton (Roberts, 2015). However, bone formation and destruction, and plotting the distribution pattern of lesions in the skeleton are the first steps towards a differential diagnosis, and may be applied when selecting affected (or probably TB infected) samples for an additional biomolecular analysis.

To verify our presumption that these features may indicate tuberculosis infection, samples were collected from all of the infected individuals and will be analyzed for the presence of mycobacterial DNA.

Currently TB research is relying especially on the analysis of ancient DNA of TB bacteria, as a result of sequencing of the TB genome. These data enable to indicate the species and genotype (strains) of the bacteria that past populations suffered (Roberts, 2015).

Conclusion

A macroscopic analysis of the skeletal collection from the 8^{th} – 12^{th} century site Borovce (Slovakia) revealed one typical case of tuberculosis, diagnosed as *Malum Potti* and 15 early or non-specific cases of this infectious disease.

Tuberculous lesions were more frequented in younger age groups, affecting mainly juveniles and adults up to 39 years.

In three subadult individuals, endocranial lesions indicative of tuberculous meningitis were observed, the central nervous system seemed to have been affected only in immature individuals.

Cribrotic changes of the orbits (*cribra orbitalia*) were present in 7 out of the 16 TB affected cases, but again most of them were immatures. According to this observation, subadult individuals seem to be more susceptible to develop stress markers.

Long bone changes were more frequented in adult individuals and based on the macroscopic analysis only, can be linked with lesions attributable to tuberculosis, such as hypervascula-

rization of vertebral bodies and periostitis of ribs.

Future research and particularly biomolecular analysis and sequencing as additional confirmation of already present macroscopic findings, has the potential to further contribute to a better understanding of the origin and evolution of tuberculosis and the development of different skeletal changes associated with this infectious disease, thus merging the disciplines of paleopathology and modern genomics.

Súhrn

Viaceré štúdie vymenúvajú celú škálu faktorov vplývajúcich na náchylnosť jedinca k tuberkulóze. Zároveň sú často spochybňované lézie poukazujúce na prítomnosť kostnej tuberkulózy. Pri diferenciálnej diagnostike TBC sa v súčasnosti vychádza z tzv. špecifických a nešpecifických lézii na kostnom tkanive, ktoré poukazujú na prítomnosť infekcie. Na základe makroskopickej analýzy 439tich jedincov zo stredovekého pohrebiska v Borovciach bolo možné identifikovať 1 prípad neskorej skeletálnej tuberkulózy a 15 nešpecifických alebo počiatočných štádií. U postihnutých jedincov sa vyskytovala hypervaskularizácia tiel stavcov, periostitída rebier a endokraniálne lézie. Tuberkulóza postihovala prevažne mladých jedincov (najčastejšie juvenilných a dospelých do 39 rokov). U troch nedospelých jedincov sa vyskytli lézie poukazujúce na tuberkulóznu meningitídu. U jedincov s tuberkulóznymi léziami sa často vyskytovali nešpecifické ukazovatele stresu ako *cribra orbitalia* (7 prípadov) a atypické zmeny na dlhých kostiach dolných končatín (7 prípadov) ako periostitída, osteomyelitída a hypertrofické zmeny diafýzy. Napriek tomu, že sa tieto zmeny vyskytovali pomerne často, nemožno ich priamo spájať s týmto infekčným ochorením, pokiaľ nie je TBC doložená výsledkami biomolekularnej analýzy. Za týmto účelom boli odobrané vzorky z postihnutých jedincov, ktoré budú následne testované na prítomnosť patogénu.

Kľúčové slová: *Pottova choroba, Mycobacterium tuberculosis, cribra orbitalia, osteomyelitída, stredovek*

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