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DIFFERENTIAL DIAGNOSIS OF ABNORMAL ENLARGEMENT AND BENDING DEFORMITIES IN THE SKELETON OF A MEDIEVAL CHILD FROM ST PETER'S CHURCH CEMETERY, RIGA, LATVIA

ABSTRACT: The aim of this research was to consider differential diagnoses for extensive skeletal deformities in the skeletal remains of a child, suggestive of a severe condition compromising the bone structure. The individual was excavated from a medieval cemetery in Riga, Latvia (15th–16th centuries AD) in 2004. Macroscopic, radiographic and biomolecular analyses were carried out on the remains. Macroscopic analysis revealed that the anterior deciduous dentition was missing ante-mortem, with the alveoli almost completely remodelled. Cortical thickening was observed on the long bones of the arms and legs, and on the ribs, and thickening of the diploic space was observed in the skull. Most bones of the skeleton were enlarged and porous. Marked bending deformities of the long bone shafts, as well as the os coxae and ribs, were also present. Radiographic analysis revealed healed fractures of the right humerus and left tibial diaphyses. Biomolecular analysis confirmed that the child was a girl. Based on the appearance of the lesions, diagnosis concentrated on healed rickets (childhood vitamin D deficiency), while juvenile Paget's disease and osteogenesis imperfecta were considered as differential diagnoses. In the palaeopathological literature, it is rare to find such a severe expression and long-standing form of possible healed rickets, especially in a population with a low prevalence of the condition. Poor DNA preservation prevented the ability to explore whether the differential diagnoses had any genetic origin.

KEY WORDS: Healed rickets – Juvenile Paget's disease– Osteogenesis imperfecta – Ancient DNA analysis

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INTRODUCTION

This study focuses on the skeleton of a child excavated from the medieval (15th–16th centuries AD) St Peter's Church cemetery in Riga, Latvia. A part of the cemetery was excavated in 2004 in advance of commercial construction work. The excavations were led by the archaeologist Roberts Spirģis from the Institute of Latvian History, University of Latvia. One of the non-adult individuals had marked skeletal deformities, mainly expressed as bending of the long bones and ribs and thickening of bones.

The aims of this study were to carry out a macroscopic, radiographic and biomolecular analysis and to consider differential diagnoses which could have caused these extensive bone changes and to discuss the most likely diagnosis in more detail. As a result, this study provides a detailed description and visual information of the observed pathological lesions, which were possibly caused by an unusually severe form of a common childhood condition in post-medieval Europe, namely rickets. This study thus adds valuable comparative information for palaeopathological studies focussing on vitamin D deficiency in particular, and children's health in medieval and post-medieval European populations in general. The archaeological and historical context of the burial was also taken into account to support discussions about community attitudes to severe illness in this population.

MATERIALS

During excavation, a trench measuring 180 m^2 was uncovered ahead of building work in the southern part of the St Peter's Church cemetery (SPCC) in Riga, Latvia (Latitude 56.503551; Longitude 24.633801). One hundred and ninety-four burials were excavated. According to associated grave goods such as coins, rings, fibulae (brooches) and other items, the excavated part of the cemetery dates to the 13th–18th centuries AD (Spirģis 2012: 199–201).

There were 70 male, 45 female and 79 non-adult individuals in this area of the cemetery (Zariņa, Dambeniece 2012). Burial 133, which is the main focus of this study, dates from the late 15th or the beginning of the 16th century AD, according to the stratigraphic records of the cemetery, as well as grave goods, which comprised mostly of brooches and coins (Spirģis 2012: 218). The grave was 2.49 m deep, and the child was buried in a wooden plank coffin (*ibid.*). The body was aligned according to Christian burial traditions, supine and extended, with the head to the west (*Figure 1*). The skeleton was very well preserved, with the skull and the post-cranial bones mostly complete and undamaged, with little surface erosion.

Historical background

St. Peter's Church was one of the earliest in Riga, and was built around the end of the 12th to the beginning of the 13th century AD. It was originally the main church of the burghers (citizens) of Riga and, at the time, it was the architectural centre of the newly built city (Spirģis 2012: 180). According to historical sources, a cemetery surrounded the church from the beginning of the 13th century (Henry of Livonia 1993). Apart from St. Peter's Church being one of the earliest churches in Riga, its burial ground was also one of the oldest and largest Christian cemeteries. The SPCC was

FIGURE 1: Burial 133 *in situ*. Photograph by Roberts Spirģis.

in use until 1773 when the council of Riga forbade burials inside the city walls (Celmiņš 2012: 96).

In the late medieval period (15th–18th centuries AD), the dead were buried inside, as well as around, every church in Riga. The tombs inside St. Peter's Church were reserved for the wealthy merchants of the Great Guild (the merchant body) and the master craftsmen, and members of the Small Guild (Šterns 1997). Lower class city craftsmen and their apprentices, who were also members of the Small Guild but could not afford burial inside the church, were buried in the adjacent cemetery (*ibid.*). St Peter's church exclusively served the German congregation (Ķiploks 1987). The German population in Riga enjoyed a higher social status than native Latvian citizens, which often also meant a better economic position due to different laws on property ownership and trade (Čerpinska 2016).

During the period in question, the treatment of the sick inhabitants of Riga was largely dependent on their social status. The old and the poor were traditionally admitted to hospices and hospitals, where they received free, but basic care and medical attention. The medieval hospitals of Riga were built and run similarly to those in western European cities, particularly Lübeck in Germany, and it is likely that the medical care in these establishments was provided in accordance with the Salerno Code of Health (Ordronaux 1870), which was a well-known standard in the hospitals of medieval Europe (Šterns 1997: 298–303). From the 16th century onwards a few medical doctors who had obtained their degrees in the universities of western Europe also offered their services in Riga, albeit for fees only affordable to the wealthier citizens (*ibid.*). Medical care for the general population of Riga was also provided by pharmacies from the 14th century onwards (Vīksna 1993: 17–20). Likewise, the Guilds provided carers for the sick members and their families, and also paid out support in shillings, which had to be paid back after returning to good health (Zeids 1978: 60).

The location of burial 133 within the cemetery, rather than inside St. Peter's Church, suggests that this child's family was not among the wealthiest in Riga, and that they were likely lower class city craftsmen, as explained above. They were, however, members of the Small Guild, and thus their sick child would have been entitled to a carer free of charge, while the financial support in shillings from the Guild could have been used for medical advice from either a private doctor, or pharmacies, or both.

METHODS

Macroscopic and radiographic analyses

To estimate the age-at-death of the child, dental development was the primary focus (AlQahtani *et al.* 2010). Long bone measurements (maximum length) for age estimation purposes were also taken of the right radius and ulna, which were complete and undamaged and did not have any pathological lesions or deformities (Maresh 1970). The measurements were used as comparators with the dental development data in order to detect any growth retardation.

All skeletal elements were observed macroscopically for abnormal (pathological) changes that involved bone formation, bone destruction, and changes in the shape and size of bones. The dentition was also observed for abnormalities. Possible differential diagnoses were considered, taking into account the characteristics and distribution of the abnormal lesions observed, as well as their radiographic appearance.

A radiographic analysis was carried out on all the bones of the skeleton using a Carestream Point-of-Care digital CR reader radiograph machine in the Department of Archaeology, Durham University (settings: 70kVp; 0.500mAs).

Biomolecular analysis

For this research, ancient DNA (aDNA) analysis of bone samples from the skeleton was used in an attempt to determine the sex of the child, and to help in assessing the differential diagnostic options for the pathological conditions observed, particularly osteogenesis imperfecta and juvenile Paget's disease.

Sample selection, preparation and analysis

A fragment of the right temporal bone was selected from the stored skeletal remains, including the petrous pyramid. This bone was chosen because previous research has shown that DNA survives best in this part of the bone because of the bone's density (Pinhasi *et al.* 2015).

The bone sample was washed with 10% sodium hypochlorate and deionized water, ultraviolet irradiated for 30 minutes from each side, and dried for 24 hours. The outer bone layer (~1 mm) was removed with a dental drill. A bone fragment, including the temporal pyramid (petrous portion), was cut out with a dental drill and ground down in a Retsch Cryomill (3 cryo cycles: 2 minutes of precooling at 5Hz and 30 seconds of grinding at 30Hz).

aDNA was extracted using a modified protocol from Keyser-Tracqui and Ludes (2005). Two grams of the bone powder in 5 ml of digestion buffer (5m*M* EDTA, 2% SDS, 10m*M* Tris-Hcl (pH 8.0), 0.3*M* NaOAc and proteinase K 1mg/mL) were incubated at 50 °C for 16 h with constant agitation to keep the powder suspended. After incubation, one volume of phenol/chloroform/isoamilalchohol (25/24/1 v/v) was added and centrifuged at 1000 g for 15 min. The aqueous fraction was transferred to a new tube, one volume of chloroform was added, and it was centrifuged at 1000 g for 15 min. The aqueous fraction was transferred to a new tube and aDNA extracted using the Zymo Research Genomic DNA Clean & Concentrator™-10 kit.

aDNA libraries were made using an Ion Xpress™ Plus Fragment Library Kit. After library amplification, the amplified library was concentrated using an Eppendorf Vacufuge Plus vacuum centrifuge to a volume of 7 µl (V-AQ mode for 25 minutes at room temperature to fully evaporate the liquid) and then resuspended in 7 µl of LowTE buffer. Two rounds of whole human genome enrichment were performed using the myBaits WGE Human kit from Arbor Biosciences. Following each round of enrichment, the library was amplified and concentrated to 7 µl. The library was sequenced on an Ion PGM machine.

Reads were aligned to human reference genome HG38 using BWA-MEM (Li 2013). Sex was determined using the script Ry_compute.py (Skoglund *et al.* 2013) and *AMELY*/*AMELX*/*SRY* amplification (Masuyama *et al.* 2017). A blank control was used, starting from the incubation step, and put through all the same steps as the sample. The full mitochondrial DNA (mtDNA) profiles of the four people involved in handling the sample were sequenced to control for modern contamination.

RESULTS

Macroscopic analysis

Most skeletal elements were preserved for analysis (*Figure 2*). According to the dental development, the age-at-death of the child was estimated to be between 2.5–3.5 years (AlQahtani *et al.* 2010), but the anterior fontanelle, which normally closes around the age of 1–2 years (Haslam 1996), was still open. The length of the right radius and ulna also suggested a considerably younger age range of 9–12 months (Maresh 1970).

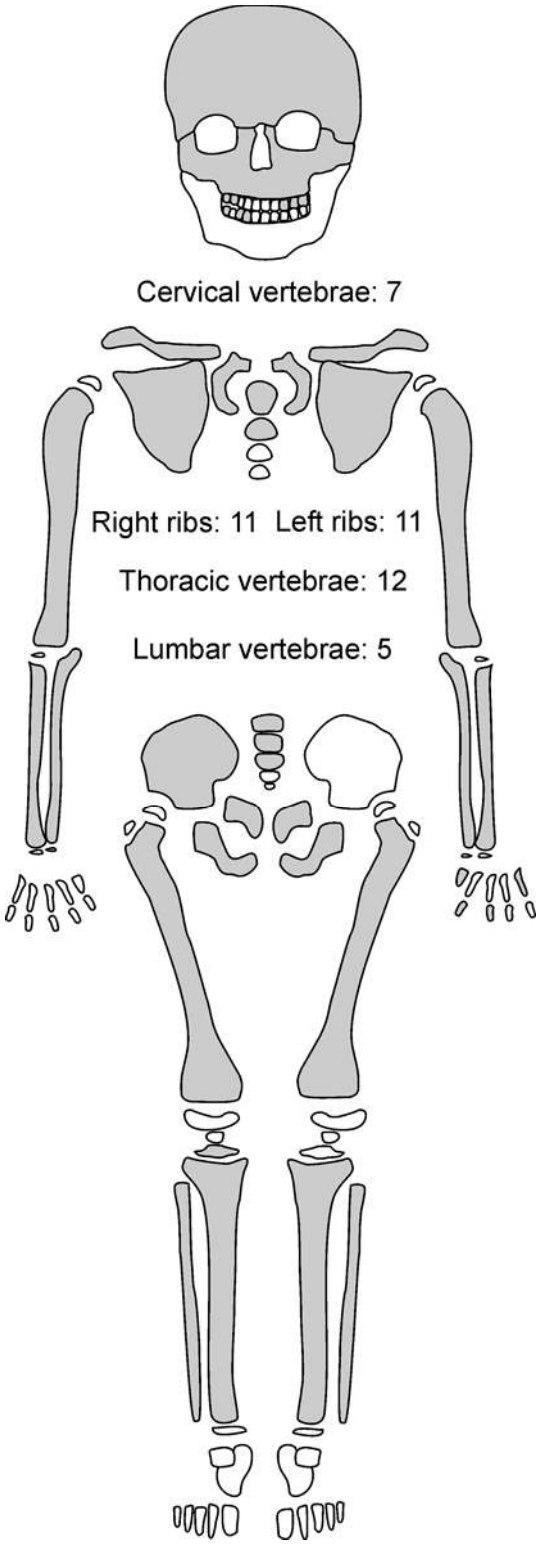

FIGURE 2: Skeletal elements present for analysis (coloured in grey). Diagram after Schaefer *et al.* (2009).

Skull and dentition

The diploë of the left and right frontal bones was thickened posterior to the orbits, while the inner and outer tables of the skull were unaffected (*Figure 3a*). The abnormal change was macroscopically observable on the left frontal bone due to a post-mortem break posterior to the orbit, showing the thickening. The rest of the frontal bone was not affected. The other bones of

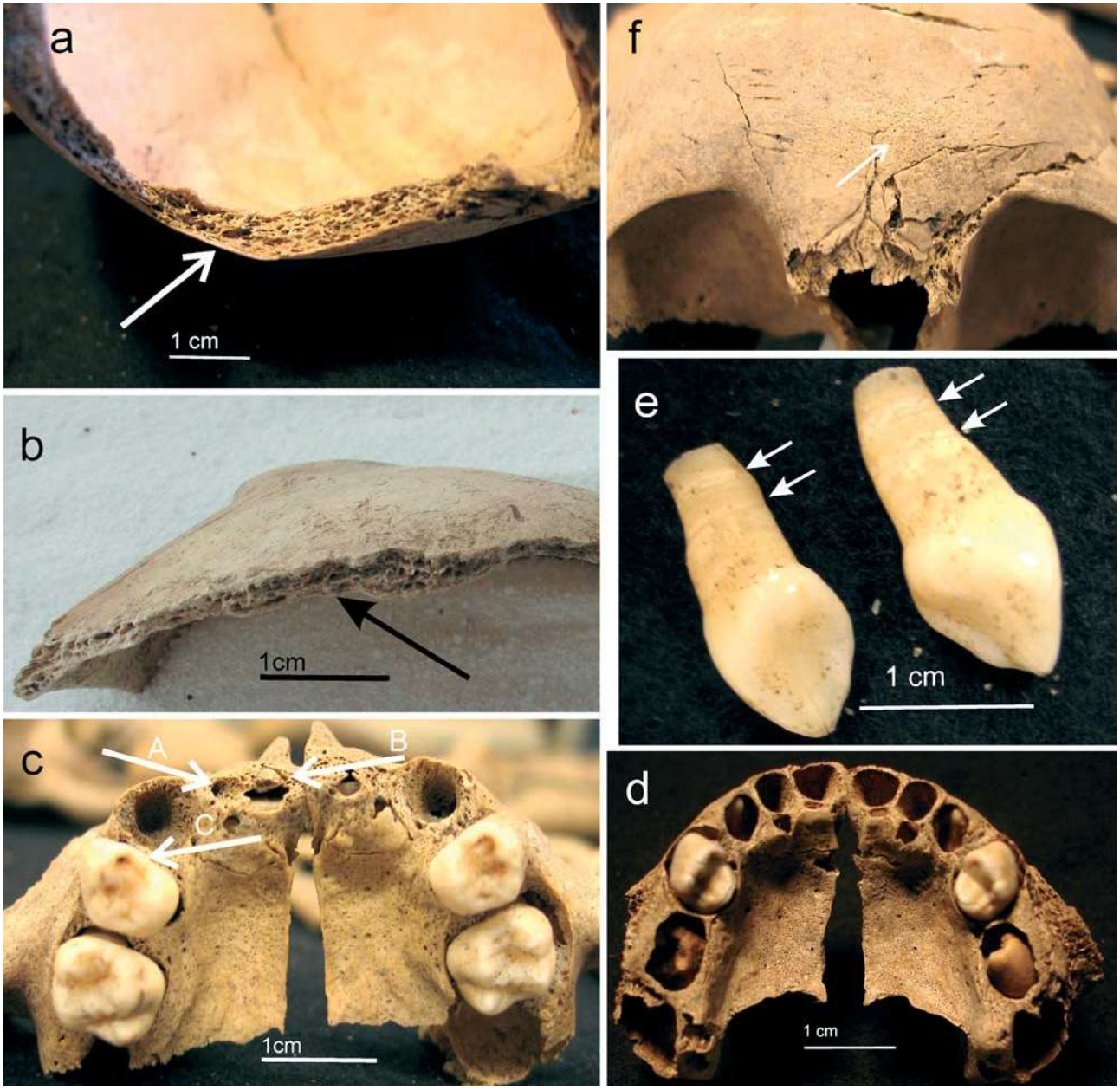

FIGURE 3: Thickening of the diploë in the left frontal bone posteriorly of the left orbit (a, arrow), and the same area of the right frontal bone of an age-matched child (b) (comparative photo with thanks to York Osteoarchaeology); anterior maxillary alveolar bone (c): the arrows show the small alveolus for the second incisor (A), the remnant of the first right incisor (B) and a small caries lesion on the first molar (C); inferior view of the maxilla from a slightly younger child with normal alveolar development (d); the left maxillary canine (e, right) and the right mandibular canine (e, left). The arrows show the "rings" on the roots; the frontal bone, showing slight woven new bone in the glabella area (f).

the cranial vault, including the temporal bones, were also unaffected. All sutures of the skull were open. No sutural ossicles were observed on the bones of the skull vault.

The left maxillary deciduous canine, the left and right first and second maxillary deciduous molars, and a loose mandibular right second deciduous incisor, right canine and right second molar were preserved. No permanent teeth had erupted, but the crowns of both first maxillary molars were present, with the initial stages of root formation evident. A small carious lesion affected the right first maxillary deciduous molar (*Figure 3c*). There was a very small alveolus medially of the right canine

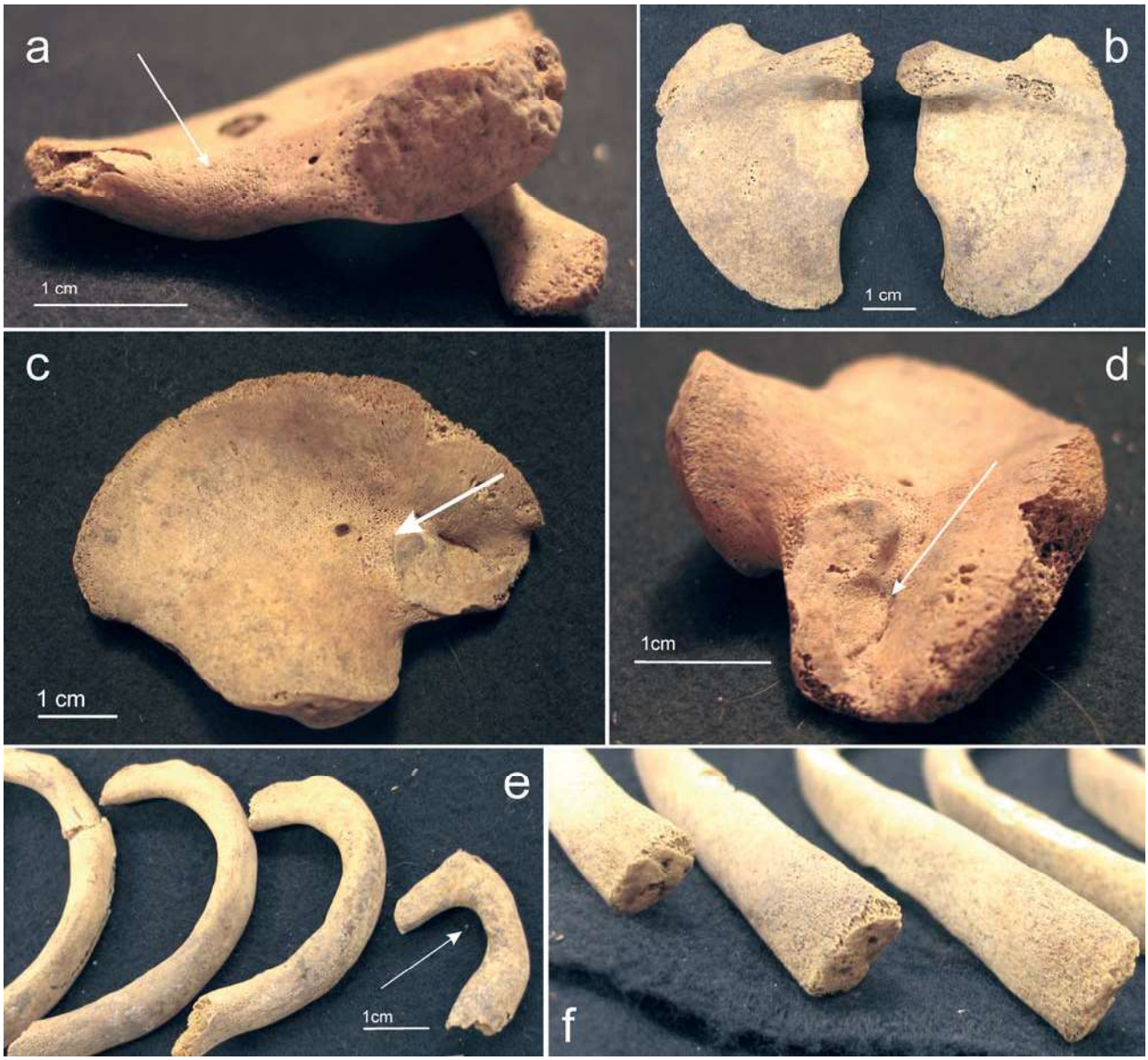

FIGURE 4: The left scapula (a), lateral view, with the arrow pointing to the concave deformity and the associated WNB; both scapulae, posterior view (b); the right ilium, medial view from different aspects (c and d): the arrows show WNB on the concave aspect of the deformity; left ribs from the first to the fourth (e); all are markedly thickened, and the first and second ribs bend superiorly at their sternal ends; the first rib shows an abnormally acute angle - arrowed (e); right lower ribs showing thickening of their shafts and slight porosity towards their sternal ends, but no costochondral flaring (f).

alveolus (*Figure 3c*), suggesting that the deciduous second incisor had been lost some time before the death of the individual; the right first and the left first and second incisors were likely lost ante-mortem and the alveolar bone was completely remodelled, although a remnant of the right first incisor was still in situ (*Figure 3c*). The crowns of the first and second permanent maxillary incisors were in situ. The alveolus for the right canine was shallower compared to the left, and it is possible that the tooth was lost ante-mortem and that remodelling was in progress, although it could have also been lost post-mortem. There were no enamel defects on any of the teeth, but the roots of all the deciduous teeth had distinctive "rings" rather than a smooth surface, similar in appearance to linear enamel hypoplasia (*Figure 3e*).

A thin layer of woven new bone (WNB) was present on small areas of the endocranial aspects of the frontal and parietal bones. Slight WNB was also present ectocranially in the glabella area, but not on the orbital roofs (*Figure 3f*). The wings of the sphenoid bone, as well as its body, and the left and right zygomatic bones, were abnormally thickened. The left and right maxillae also appeared enlarged due to thickening of the trabecular bone. The lateral aspect of the greater wing of the sphenoid bone showed abnormal porosity, and there was WNB on its medial aspect, particularly around the foramen rotundum.

Postcranial skeleton

The scapulae, ribs and the right ilium were abnormally thickened and exhibited bending deformities (*Figure 4a, b, c, d, e*). The scapulae were bent anteriorly, and the ilium medially, particularly in the area of the iliac crest above the auricular surface. WNB was present on the concave aspect of the deformity of the scapulae and the ilium (*Figure 4a, c* and *d*). The sternal ends of the first to fifth ribs, particularly on the left, were porous and bowed superiorly, with the first left rib showing abnormal acuteness of the angle, while no bending deformities were present on the lower ribs (*Figure 4e* and *f*). The shafts of all the ribs were markedly thickened.

On the right humerus there was a sharp medially orientated angular deformity on the distal third of the shaft, and there was remodelled lamellar bone on the concave aspect of the deformity. The whole shaft was thickened and porous (*Figure 5a*). The left humerus appeared normal distally, but the proximal part was also thickened and porous, bending postero-laterally. The radii and ulnae, while markedly thickened too, did not show bending deformities or porosity of their shafts (*Figure 5b*). The long bones of the arms and legs were markedly thickened and showed distinctively thickened cortical bone (visible where the bones had post-mortem breaks, *Figure 5c*). The femora, tibiae and fibulae exhibited severe antero-posterior and medio-lateral bending deformities of their diaphyses (*Figure 5d*).

Other bones were also thickened: the shafts of the surviving metacarpals and hand phalanges, and the shafts of the femora, especially at their distal ends (*Figure 5d*). The femora also displayed coxa vara deformity of their necks. The distal part of their shafts was also porous, the distal third of the right femoral shaft was bent postero-medially at a sharp angle, and there was remodelled lamellar bone on the concave aspect of the deformity (postero-medial side). The left femoral shaft had a similar bending deformity in the same area as on the right side, but the change was less marked. Remodelling new bone was present on the concave aspect of the deformity.

The tibiae were also markedly thickened, and the proximal thirds of their shafts were bent laterally (*Figure 5d*). The proximal bending deformity seemed to be more pronounced on the right bone; WNB was present along the lateral shaft, on the concave aspect of the deformity. The left tibia, although only having slight lateral bending of the proximal third of its shaft, had considerable lateral angulation of its distal shaft (*Figure 5d*). The distal shaft was also porous, with WNB deposits on the concave aspect of the angulation (*Figure 5e*).

The right fibula was also bent medio-laterally, and the whole of the lateral side of the shaft was covered in WNB. There was marked porosity of the proximal shaft, resembling the "slit-strut" porosity seen in palaeopathological examples of rickets (e.g. Ives 2018), albeit with signs of remodelling (*Figure 5f*). The entire shaft of the left fibula was flattened and mirrored the deformity of the tibia. The lateral side of the shaft was covered with WNB (*Figure 5g*). Although the metaphyseal ends of the long bones, and those of the legs in particular, were mostly damaged by factors in the burial environment, the original surfaces, where preserved, were not porous.

Radiographic analysis

The radiographs confirmed that the permanent upper first and second incisors were in situ and that these were developing normally. However, the pulp chambers of the deciduous molars were enlarged (*Figure 6a*). The diploic space appeared normal on the frontal bone, although the thickened area was visible (*Figure 6b*). The trabecular structure of all bones was

FIGURE 5: The right humerus, antero-lateral view (a): the bending deformity of the distal shaft is circled; the thickened right radius and ulna (b); thickened cortical bone on the shaft of the left tibia (c); the long bones of the legs in anatomical position (d); detail of WNB on the concave aspect of the bending deformity of the left distal tibia (e); porosity on the shaft of the right fibula (f); porous WNB on the concave aspect of the angulation deformity of the left fibula (g).

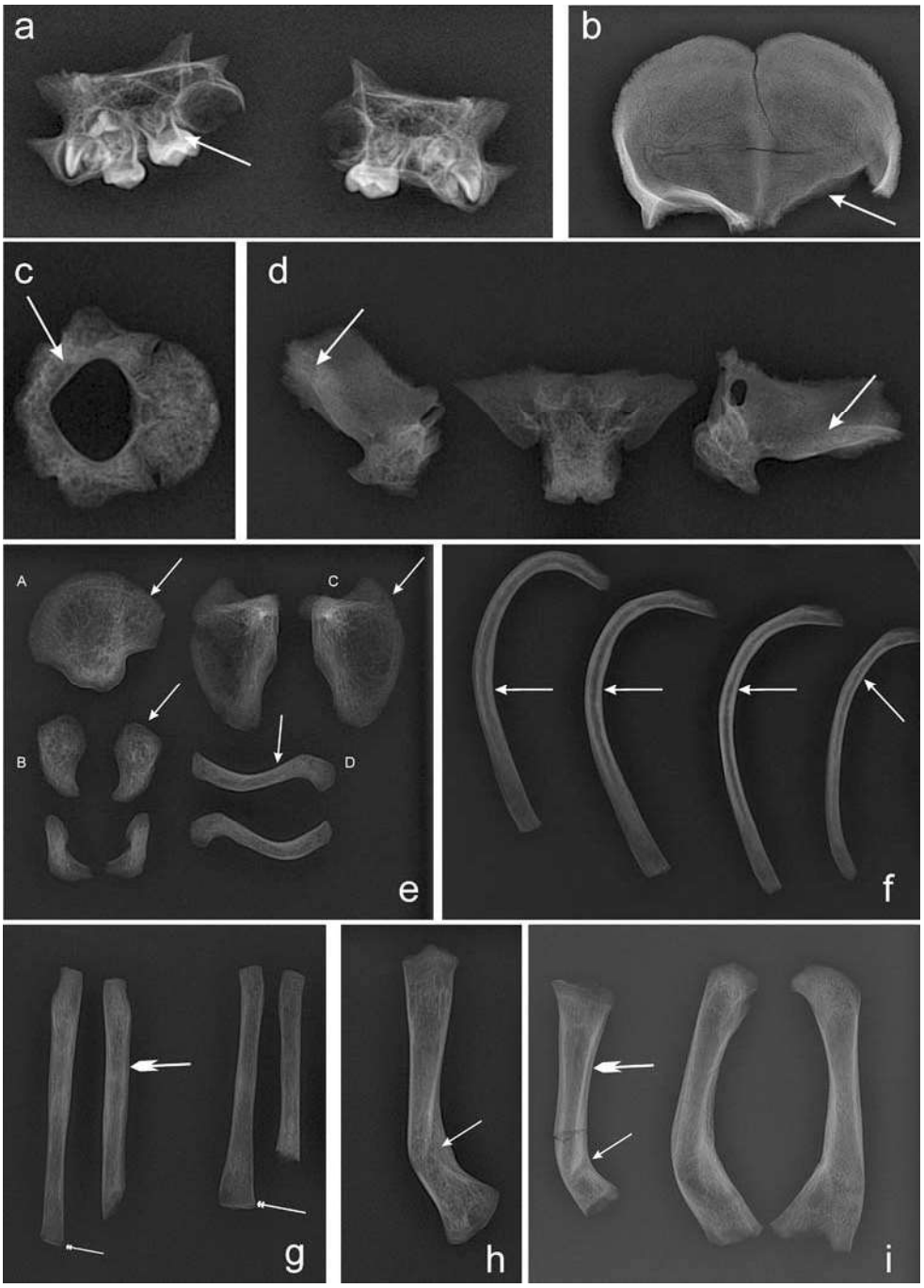

FIGURE 6: Radiographs of the right and left maxilla; the arrow points to the enlarged pulp chamber of the second deciduous molar (a); The frontal bone, with the arrow pointing to the thickened area (b); coarse trabecular pattern on the lumbar vertebra (c, arrow); increased density of the wings of the sphenoid bone (d, arrows); coarse trabecular structure, but no increase in the cortical thickness (arrows) of the right ilium (A), the right and left ischia and pubic bones (B), the scapulae (C) and the clavicles (D) (all 6e); thickened cortices of the ribs (f, arrows); radii and ulnae (g), with double arrows pointing to well-defined metaphyseal ends, and the long arrow pointing to periosteal new bone; the right humerus (h), and the left tibia and both femora (i); arrows show the healed fractures on the right humerus and the left tibia; the long arrow points to periosteal new bone on the tibial shaft.

coarse and particularly evident on vertebrae (*Figure 6c*). The wings of the sphenoid bone showed increased density (*Figure 6d*). The cortices of the scapulae and the os coxae showed no increase in their thickness (*Figure 6e*), while the cortices of the ribs were thickened (*Figure 6f*).

On all the long bones of the extremities, the radiographs showed that the original cortex was covered with periosteal new bone, particularly on the concave aspect of the bending deformities (*Figure 6g, h* and *i*). The distal metaphyseal ends of the radius and ulna were well-defined and did not show any irregularity or fraying (*Figure 6g*). The metaphyseal ends of the long bones of the legs were less well defined and were particularly visible in the distal ends of the femora, and the proximal and distal ends of the tibiae, but this was due to post-mortem damage. The radiographs of the long bones showed healed fractures of the right humerus and the left tibia, located towards the distal ends of their shafts (*Figure 6h and i*). These two bones exhibited the most extensive bending deformities.

Biomolecular analysis

The reads were screened for alignment to genes that are implicated in diseases that were suspected to have caused the abnormalities: *COL1A1, COL1A2, CRTAP, IFITM5, P3H1, PPIB, SERPINF1* for Osteogenesis Imperfecta and *TNFRSF11B* for juvenile Paget's disease. The number of reads aligning to the regions involved in OI or JPD was extremely low, not enabling the detection of the genotype at the critical positions.

From a total of 51 923 227 reads, 18 789 983 mapped to the human reference sequence hg38. The coverage ranged from 0.16X to 1.24X for the chromosomes and was 162.12X for mitochondrial DNA. mtDNA haplogroup was determined to be T2b4a1 using HaploGrep2 (Weissensteiner *et al.* 2016, van Oven 2015). The haplogroups of the people involved with handling the sample were previously determined to be H5a1a, U8a1a1b1, J2b1f and J1c5a, confirming no contamination from the personnel. The blank control contained 277 606 reads, of which 9851 mapped to the human genome.

Using reads of quality ≥30, the Ry ratio was 0,0065 with a confidence interval of 0,0064-0,0067, indicating an XX sex (female). The *AMELY/AMELX/SRY* amplification also showed an XX genotype for both sense and antisense strands (*Figure 7*).

DISCUSSION

According to the results of the macroscopic and radiographic analyses, this child was experiencing a systemic condition at the time of her death, which led to weakening of her bone structure and growth retardation. Taking into consideration the appearance, the distribution and the extensive nature of the observed pathological lesions, diagnosis focused on

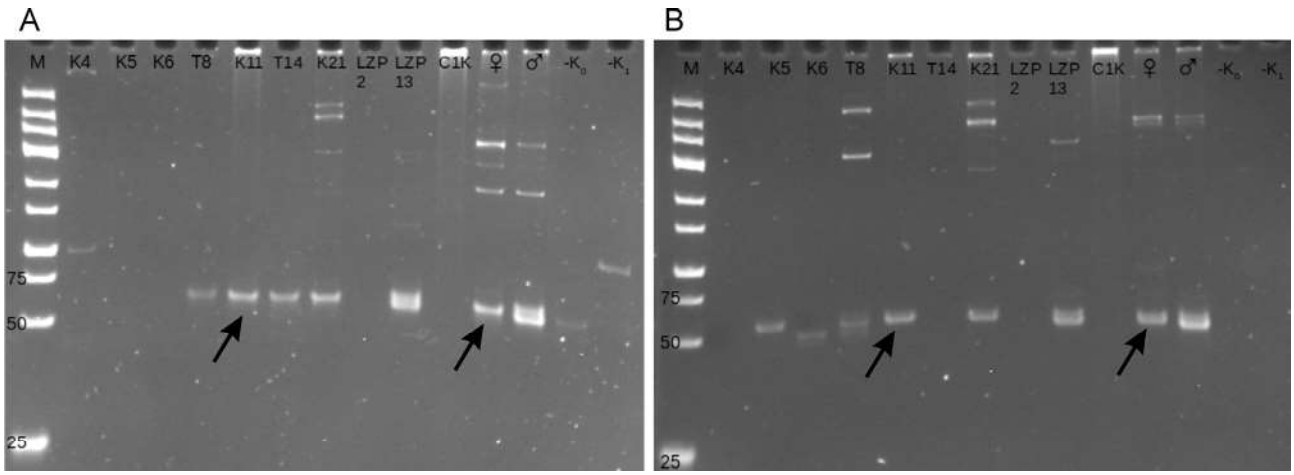

FIGURE 7: PCR fragments of *AMELY/AMELX/SRY* on 15% polyacrylamide gel. A) sense strand; B) antisense strand. K11 – sample described in this paper. M – Generuler DNA Ladder Low Range. Arrows show the sample (left) and XX control (right).

healed severe vitamin D deficiency, which was induced by dietary deficiency and/or inadequate exposure to sunlight. Juvenile Paget's disease (JPD, a rare genetic bone disorder characterised by excessive bone resorption and bone formation that results in bone enlargement and deformities) and osteogenesis imperfecta (OI, a condition that causes a decrease in bone mass and results in bone fragility and multiple fractures) were both considered as differential diagnoses. A brief summary of pathological lesions commonly occurring as a result of these conditions, and their presence or absence in Individual 133, is given in *Table 1*.

The importance of employing various approaches for the differential diagnoses, as recently pointed out by Mays (2018), was taken into account. In particular, comparative and biological approaches were used in this research, since comparative palaeopathological studies were not available for the rare JPD, while only a few studies of OI have been reported in archaeological populations.

Vitamin D deficiency rickets

Vitamin D deficiency in humans, especially infants and children, most frequently occurs as a result of inadequate exposure to sunlight for prolonged periods and/or nutritional deficiency, although sometimes defects in vitamin D metabolism in the body can also cause the condition (Holick 2006). This is because the major natural source of vitamin D in humans is

TABLE 1: Observed pathological changes and their presence/absence in differential diagnoses of healed vitamin D deficiency rickets, juvenile Paget's disease and osteogenesis imperfecta types I and IV. [1]Adams *et al.* 2012; Brickley *et al.* 2018; D'Ortenzio *et al.* 2017; Foster, Hujoel 2018; Hess 1929; Pettifor, Daniels 1997; Pettifor 2012; Pitt 1988; Pommer 1885; Schmidt 1929: 32. [2](Juvenile Paget's disease) Adams *et al.* 2012; Blanco *et al.* 1977; Chong *et al.* 2003; Golob *et al.* 1996; Gonc *et al.* 2018; Horwith *et al.* 1976; Mitsudo 1971; Polyzos *et al.* 2018; Saki *et al.* 2013; Whyte *et al.* 2014. [3](Osteogenesis Imperfecta) Bishop 2010; Glorieux, Rowe 2012; Rauch, Glorieux 2004; Renaud *et al.* 2013; Sillence *et al.* 1979.

Macroscopic changes	Healed rickets[1]	JPD[2]	OI, types I and IV[3]
Skull and dentition			
Thickening of the skull vault without cranial synostosis	YES	YES	NO
Thickening of the other bones of the skull	YES	YES	NO
Premature loss of deciduous dentition	NO	YES	NO
Delayed closure of fontanelles	YES	YES	YES
Axial			
Enlargement of ribs	YES	YES	NO
Long bones			
Widening of diaphyses	YES	YES	NO
Bending deformities	YES	YES	YES
Healed fractures associated with bending deformities	YES	YES	YES
Deposits of new bone on the concave aspects of deformed long bones	YES	YES	NO
General changes			
Growth retardation and short stature	YES	YES	YES
Radiographic changes			
Enlarged pulp chambers of the deciduous teeth	YES	NO	NO
Coarse trabecular pattern in all bones	YES	YES	NO
Thickened cortices of the long bones	YES	YES	NO

through skin photosynthesis following ultraviolet (UV-B) solar exposure (Hess 1929, Holick 2008, Palaniswamy *et al.* 2017). The condition can be exacerbated by an inadequate diet, if it lacks foods that are naturally high in vitamin D such as oily fish and eggs (Holick 2006, Merewood *et al.* 2010).

Vitamin D is necessary for absorption and maintenance of adequate levels of serum calcium and phosphorus in the body, which are responsible for mineralisation of bone protein (osteoid), as well as for maintaining most metabolic functions (Bouillon 2001, Holick 1994, 2006, Mankin 1974). For this reason, one of the main consequences of vitamin D deficiency is poor bone mineralisation leading to a weakened bone structure, which often leads to deformities of the weight-bearing bones. The deformities are more pronounced in children (rickets) than adults (osteomalacia) because of rapid bone growth and remodelling (Huldschinsky 1928, Pettifor 2005).

In the early 20th century and with modern clinical examination methods, the diagnosis of rickets is often supported by radiographs of the most rapidly developing joints, including the sternal rib ends, the distal femur, the proximal humerus, the proximal and distal tibia, and the distal radius and ulna (Hess 1929, Huldschinsky 1919, Huldschinsky 1928, Pettifor 2005). In these joints, the development of the growth plate is visibly disrupted, resulting in fraying and/or cupping of the metaphyseal line (Chang *et al.* 2016, Pitt 1988). In archaeological populations, however, a range of dry-bone manifestations has been described, which would not be possible to observe in modern patients. These are described in detail by Ortner and Mays (1998) and Mays *et al.* (2006), and more recently outlined by Brickley *et al.* (2014, 2018). Among the most common pathological changes observable macroscopically in active rickets are a porous appearance of the metaphyseal ends of long bones, skull vault and orbits, and long bone metaphyseal and rib flaring, although abnormal bending of the long bone shafts is also a characteristic feature, as is delayed closure of the fontanelles (Hess 1929, Pettifor 2012, Mays *et al.* 2006, Ortner, Mays 1998). A recent study has shown that bone changes in archaeological individuals are dependent on age, and thus their presence on certain skeletal elements may vary (Brickley *et al.* 2018).

Apart from macroscopic examination, histological analysis of human teeth can also aid the diagnosis of rickets, as the condition results in mineralisation defects of the dentine, expressed as the presence of interglobular dentine (D'Ortenzio *et al.* 2017). These mineralisation defects can also be traced by observing the morphology of the pulp horns of the teeth by radiographic analysis (D'Ortenzio *et al.* 2016, 2017). Essentially, these are expressed as constricted pulp spaces with chair-shaped pulp horns in permanent teeth (*ibid.*). In deciduous teeth, rickets can cause the expansion of pulp chambers (McDonnell *et al.* 1997).

Several palaeopathological studies focusing on vitamin D deficiency have described lesions that are characteristic of healing or a healed stage of the condition (e.g. Brickley *et al.* 2018, Ives 2018, Mays *et al.* 2006). These include some of the most prominent skeletal changes observed in the current study, such as thickening of the long bones by deposition of new layers of woven and subsequently, lamellar bone, completely healed fractures, and the presence of new bone formation on the concave aspects of the bending deformities. Essentially, normal mineralisation of newly formed bone is only possible once vitamin D deficiency has ceased (Adams 2018: 979). For this reason, deposits of lamellar bone on long bone shafts represent mineralisation of the osteoid accumulated during the active phase of deficiency (*ibid.*), while porous deposits on the concave aspects of long bone deformities likely represent gradual biomechanical adaptation, i.e. reinforcing the part of the bone most subject to compressive forces (Brickley *et al.* 2018, Mays *et al.* 2006).

Likewise, in Individual 133 the metaphyses of the long bones, particularly of the legs, did not show marked fraying and/or cupping, as is common in active rickets (and the metaphyseal ends were well defined in the distal radius and ulna – *Figure 6g*). This was of particular importance because radiographic analysis of the wrist is commonly used to help diagnose the condition in patients today, since it is among the first joints affected (Chang *et al.* 2016, Hess 1929, Huldschinsky 1919, Huldschinsky 1928, Pettifor 2005). Likewise, the metaphyseal ends of the proximal and distal femora and tibiae, where preserved, were not porous, which is considered as one of the most reliable signs of active rickets in archaeological human remains (Brickley *et al.* 2018, Ortner, Mays 1998).

The long bones which were not affected by bending deformities, particularly the radii and ulnae, exhibited smooth cortical bone surfaces, while porosity was observed on the bones with marked bending deformities and healed fractures. The appearance of the porosity, however, was different from the pronounced "slit-strut" defects observed on the growth plates of long bones in archaeological skeletons

showing active rickets, representative of deposits of unmineralized osteoid at the time of death (e.g. Brickley *et al.* 2018, Ives 2018, Ortner, Mays 1998), that is: the porosity was further from the growth plate and thus might represent healed, or healing, lesions which had formerly affected the growth plate but had now become part of the diaphysis as a result of normal bone growth (Adams 2018: 978). This possibility was supported by the smooth edges of the remaining pores (see *Figure 5f*), suggestive of remodelling.

The apparent expansion of the diploic space of the frontal bone, without evidence of porosity on either of the skull tables, might also be a result of healed rickets: deposition of porous new bone on the outer, or both, tables of the skull can cause considerable thickening of the skull vault in severe rickets, when extensive amounts of osteoid formed during the active phase of the disease mineralise (Ortner 2003: 395–6). This would also be true for the facial and sphenoid bones (*ibid.*). Upon healing, the lesions might become undetectable on the original, lamellar, surfaces of the bones. In summary, the observed evidence for both completely healed lesions (e.g. healed long bone fractures, thickened bones of the skull and long bones with normal cortical surfaces) and healing lesions (presence of woven new bone on the concave aspects of the bending deformities of the long bones) might suggest that this child had experienced one or more active phases of vitamin D deficiency, followed by a period of healing, which was ongoing at the time of death.

Although vitamin D deficiency rickets is not known to cause premature loss of the deciduous dentition, caries is a usual finding because dental enamel defects weaken the enamel and make it more susceptible (Zerofsky *et al.* 2016). Since the maxillary incisors were not available for study, it is unknown whether enamel defects were present on them, but a small caries lesion was present on the right first maxillary deciduous molar, as described above. It therefore remains a possibility that at least some of the incisors were lost to caries, which has been reported in patients with severe rickets (McDonnell *et al.* 1997). The teeth might also have been lost due to trauma – traumatic loss of deciduous teeth has been reported in the clinical literature, with the incisors most frequently affected (Holan, Needleman 2014). Both of these possibilities would also explain the remnant of the right first incisor, which might have been damaged by caries or broken due to trauma.

With regard to the time of onset of the disease, the straight radii and ulnae suggest that when the child was beginning to sit up and crawl (on average, around six to nine months of age, respectively in healthy children (WHO Multicentre Growth Reference Study Group, de Onis 2006)), the condition was not active, or was not severe enough to cause bending deformities in the forearms. When the girl was able to stand alone and thus put more weight on the legs (from the age of one year onwards in healthy children, *ibid.*), the condition became apparent. The severely deformed humeri suggest that she had been using her elbows to support the upper part of her body and/or to move around at some point, probably as an alternative to walking due to the fractured tibia. The first descriptions of nutritional rickets in European populations in Leiden, the Netherlands (1645, by Daniel Whistler) and London, the United Kingdom (1650, by Francis Glisson) observed that it was most prevalent in children from wealthy families aged between six months and 2.5 years, after which most children recovered (Pettifor 2012: 627). This age pattern is consistent with this girl and has been explained by the cultural childcare practices of wealthy families of that time, whereby children were largely kept indoors before being able to walk and play outside independently (*ibid.*).

The prevalence of vitamin D deficiency increased in European cities during and after the onset of industrialisation, before the role of sunshine in preventing the condition was understood in the early 19th century (Holick 2006, Newman, Gowland 2017), and it has been reported more frequently in archaeological populations in recent years due to improvements in diagnostic criteria in archaeological remains (e.g. Ortner 2003: 393–404). In post-medieval skeletal populations, less than 8 % of children were affected in London (Lewis 2002), 13 % in Birmingham (Mays *et al.* 2006), and over 30 % in Beemster, the Netherlands (Veselka *et al.* 2015). In a high-status contemporary population from Jelgava, Latvia, the prevalence of rickets was 7.1 % (Pētersone-Gordina *et al.* 2013). The data on rickets in people buried in St. Peter's Church cemetery have not been published yet, but preliminary skeletal analysis suggests that only one of 79 children (1.3 %), apart from the child considered in this study, and two of 115 adults (1.7 %), showed mild pathological changes probably associated with rickets and osteomalacia (vitamin D deficiency in adults); these conditions were therefore not common in this population. The relatively low prevalence of rickets in children from the cemetery populations from Latvia suggests that this condition was not a major

health problem in the region, compared to the more industrialised Western European cities in the post-medieval period. The presence of such a severe case of rickets in this population therefore suggests that the affected child was an exception and that the condition was caused by reasons other than seasonal vitamin D deficiency or common childcare practices. One of the possible explanations is that the girl had been cared for indoors almost since birth because of other health problems, a scenario that has been suggested by Ortner and Mays (1998) who found a high prevalence of the condition in a rural medieval population in Northern England. Another possibility is that the child came from elsewhere in Europe, from a community where childcare practices were different, considering that the cemetery was reserved for the German population of Riga, who were not necessarily all born in the city.

The survival of the child with long-standing, serious health problems for several years after birth suggests that she was well cared for. Having a higher social status than the native Latvian population, the family might have been able to afford visits of a private doctor, and also access remedies available from the pharmacies of Riga. The long-standing vitamin D deficiency, however, likely compromised the immune system of the child and might have led to her death (Pettifor 2012: 635, Zerofsky *et al.* 2016). At death, the child was buried in a wooden coffin, in a single grave among other members of her community. This suggests that severely ill children were not treated differently in death when compared to other children in the SPCC with respect to the burial ritual.

Differential diagnoses

Juvenile Paget's disease

JPD is a rare genetic bone disorder, which is characterised by excessive bone resorption and bone formation. The disease is a consequence of mutations in the TNFRSF11B gene, which causes loss of osteoprotegerin (Whyte *et al.* 2002), a receptor which regulates osteoclast development and function (Udagawa *et al.* 2000). This, in turn, causes extremely rapid bone turnover, which severely affects the growing skeleton (Polyzos *et al.* 2018). The condition also causes abnormally raised activity of serum alkaline phosphatase (ALP) and is therefore also called idiopathic juvenile hyperphosphatasia (Daroszewska, Ralston 2005). In clinical patients today, skeletal deformities develop in childhood and worsen in adolescence. Skeletal manifestations almost always include bone enlargement and deformities (Golob *et al.* 1996, Polyzos *et al.* 2018). The disease has severe, intermediate and mild phenotypes, resulting in different onsets and appearances of deformities. In the severe form, skeletal deformities develop in early infancy, and are later followed by skull enlargement, bending of long bones, kyphosis of the spine, and other deformities (Blanco *et al.* 1977, Chong *et al.* 2003, Gonc *et al.* 2018). Notably, long bone fractures and cortical thickening are more common in the intermediate and mild phenotypes, since children with the milder form of the disease are more active and can often move around independently (Chong *et al.* 2003). Apart from tubular bone and skull involvement, chest deformities arising from widening of the costochondral junctions of the ribs have also been reported; these can lead to severe chest infections, which can even cause death (Chong *et al.* 2003, Saki *et al.* 2013). Likewise, short stature and problems with dental development are common, with delayed eruption of the teeth, premature loss of deciduous and permanent teeth due to poor mineralisation, and absorption of malformed teeth reported in some patients (Blanco *et al.* 1977, Chong *et al.* 2003, Horwith *et al.* 1976, Mitsudo 1971, Naot *et al.* 2014, Whyte *et al.* 2014).

Radiographic features include widening and bending of the diaphyses of the long bones with a disorganised trabecular structure, rapid deposition and remodelling of woven bone, thickening of the cortices of the long bones, increased sclerosis and thickening of the cranial vault (Adams *et al.* 2012: 293–4). Fractures are also common due to the weakened bone structure (Saki *et al.* 2013).

Although rare, the disease is more common in children born to parents who are blood relatives, for example, first cousins (Polyzos *et al.* 2018). This is because in autosomal recessive disorders including JPD, both parents have to carry the faulty gene and pass it onto their offspring. In each such pregnancy, the likelihood of the offspring developing the disease is 25 % (Groden *et al.* 2014).

Likely, because of its rarity in living populations, the disease has never been described in an archaeological population, and Brickley and Ives (2008: 226) have advised that lesions similar in appearance to Paget's disease of bone in juveniles are interpreted with caution before suggesting the diagnosis of JPD.

JPD was considered as a possible diagnosis for this child mainly because of enlargement of all the bones, together with thickened long bone and rib cortices due

to deposits of remodelled new bone, bending deformities, diploic thickening of the frontal bone, growth retardation, deciduous tooth loss, and radiographs showing healed fractures of the humerus and femur. A number of other characteristic changes were, however, absent in Individual 133 (*Table 2*). For this reason, and also due to the rarity of the disease, the diagnosis of JPD remains inconclusive for this girl, even though it could be the first possible example in an archaeological population. Unfortunately, this diagnosis could not be supported through aDNA analysis. This was due to the extremely low number of reads aligning to the regions involved in OI or JPD, not allowing us to detect the genotype at the critical positions.

Osteogenesis Imperfecta, types I and IV

Osteogenesis imperfecta (OI) or "Brittle Bone Disease" is a condition that causes a decrease in bone mass which results in bone fragility. It affects children of both sexes and is caused by mutations in the genes encoding type 1 collagen and, until recently, there was no medical treatment for this condition (Glorieux, Rowe 2012). Like JPD, OI also causes increased bone turnover, and is characterised by increased bone mineral density, but a weaker structure, which can lead to deformities and fractures (Sinikumpu *et al.* 2015). Originally, OI was classified into four main types, each different in severity, signs and symptoms (Sillence *et al.* 1979). The classification was later expanded to include four more main types and several subtypes to distinguish between specific gene mutations, as well as radiological, clinical and histological features (Van Dijk *et al.* 2010).

Type I, or mild, OI is predominantly inherited, and patients have been reported to have their first fracture in the preschool years; mild limb deformities might be present, but stature is normal, or slightly short, in most patients; dental defects are infrequent in this group (Bishop 2010, Glorieux, Rowe 2012, Sillence *et al.* 1979). Apart from the fractures, patients have mild or moderate radiographic changes, and the rate of fractures decreases with increasing age (Adams *et al.* 2012: 289–91).

Type IV is the most clinically diverse group, with signs and symptoms ranging from mild to severe, and moderately short stature and *dentinogenesis imperfecta* being common (Bishop 2010, Glorieux, Rowe 2012, Sillence *et al.* 1979). Sutural ossicles are present in about 50 % of patients (*ibid.*). Because of the diversity of signs and symptoms for patients with the same type of the disease, as well as a lack of a single genotype/phenotype which would be present in all individuals with OI, it is suggested that the description of its severity, rather than its type, is used in modern clinical practice (Rowe, Shapiro 1998).

In archaeological populations, OI is a relatively rare finding. Most of the affected individuals have been found in Egypt, where the condition has been reported in a two-year-old child from Speos Artemeidos (Gray 1970), in a 33–44 week-old foetus from the Dakhleh Oasis (Cope, Dupras 2011), and in five individuals in their late teens or early adulthood from the same site (Sheldrick 1980, 1999). Ortner (2003: 494–5) reported possible evidence of OI in a late adolescent from Juhle, Maryland, USA, and Wells (1965) suggested that the condition caused the deformities seen in an 18-year-old individual from the Burgh Castle

TABLE 2: Pathological changes commonly occurring in differential diagnoses of JPD and OI, but not observed in Individual 133. *Acronyms and references for each condition as in *Table 1.*

Condition*	Characteristic changes not present in Individual 133	Mode of observation
JPD	Irregular trabecular structure (General)	Radiographic
	General sclerosis of bone	
	Involvement of the spine (kyphosis)	Macroscopic
OI, types I and IV	Decreased cortical width (long bones)	Radiographic
	Dentinogenesis imperfecta (teeth)	Macroscopic
	Sutural ossicles (skull vault)	
	Involvement of the spine (vertebral fractures)	

Anglo-Saxon cemetery in Suffolk, England. OI has also been recently reported in a medical description from the 17th century, affecting a woman in her late twenties from Paris, France (Charlier *et al.* 2017).

OI was considered as a differential diagnosis for the child because it causes fragility of bones, fractures and bending deformities. Although OI Types I and IV may indeed cause bending deformities and fractures of the long bones, they are often accompanied by overtubulation, or thinning of the diaphyses (Rauch, Glorieux 2004, Renaud *et al.* 2013), which was not present in the girl's skeletal remains. Other radiographic findings in modern clinical patients include thinner than normal bone cortices and decreased amounts of trabecular bone (Rauch, Glorieux 2004). The most common characteristic changes in OI not present in Individual 133 are summarised in *Table 2* above. Bone thickening, which was observed in the child's skeleton, is not a common occurrence in modern clinical OI patients, based on the published literature. Likewise, OI is not known to cause the loss of deciduous teeth in the absence of *dentinogenesis imperfecta*, which was not observed in this individual. Consequently, OI is the least likely differential diagnosis, but given the diverse range of signs and symptoms, particularly in type IV OI, it remains a possibility, even though it could not be confirmed with aDNA analysis.

CONCLUSIONS

Individual 133 from the SPCC population of Riga had experienced severe skeletal deformities likely caused by a condition that weakened her bone structure. Three differential diagnoses were considered: healed severe vitamin D deficiency; JPD, which is a very rare autosomal recessive disorder and causes bone enlargement and fragility, as well as premature tooth loss; and OI types I or IV, which also cause bone fragility. Unfortunately, although biomolecular analysis confirmed that the child was a girl, due to poor aDNA preservation it was not possible to explore any potential underlying genetic condition that may have led to the observed bone lesions.

Macroscopic and radiographic analyses suggested that the lesions might have been caused by severe rickets earlier in life. Dental caries and trauma were suggested as the most likely differential diagnoses for the premature loss of deciduous dentition. With regard to JPD and Type I and IV OI, both remain as differential diagnoses, given the severity of the observed lesions and a number of characteristic features present in the skeleton.

To aid a more specific diagnosis, further research will focus on microscopic analysis to explore the bones and teeth of this skeleton, and particularly the structure of the dentine. Comparing carbon and nitrogen isotope values between this child and other children in the cemetery may also reveal dietary and/or physiological differences, while strontium isotope analysis will help to determine whether she was born locally or had arrived in Riga from elsewhere. The isotope analysis may therefore add to discussions about the presence and severity of rickets in this child.

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