

## The earliest recorded case of lepromatous leprosy in continental Croatia

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### Abstract

Among 89 skulls from the Bijelo Brdo site in mainland Croatia dated between the 10<sup>th</sup> and 11<sup>th</sup> centuries, two show osteological features characteristic for lepromatous leprosy. Both skulls were female. The older, estimated between 30 to 40 years age-at-death exhibits inflammatory changes on the palatine process and on the alveolar process of the maxilla, on the inferior nasal conchae and the nasal septum, as well as on the anterior nasal spine. The younger, aged between 15 to 17 years at time of death exhibits less pronounced changes on the inferior nasal conchae, and on the anterior nasal spine. Differential diagnosis excluded fungal infections (aspergillosis, mucormycosis), bacterial infections (actinomycosis, tuberculosis), and granulomatous disorders (sarcoidosis, and treponemal diseases). Molecular genetic analysis targeting the repetitive elements RLEP (36 copies/cell) and RepLep (15 copies/cell) of the *M. leprae* genome confirmed the presence of the disease in the older individual. The possible geography of the spread of this infectious disease in Croatia is discussed.

Key words: leprosy, Bijelo Brdo, Medieval period, Croatia

## 1. Introduction

Leprosy is a chronic granulomatous infection caused by *Mycobacterium leprae* with different clinical manifestations. Depending on the immune response of the host it varies from relatively milder (tuberculoid) form, through one or more intermediate stages to very severe (lepromatous) (Ortner and Putschar, 1985; Renault et al., 2015).

The infection usually involves the skin, mucous membranes, soft tissues, and nerves, while skeletal involvement is present in between 3 to 5% of patients (Resnick and Niwayama, 1995) generally in the lepromatous (or low-resistant) form of the disease, indicating a less-developed host immune system (Roberts and Manchester, 2005). When skeletal elements are involved, the face and small bones of the hands and feet are mostly frequently affected (Ortner and Putschar, 1985).

Cases of lepromatous leprosy have occasionally been recorded in prehistoric and antique series (Köhler et al., 2017; Mariotti et al., 2005; Molto, 2002; Robbins et al., 2009), but the vast majority of cases in Europe occur during the Medieval period. Cases are reported from Italy (Belcastro et al., 2005; Rubini and Zaio, 2009; Rubini et al., 2012), Hungary (Donoghue et al., 2015; Marcsik et al., 2002; Palfi, 1991; Palfi et al., 2002), the Czech Republic (Likovsky et al., 2006; Strouhal et al., 2002), Scandinavia (Andersen, 1969; Arcini, 1999; Boldsen, 2005, 2006), and the United Kingdom (Farley and Manchester, 1989; Manchester, 1981; Rawcliffe, 2006; Roberts, 1986, 2002; Taylor et al., 2000).

Four cases, dated to the period between the 8<sup>th</sup>-9<sup>th</sup> centuries AD have also been recorded in Croatia (Šlaus, 2006). They originate from the medieval cemetery Radašinovci located in the hinterland of the Adriatic coast (Adamić and Šlaus, 2016) and in all these cases the presence of leprosy has been confirmed by DNA analysis (Watson and Lockwood, 2009).

The osteological presence of leprosy in Croatia coincides well with the first historically documented mention of the disease in 804 AD when bishop St. Donatus of Zadar brought the

relics of St. Anastasia to Zadar from Constantinople. Allegedly, numerous lepers from Zadar and the surrounding area were miraculously healed during the procession of these relics (Jeren, 2005). While it is debatable to what degree medieval chroniclers were able to accurately diagnose the presence of leprosy, the mere fact that it is recognized as an independent disease in the 9<sup>th</sup> century argues that it was present in the Croatian population of that time.

As in the rest of the Europe, leprosy was widespread in Croatia between the 10<sup>th</sup> and 14<sup>th</sup> century (Jeren, 2005). The first leprosarium was established in Dubrovnik (Ragusa) in 1272 with the town statute of that same year expressly prohibiting the sheltering of lepers in the city. Additional hygienic regulations of the statute concerned water, sewage and waste disposal, as well as the expulsion of tanneries from the city. These were forced out of town into areas previously inhabited by lepers so that they in turn were forced into more inhospitable areas away from the city (Bakić, 2011). Subsequently, leprosaria were founded in other Eastern Adriatic communities: Trogir (1322), Split (1332), Zadar (1417), Ston (1449), and Šibenik (1467) (Bakija-Konsuo and Mulić, 2009; Bakić, 2011).

The last leprosarium in Croatia was erected in 1905 in the Metković area in order to accommodate all lepers from Dalmatia in times when leprosy was no longer considered to be a priority danger for local communities. The site may have been chosen because of its proximity to Bosnia and Herzegovina that may have harboured an endemic focus of the disease.

In contrast to the relative abundance of historical data available for Dalmatia, historical sources mentioning leprosy and leprosaria in continental Croatia are rare. Only three leprosaria from this part of Croatia are mentioned: Zagreb, Čazma and Oborovo (Ćepulić, 1942; Karbić, 1991). A document of property from Prevlaka (near Oborovo) from 1347 also mentions "A ship of lepers" on the Sava River where local lepers were isolated. Prevlaka

belonged to the Order of Hospitallers whose purpose, among others, was to provide health care and in that context L. Dobronić suggests they provided care for lepers at "The ship of lepers" on Sava River (Belaj, 2007; Dobronić, 1984).

There are no other historical sources regarding leprosy in continental Croatia. Therefore, the two skulls from Bijelo brdo represent the earliest examples of lepromatous leprosy in this part of Croatia.

### 1.1. Archaeological context and osteological material (Historical background)

Bijelo Brdo is located 16 km east of Osijek, and is one of the most important archaeological sites in continental Croatia (Figure 1). It is characterized by the presence of a material culture from the Bronze Age and two medieval cemeteries: an Avaro-Slav cemetery (Bijelo Brdo I) and the Bijelo Brdo culture cemetery (Bijelo Brdo II). The site name later became eponymous for the whole culture.

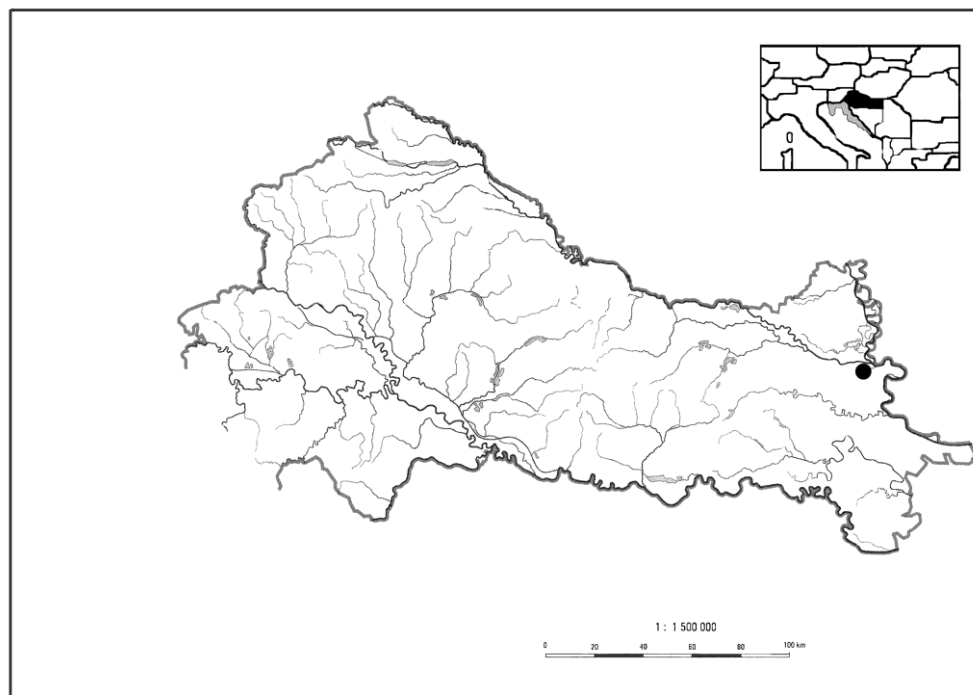


Figure 1. Geographic location of the Bijelo Brdo site.

The Bijelo Brdo culture existed from the second half of the 10<sup>th</sup> century to the beginning of the 12<sup>th</sup> century. This was a multiethnic culture covering an area that includes modern Slovakia, Hungary, Slovenia, continental Croatia, north Serbia, and western Romania. In archaeological terms its main features are skeletal burials arranged in more or less parallel rows in cemeteries without churches, and various material artifacts with similar traits. In terms of subsistence strategy the culture was characterized by small villages practicing a rural and sedentary way of life based on agriculture (Demo, 2009).

Excavation of the Bijelo Brdo II horizon lasted from 1895 to 1907 and revealed the presence of 236 graves. The graves were oriented west-east, with the heads of the deceased positioned to the west (Brunšmid, 1903/4). According to the varied and rich grave goods (jewellery, pendants, buttons, knives, and coins) the cemetery is dated from around 965 to approximately 1061 (Tomičić, 2006).

Unfortunately, as was the custom of the time, osteological material was selectively collected. Only 89 skulls (36 male, 39 female and 14 subadults) are preserved, and are currently curated at the Archaeological Museum in Zagreb, and the Croatian Natural History Museum in Zagreb. Previous studies carried out on this material report on the craniometric features of the series (Pilarić, 1968; Pilarić and Schwidetzky, 1987), and on various dental characteristics (Kranjčić et al., 2012; Vodanović et al., 2004; Vodanović et al., 2005; Vodanović et al., 2006; Vodanović et al., 2007). We were granted access to these skulls in 2013 when a detailed paleopathological analysis of the material was undertaken.

## 2. Material and methods

The skull recovered from grave 83 shows unambiguous skeletal evidence for the presence of lepromatous leprosy, while osteological changes in another skull, from grave 200, while less pronounced are also suggestive of the disease. Unfortunately, the cemetery plan containing the location of grave 83 in the cemetery is not preserved. We do, however, have data on the

position of the skeleton in the grave. The individual from grave 83 was buried in a contracted position without any grave goods (Brunšmid, 1903/4). This skeleton was included in Szabó's later study about deviant burial rites in the Arpad era (1976), and according to his methodology, the individual belongs to II.2 burial type meaning the skeleton was laying on the side with one or both flexed legs. This is unusual, as the vast majority of Bijelo Brdo inhumations were placed on their back, in a prone position with arms variously placed along, or over the chest. To put this in perspective only one other grave (grave number 144) from Bijelo Brdo contained an individual buried in a contracted position (Brunšmid, 1903/4).

We know the location of grave 200 in the cemetery as this part of the cemetery plan is preserved (Figure 2). This individual was placed on his back with both hands crossed on the stomach region where a bronze ring with nodules was recovered (Brunšmid, 1903/4).



*Starohrvatsko groblje u Bijelombrdu kod Brjeka.*

Figure 2. Plan of the Bijelo Brdo cemetery. The arrow indicates the position of grave 200 (the plan was obtained from Archaeological museum in Zagreb).

As in both cases just the skulls were available for analysis, sex was determined on the basis of cranial morphology following standards set by Buikstra and Ubelaker (2004). Age-at-death was determined using dental attrition criteria established by Smith (1984) and Brothwell (1981), as well as from the state of dental formation and eruption (Moorees et al., 1963).

Identification of the pathological features characteristic of leprosy focused on facial changes. These criteria were first established by Møller-Christensen and termed *facies leprosa* in 1978, and later as rhinomaxillary syndrome by Andersen and Manchester (1992). The changes are recognizable as inflammatory change of pitting and new bone formation of the palatine process of the maxilla, inflammatory erosion of the conchae and the nasal septum, loss of bone around the pyriform aperture, absorption of the anterior nasal spine and absorption of the alveolar process of the maxilla (Manchester, 2002).

## 2.1. Molecular examination

Skeletal samples were examined for the presence of DNA from *M. leprae*. Recommended protocols for ancient aDNA work were followed (O'Rourke et al., 2000; Taylor et al., 2010), with separate rooms and equipment for different stages of the process. Small samples, 29 mg of bone scrapings from the left palatine process of the skull from grave 83, and 23 mg from the inner part of the left nasal bone from the skull from grave 200 were taken. These were crushed in a sterile pestle in a mortar and added to 400µl of Proteinase K/EDTA. The slurry was added to labelled sterile screw-capped Eppendorf tubes each containing 10 glass beads (2-3 mm diameter), incubated at 56 °C (Donoghue et al., 2005), and mixed on a bead beater daily.

When the sample was solubilised, it was divided and one aliquot treated with 40µl of 0.1 mol<sup>-1</sup> of N-phenacylthiozolium bromide (PTB), to cleave any covalent cross-links thus

enabling DNA strand separation and amplification (Poinar et al., 1998). Sample tube contents were transferred into separate 9ml tubes of lysis buffer and incubated for 1–3 days at 56 °C.

To complete the disruption of bone and any mycobacterial cell wall remnants, samples were re-mixed in the bead beater. Sample tubes were centrifuged at 10000g for 5 min, and the supernatants carefully removed into clean, sterile tubes. DNA was captured with 40µl silica suspension and mixing on a shaker for 1 h. Tube contents were centrifuged and silica pellets washed once with wash buffer (guanidium thiocyanate), twice with 70% (v/v) ethanol (−20° C) and once with acetone (−20° C). Tubes were dried in a heating block.

When ready to perform PCR, DNA was eluted using 60µl elution buffer, aliquoted and used immediately or stored at −20° C. Silica supernates (500µl) from PTB-negative samples were also collected from the 2.0 ml screw-capped Eppendorf tubes. After chilling at 5° C, supernates were mixed vigorously for 20 seconds with 200µl of Protein Precipitation Solution (SLS Ltd., UK) and centrifuged for 3 minutes at 10,000g. Any pellet was discarded and 600µl isopropanol (−20° C) added to 550µl of each supernate. Tubes were mixed by inversion 50 times and spun 3minutes. Supernates were discarded and tubes washed once with 500µl 70% ethanol (−20° C). After draining, tubes were dried in a heating block. Any precipitated DNA was re-hydrated with 60µl elution buffer, aliquoted and used immediately or stored at −20° C. Negative extraction controls were processed in parallel with the test samples.

### 2.1.2. DNA amplification and detection

Specific regions of the *M. leprae* genome were targeted – the repetitive elements RLEP (36 copies/cell) and RepLep (15 copies/cell). Specific *M. leprae* primers and a fluorescent probe were used, to enable shorter DNA fragments to be detected in a real-time PCR reaction:

The PCR mix included 2mM bovine serum albumin to reduce PCR inhibition (Abu Al-Soud



and Rådström, 2000; Forbes and Hicks, 1996), 2.0mM MgCl<sub>2</sub> and annealing was at 60°C. A hot-start *Taq* polymerase was used to minimize non-specific primer and template binding. Negative DNA extraction and PCR controls were processed alongside the test sample.

Amplification was performed in a final volume of 25µl using a RotorGene<sup>®</sup> 3000 (Qiagen) real-time platform (Taylor et al., 2007). The specific probe enables direct observation of specific amplicons and the determination of cycle threshold (Ct) indicates relative concentration of template. The silica supernates that were used here usually give the best results as these contain the shortest aDNA fragments and aDNA is typically highly fragmented.

### 3. Results

#### Descriptions of the osteological material

The skull from grave 83 belongs to a female individual aged between 30 to 40 years at time of death. Sex was determined based on vertically oriented and smooth frontal bone without projection at the midline, sharp borders of supra-orbital margins, very small mastoid processes, and small projection of the mental eminence of the mandible (Buikstra and Ubelaker, 2004). Age was determined according to degree of dental wear: on the incisors and canines a large dentine area is present, while on the premolars at least one large dentine exposure on one cusp is visible (Smith, 1984). According to parameters of the Brothwell chart (1981) first molar was scored as 5, and the second molar as 4.

Although the maxillary region of the face exhibits some postmortem damage, changes consistent with leprosy are clearly visible. The edge of the inferior nasal aperture is rounded with a lesion 8×3 mm in diameter on the right side (Figure 3 and 4). The inner surface of the nasal bones exhibits moderate porosity (Figure 4). Partial absorption of the anterior nasal

spine is present. The alveolar process of the maxilla is absorbed where *prosthion* has receded above a plane connecting the most prominent point of the alveolar process between the lateral incisor and the canine in both sides of the upper jaw. This resulted in the antemortem loss of both central incisors, subsequent remodelling, and complete absorption of the related alveoli. Antemortem loss of the lateral incisors with alveolar remodelling is also present, although unlike the central incisors they are not yet completely absorbed. Severe porosity of the palatine process of the maxilla with new bone formation is recorded (Figure 5).



Figure 3. Bijelo Brdo, grave 83. Remodelling of inferior nasal aperture, absorption of the alveolar process of the maxilla with antemortem loss of all incisors.

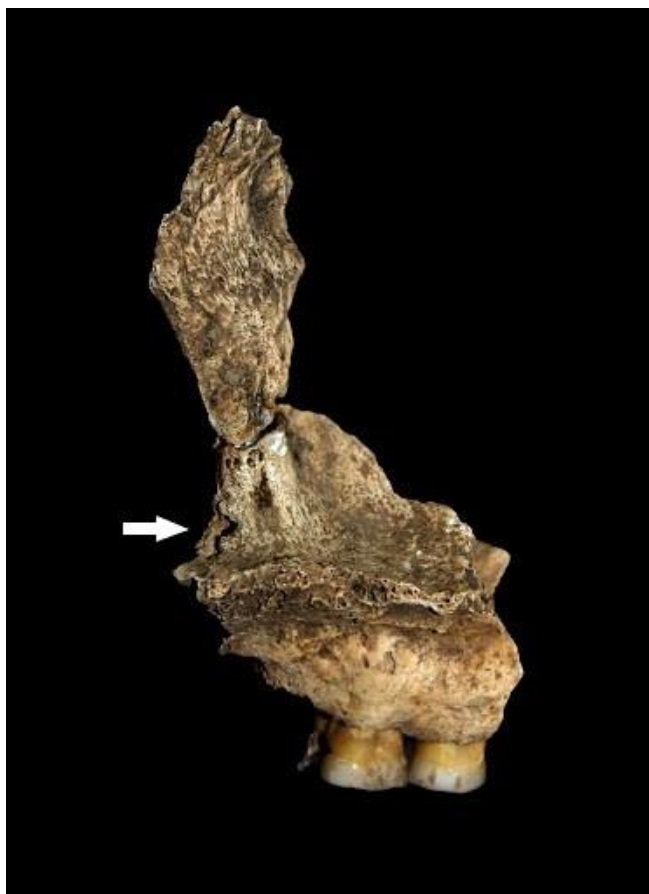


Figure 4. Bijelo Brdo, grave 83. Moderate porosity on the inner surface of the right nasal bone. The arrow pointing to the lesion 8×3 mm in diameter.



Figure 5. Bijelo Brdo, grave 83. Severe porosity and new bone formation on the palatine process of the maxilla.

The skull from grave 200 belonged to a female aged between 15 to 17 years. Sex was determined based on vertically oriented and smooth frontal bone without projection at the midline, sharp borders of supra-orbital margins, small mastoid processes, and smooth external surface of the occipital bone without any bony projections (Buikstra and Ubelaker, 2004). Age was established according to development of the third molar whose root length is approximately two thirds completed (Moorees et al., 1963).

Osteological changes characteristic of leprosy are also detected but unlike the previous case they are not as pronounced. The inferior nasal *conchae* are mildly rounded with absorption of the anterior nasal spine (Figure 6). The central part of the maxilla is intact and absorption of the alveolar process and destruction of the *prosthion* is not present. Moderate, active *cribra orbitalia* is present in both orbits (Figure 7). Mild porosity is present on the palatine process of the maxilla.



Figure 6. Bijelo Brdo, grave 200. Remodelling of the margins of the nasal aperture with the absorption of the anterior nasal spine.



Figure 7. Bijelo Brdo, grave 200. Moderate active *cribra orbitalia* in both orbits.

### 3.1. Differential diagnosis

Since in both cases only the skulls were preserved, changes in the rhino-maxillary region were considered for differential diagnosis. In both skulls the edges of the inferior nasal aperture are rounded, together with absorption of the anterior nasal spine.

To confirm a diagnosis of lepromatous leprosy, the following diseases must be excluded: fungal infections (aspergillosis, mucormycosis), bacterial infections (actinomycosis, tuberculosis), and granulomatous disorders (sarcoidosis, and treponemal diseases - syphilis).

Aspergillosis comes in four forms: allergic Aspergillus sinusitis and aspergilloma are benign non-invasive saprophytic infections, while limited (chronic) and fulminant (acute) forms are invasive. In the latter, infection usually advances with a rapid malignant course. Initial symptoms include ulceration of the nasal mucosa, destruction of the inferior turbinates, erythema and oedema, with the infection progressing with destruction of the sinuses, angio-invasion, and eventual extension into the orbit and brain (Arndt et al., 2009; Milroy et al.,

1989). Bone involvement in invasive aspergillosis is rare, Denning and Stevens (1990) report a clinical study of 2121 cases in which only 1.8% showed bone involvement.

Mucormycosis (phycomycosis) is a rare, invasive fungal infection that affects less than two people per million a year (Bouza et al., 2006). The most common form is rhinocerebral mucormycosis often seen in patients with diabetes mellitus (Roden et al., 2005). The infection starts in the paranasal sinuses after inhalation of fungal sporangiospores. It can rapidly spread to the palate, the sphenoid sinus, and the cavernous sinus to involve the orbits, or cranially to the brain (Hosseini and Borghei, 2005). Generally it affects only one maxillary sinus so hard palate perforation is more often unilateral (Baker, 1971).

Actinomycosis is a rare saprophytic infection caused by *Actinomyces* bacteria characterized by granulomatous and suppurative lesions (Bennhoff, 1984; Smego and Foglia, 1998). Bone is rarely affected, and when it is the mandible, ribs, and spine are most frequently involved (Warrell et al., 2012). Actinomycotic osteomyelitis is uncommon in the maxilla possibly because of its better circulation which provides increased oxygen supply (Crossman and Herold, 2009; Marx and Stern, 2003). Morphologically it is recognized as localized areas of bone destruction surrounded by areas of increased bone density (Warrell et al., 2012).

Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis* that is most often transmitted through the respiratory system. The primary infection usually starts in the lungs, after which it disseminates by the blood stream to other parts of the body – the kidneys, brain and sometimes bones. The spine is the most common (in approximately 40% of cases affected bone element while the skull is a rare area of involvement (Aufderheide and Rodriguez-Martin, 1998; Ortner, 2003). Following long-standing tuberculosis of facial skin and soft tissues (lupus vulgaris), secondarily involvement of the facial bones and bony walls of the nasal cavity can occur (Ortner, 2003). The anterior alveolar process is, however, rarely affected (Møller-Christensen, 1967).

Sarcoidosis is a multisystem, granulomatous disorder of unknown aetiology that most commonly affects the lungs, intrathoracic lymph nodes, the eyes and skin (Chen and Moller, 2011). When involving the skull, it generally affects the nasal bones, but not particularly the anterior nasal spine and never the nasal crest (Robbins and Cotran, 2002).

Treponemal infections are caused by spirochetes of the genus *Treponema*, and manifest themselves in four clinically different syndromes: syphilis, bejel, yaws, and pinta. As pinta does not affect the skeleton it can be ruled out. Bejel and yaws are limited to specific geographical areas (yaws to tropical, and bejel to subtropical areas) and can, therefore, also be excluded. In its tertiary stage, venereal syphilis involves different organs including the skeleton - most commonly the tibia, bones surrounding the nasal cavity, and the cranial vault. The most frequently affected facial bones are the nasal bones, the bony nasal septum, the hard palate, the turbinates, and the lateral walls of the maxillary antrum (Ortner, 2003). The inferior nasal spine and anterior alveolar process are, however, usually spared (Møller-Christensen, 1967; Rogers and Waldron, 1989). Additionally, the first appearance of gummatous, osteoperiostitic lesions in syphilis are usually in the frontal bone, with new lesions occurring in adjacent parietal or facial bones only in later stages (Ortner, 2003).

As none of the diseases previously mentioned match the pathological changes recorded in the Bijelo Brdo skulls, a diagnosis of lepromatous leprosy is the most probable one.

Absorption of the alveolar process of the maxilla resulting in antemortem loss of all incisors is seen only in the skull from grave 83. Alveolar destruction is a slow process caused by osteoclastic stimulation which is usually related to lepromatous leprosy (Marks and Subramaniam, 1978; Subramaniam et al., 1983). A clinical study from Jerusalem (Michman and Sagher, 1957) directly connected resorption of the maxillary alveolar bone and anterior nasal spine, and both processes increase with the duration of the disease. Later, two separate studies from Thailand, and one from Malaysia did not found a direct correlation between two

manifestations, and concluded they occur independently (Marks and Grossetete, 1988; Møller-Christensen, 1974; Reichart, et al., 1976). This could be the reason why resorption of the maxillary alveolar bone was not found in the specimen from grave 200.

*Cribra orbitalia* was recorded in the skull from grave 200. *Cribra orbitalia* may originate from insufficient nutrition and chronic inflammation (Henschen, 1961), however a high frequency of *cribra orbitalia* (63.1%) was noted in leprosy specimens by Møller-Christensen (1961). Some infections of the eyes in leprosy cases result in blindness (Aufderheide and Rodriguez-Martin, 1998), therefore it is possible that *cribra orbitalia* in our specimen is due to chronic infection of the eyes caused by leprosy.

In both skulls inflammatory change on the oral surface of the palatine process of the maxilla are present. In the skull from grave 83 this process is characterized by severe porosity and new bone formation. In clinical cases the prevalence of oral lesions ranges from 19 to 60% with the hard palate being the most frequently affected site. It is directly proportional to the duration of the disease and is thus indicative of its later manifestations (Costa et al., 2003; Varghese and Prakash, 2011). The skull from grave 200 exhibit only mild porosity on the palatine process.

### 3.2. *RLEP and RepLep primers and fluorescent probes*

There are 36 copies of the RLEP repetitive sequence in *M. leprae* and 15 copies of the RepLep repetitive sequence so both are sensitive screening methods. In Real-Time PCR the cycle threshold ( $C_t$ ) is the point where exponential amplification occurs. A comparison of the  $C_t$  indicates the relative concentration of the target DNA, the lower (earlier) the  $C_t$  the more target DNA is present. It is possible to calibrate the reaction with a standard DNA sample but this was not done for these archaeological samples.



In the experiments described below, the sample from grave 83 was positive for *M. leprae* with a lower  $C_t$  with the RepLep target sequence, while the sample from grave 200 was negative. A positive archaeological sample (sample 188 from Moravia dating from the 12<sup>th</sup> century) is used as a positive control.

If there is sufficient target DNA it may be possible to genotype and sub-genotype the aDNA from sample 83. The PCR reactions have been done but the amplified DNA has yet to be sequenced.

As with all work on ancient DNA, the absence of findings does not provide any proof of absence of infection. Stored re-hydrated or eluted aDNA extracts are not stable so the characterization of the aDNA needs to be done as quickly as possible once it is rehydrated.

#### 4. Discussion and conclusion

While analyzing old Slavic names of diseases Grmek (1954) noticed that "the Slavic name for leprosy (*guba*) designated not only the disease itself but also a type of fungi with numerous holes making the relationship unpleasantly picturesque". This may explain part of the intense odium that medieval society had towards lepers. According to Fisković (1963) and Karbić (1991) ill people (*infirmi*) were not excluded or marginalized in Late Medieval Croatian societies with the exception of those suffering from chronic contagious diseases. In this context leprosy was not considered as shameful, but rather as a misfortune as well as a great hazard for the rest of the society. Being ill, and unable to fend for themselves, lepers lost their socioeconomic status, and had to be isolated. Late medieval society took pains to protect these individuals and at the same time protect healthy individuals from contracting the disease. Under forced isolation, all lepers were part of the same social group, often with elements of formal organization (Fisković, 1963; Karbić, 1991). This, however, appears to have been a later convention absent in earlier times. In the Bijelo Brdo cemetery the individuals with

leprosy were buried in the recognized cemetery and the same is true for leprosy sufferers from Radašinovci. The bodies exhibit the same orientation (west-east) and have the same grave finds and grave architecture as the rest of the interred individuals. The same pattern is noted during the early periods of the Middle Ages all over Europe (Balcastro et al., 2005; Manchester, 1984; Roberts, 2002; Rubini et al., 2012).

In this context the position of the individual recovered from grave 83 is interesting. This individual was just one of two cases buried in a contracted position in the cemetery which marks him as a burial differing from the normal burial ritual of the period, region and cemetery. Ethnographic studies suggest that some individuals, because of their special lives or deaths, did not receive normal burials and are treated differently after death (Aspöck, 2008). As the individual from grave 83 differed from her compatriots because of the facial changes caused by leprosy, it is possible that she was buried in a different manner to mark this. While not physically segregated from the rest of her community, distinction may have been accomplished through different body position.

The nearest contemporaneous cases of leprosy come from eastern and southern Hungary. Several archaeological sites dated from the 10<sup>th</sup> to the 11<sup>th</sup> century have skeletons exhibiting pathological changes characteristic of leprosy, with some having additional DNA confirmation of the presence of the disease (Csóri et al., 2009; Donoghue et al., 2002, 2005; Haas et al., 2000; Pálfi et al., 2002). As there is clear archaeological evidence for the existence of trade between continental Croatia and the areas comprising modern Hungary (Demo, 2009; Tomičić, 1991), it appears that the presence of leprosy in continental Croatia is related to the spreading of this infectious disease through contacts with populations from Hungary. Contagion from the Dalmatian hinterland seems less likely because the cases from Radašinovci are not temporally concurrent with Bijelo Brdo, Radašinovci is more distant and has significant geographical barriers (mountainous region) that need to be crossed, and there

is scant evidence for the exchange of merchandise and goods between Dalmatian and continental Croatia.

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