International Journal of Paleopathology 33 (2021) 280–288

Contents lists available at ScienceDirect

International Journal of Paleopathology

journal homepage: www.elsevier.com/locate/ijpp

Research article

A critical review of the anthropological and paleopathological literature on osteopetrosis as an ancient rare disease (ARD)

Julia Gresky [a,*], Elena Dellú [b], Matteo Favia [c], Davide Ferorelli [c], Francesca Radina [b], Arnaldo Scardapane [d], Emmanuele Petiti [a]

[a] Department of Natural Sciences, German Archaeological Institute, Berlin, Germany
[b] Superintendence Archaeology, Fine Arts and Landscape for the Metropolitan City of Bari, Italy
[c] Interdisciplinary Department of Medicine, University of Bari, Italy
[d] Unit of Radiodiagnostics of the University of Bari, Italy

ARTICLE INFO

Keywords:
Palata 2
Osteosclerosis
Skeletal dysplasia
Metaphyseal flaring
Genetic disorders
Increased bone density

ABSTRACT

Objective: A reappraisal of the available evidence of osteopetrosis in the archaeological record as first step in promoting new approaches to rare diseases in paleopathology.
Materials and methods: Three different approaches are combined: a survey of the last 50 years of bio-archaeological publications; an online search addressing six of the more widely used search engines; macroscopic and radiographic analyses of the human remains from the Neolithic site of Palata 2 (Italy).
Results: The combined results of the literature survey and the online search identified six cases of osteopetrosis. The majority of search hits place this disease into differential diagnoses. The investigation of the remains from Palata 2, one of the six cases in literature, indicates a non-specific sclerosis of the cranial vault.
Conclusions: Of the six cases of osteopetrosis, only two, one of the autosomal-recessive type (ARO) and one of the autosomal-dominant type (ADO), are supported by direct osteoarchaeological evidence. Therefore, inaccurate differential diagnoses generate an inflated number of cases in the paleopathological record.
Significance: This reappraisal calls for a more informed and evidence-based approach to osteopetrosis and, more generally, to rare diseases in paleopathology.
Limitations: Lack of specific publications on osteopetrosis; more case studies may be present in "gray literature".
Suggestions for further research: Cases of osteopetrosis from archaeological and historical collections as well as medical literature are needed to increase knowledge about this rare disease. More precise differential diagnoses are required, particularly when dealing with rare diseases.

1. Introduction

Because of their very low incidence, rare diseases are often unknown to modern clinicians and paleopathologists alike. Today, rare diseases are defined by threshold numbers or point prevalence; for example, in Europe a disease is defined as rare if it affects less than 1 in 2000 people (Nguengang Wakap et al., 2020).

While each of these conditions is rare individually, there are 7000 documented rare diseases affecting about 400 million people worldwide (Blencowe et al., 2018). Rare diseases have a variety of etiologies and thus represent a very heterogeneous class, although 436 of them are primarily genetic disorders of the skeleton (Bonafe et al., 2015). Furthermore, altogether 3792 conditions have the potential to involve the skeletal system and are also of interest to paleopathologists (Köhler et al., 2017). A larger overview of the present state of the paleopathological research on rare diseases has been presented elsewhere in this issue (Gresky et al., 2021). The present article focuses specifically on one rare condition: osteopetrosis.

Rare diseases today, as primarily defined by their prevalence in a population, will be referred to here as modern rare diseases (MRD), while the same diseases assumed to have been rare in individuals from archaeological contexts are referred to as ancient rare diseases (ARD).

1.1. Osteopetrosis, definition and etiology

Osteopetrosis (marble bone disease, Albers-Schönberg disease,

* Corresponding author at: Im Dol 2-6 Haus 4, 14195 Berlin, Germany.
E-mail address: Julia.gresky@dainst.de (J. Gresky).

https://doi.org/10.1016/j.ijpp.2021.05.006
Received 26 October 2020; Received in revised form 17 May 2021; Accepted 17 May 2021
Available online 31 May 2021

osteosclerosis fragilis generalisata, ICD-11: LD24.10) was first described in 1904 by the radiologist Heinrich Albers-Schönberg and is a developmental anomaly characterized by increased bone density (Albers-Schönberg, 1904). The disease is either caused by spontaneous mutation or by genetic transmission and occurs particularly frequently in cases of consanguinity (Enell and Pherson, 1958). With a prevalence of 5 in 100,000 in autosomal dominant osteopetrosis (ADO) and 1 in 250,000 births in autosomal-recessive osteopetrosis (ARO) (NORD, 2020), it is considered a rare disease today. At least 13 different types can be distinguished genetically (Bonafe et al., 2015). Without further genetic testing in skeletons from archaeological contexts, two main types of osteopetrosis can be distinguished: ARO in infants and ADO in adults (Table 1).

ARO begins infancy and left untreated leads to death in the first decade of life (Loría-Cortés et al., 1977). Frequently occurring clinical symptoms are loss of vision, an increased fracture rate, failure to thrive and recurrent infections due to underlying anemia (Gerritsen et al., 1994; Wilson and Vellodi, 2000). Bone marrow transplantation is currently the only successful treatment for this disease (Wilson and Vellodi, 2000).

Table 1
The two main types of osteopetrosis and their skeletal changes distinguishable in skeletons from archaeological contexts.

Osteopetrosis	Autosomal-Dominant (ADO)	Autosomal-Recessive (ARO)
Prevalence	1 : 20,000 births (1)	1 : 250,000 births (1)
Age of onset	late childhood or adolescence (1)	first few months of life (1)
Life expectancy	subnormal to normal (2)	death in first decade of life (2)
Sex dependence	no predilection (3)	no predilection (4)
Skeletal changes (macroscopic)	generalized osteosclerosis, obliteration of the medullary cavity (5) heavy weight of the bones (5) flaring of the metaphysis (particularly proximal humerus, distal femur) (6)	
	mild osteosclerosis of the cranial base (5) potential narrowing of the cranial nerve foramina (5)	severe osteosclerosis of the cranial base (4) narrowing of the cranial nerve foramina (4) macrocephaly and frontal bossing (4) Hypertelorism (4) short stature (6) delay and defects of dental development (7)
	increased cortical thickening and increased overall bone density in skull (base), spine, pelvis and appendicular bones (6) loss of medullary cavity diameter (femoral block) (6) transverse bands of osteosclerosis in long bones (6) flaring metaphyses particularly in proximal humerus and distal femur (6) Bone-within-bone appearance, mainly in iliac wings, vertebrae, phalanges (6) sclerosis of vertebral end plates (“sandwich” vertebrae, “rugger-jersey” spine) (6)	
Skeletal changes (radiographic)	degenerative osteoarthritis of the hip joint (primary or secondary complication) (2,6)	defective dentition with incomplete enamel formation and/or caries (7)
		poorly pneumatized paranasal sinuses (4,6) mandible: characteristic triangular opacity representing calcification within the secondary condylar cartilage ossification centre (7)
Additional changes		"hair-on-end" appearance of the cranium (7)
	increased fracture rate (6), osteomyelitis (2,6)	

Key: 1) Orphanet; 2) Beighton and Cremin, 1980; 3) Bode and Peters, 2002; 4) Loría-Cortés et al., 1977; 5) Bollerslev and Andersen, 1989; 6) Resnick, 1981a; 7) Elster et al., 1992.

ADO develops during adolescence and has a benign course. It can continue without outward symptoms (Johnston et al., 1968), but it is known to have an increased fracture rate due to the instability of the affected bone (Bollerslev and Andersen, 1989; Waguespack et al., 2007). Less often, osteomyelitis and visual loss can be experienced (Waguespack et al., 2007). In both types of the disease, males and females are affected in equal proportion (NORD, 2020). The cause for osteopetrosis is a mutation that leads to a dysfunction of osteoclasts in either their genesis or function (Schulz and Kornak, 2018). Imbalance of bone resorption and formation leads to retention of cartilage and primary bone (Schulz and Kornak, 2018). Accumulation of less stable material affects the stability of bone, and although it appears denser and more compact, the bone has less mechanical strength (Schulz and Kornak, 2018). This results in typical morphological characteristics of this disease group: increased cortical thickening with loss of medullary cavity diameters, transverse bands of osteosclerosis in long bones, and bone-within-bone appearance mainly in iliac wings and vertebrae (Resnick, 1981a).

1.2. Osteopetrosis in paleopathological studies

Although osteopetrosis produces rather distinctive bone changes that can potentially be detected in archaeological skeletons, paleopathological observations of this disease are extremely scarce (Gresky et al., 2021, in this issue). The present contribution critically approaches the available evidence for osteopetrosis in the bioarchaeological and paleopathological literature by taking stock of the present state of research on this disease and by outlining a direction for future studies.

As such, our research is presented following three main steps: (a) a description of the bony changes specific to osteopetrosis and differential diagnosis; (b) a critical review of the evidence in the literature; and (c) a re-examination of the individual from the Neolithic archaeological site of Palata 2 (Italy). The latter is the oldest and most widely cited case of osteopetrosis in the paleopathological literature (type ADO, see below).

The scope of this article goes beyond a mere literature review. Our results suggest that thoroughly vetting the published evidence, as well as streamlining differential diagnostic procedures, are the first steps in promoting specific research fora and ultimately to address the issue of the definition of rare diseases in paleopathology.

2. Material and methods

2.1. Identifying osteopetrosis in skeletons from archaeological context

ADO and ARO display similar skeletal changes due to the same pathophysiological mechanism: delayed or disturbed osteoclast activity. These changes mainly affect the axial skeleton, but also occur bilaterally in the long bones (Bollerslev, 1989). The changes in ARO are more severe as they start earlier in life and its effects on the skeleton are more pronounced. The most valuable diagnostic method is radiography, as it can reveal the internal as well as external features that are pathognomonic of the disease. Computed tomography and microscopic methods may also aid in diagnosing osteopetrosis (Gresky et al., 2020). Relying solely on macroscopic analysis is insufficient, however, as the internal structure of the bones cannot be evaluated. Although changes due to osteopetrosis are rather distinct, particularly in ADO, the different onset of the disease in adolescence and the gradual appearance of the skeletal changes have to be considered, as well as the representation and state of preservation of skeletal remains which can hamper diagnosing.

2.1.1. Macroscopic characteristics

Macroscopically, bones with osteopetrosis attract attention due to their dense appearance and pronounced weight (Albers-Schönberg, 1904). While obliteration of the medullary cavity may be visible when the bones are broken postmortem, this is a non-specific criterion because osteosclerosis is a feature of many diseases (Table 2) and cannot be used

Table 2
Basic guideline for the differential diagnosis of osteopetrosis (ARO and ADO).

Disease /reference	Sex	Age of onset	Distribution	Anatomic district	Osteosclerosis of the cranial district	Area of bone	Bone changes						Additional features
							Type of osteosclerosis	Distribution of osteosclerotic areas	Morphological changes of the medullar cavity	Metaphyseal flaring	Transverse bands of osteosclerosis	Bone within bone	
Osteopetrosis (1-3)	M = F	ARO: infancy ADO: adolescence	Symmetrical	Axial + appendicular skeleton	Base	Dia- and metaphyses	Cortical	Generalized	Narrowing	Present	Present	Present	Increased fractures, osteomyelitis, caries, hip osteoarthritis
Hyperostosis (former ADO I) (3)	M = F	From childhood on	Symmetrical	Mainly appendicular skeleton	Vault	Dia- and metaphyses	Cortical	Generalized	Narrowing	Absent	Absent	Absent	No increased fracture risk
Pyknodysostosis (1,2)	M = F	From childhood on	Symmetrical	Axial + appendicular skeleton	Base and vault	Literature inconsistent	Cortical	Generalized	Narrowing	Absent	Absent	Absent	short stature, hypoplasia of clavicle and phalanges, frontal + occipital bossing, macrocephaly, prominent nose, obtuse mandibular angle
Melorheostosis (2)	M = F	From childhood on	Segmental	Mainly appendicular skeleton	Absent	Dia-, meta-, epiphyses	Periosteal, (endosteal when advanced)	Localized, mainly lower extremities	Possible narrowing when endosteal	Absent	Absent	Absent	*Myositis ossificans*-like ossifications of soft tissue, particularly para-articular
Sclerosteosis (1,4)	M = F	Early childhood	Symmetrical	Axial + appendicular skeleton	Base and vault	Dia-, meta-, epiphyses, proximal	Cortical	Generalized	Narrowing	Present (4)	Present	Absent	Possible syndactyly, severe distortion of the phalanges, increased height, massive mandible
Van Buchem disease (1,2)	M = F	Puberty	Symmetrical	Axial + appendicular skeleton	Base	Dia-, meta-, epiphyses	Cortical	Generalized	Narrowing	Absent	Absent	Absent	massive sclerosis of mandible
progressive diaphyseal dysplasia (1,5)	M = F	From childhood on	Symmetrical	Mainly appendicular skeleton	Base	Diaphyses	Periosteal	Generalized	Enlargement	Present	Absent	Absent	fusiform bony enlargement
Paget's disease (sclerosing form) (2)	M > F	Older adulthood	Asymmetrical	Axial + appendicular skeleton	Base and vault	Dia-, meta-, epiphyses, proximal	Periosteal	Irregular	Absent	Absent	Absent	Absent	bowing of long bones, different microscopic picture
Myelofibrosis(2)	M = F	Older adulthood	Symmetrical	Axial + appendicular skeleton	Absent	Dia-, Meta-, Epiphyses,mainly distal femur, prox. tibia	Endosteal sclerosis, periostal possible	Diffuse	Narrowing	Absent	Absent	Absent	no bony architectural distortion, most affected: pelvis, spine, ribs, humerus, femur
Lymphoma, osteoblastic metastases (2)	Disease-dependent		Asymmetrical	Mainly axial skeleton and femur		Irregular	Irregular	Irregular	Absent	Possible	Absent	Absent	Osteolytic changes and reactive sclerosis
Poisoning by beryllium, lead, bismuth (1)	M = F	Childhood	Symmetrical	Mainly axial skeleton	Absent	Metaphyses	Mainly as sclerotic metaphyseal bands	Localized	Absent	Present (mainly fibula and ulna)	Present	Present	contact with the materials in Neolithic times quite unlikely
Fluorosis (1,2)	M = F	All ages	Symmetrical	Mainly axial skeleton	Base	Dia-, meta-, epiphyses	Periosteal, cortical	Diffuse	Narrowing	Absent	Absent	Absent	ossification of attachments of ligaments and tendons
Primary hyperoxaluria (2,6)	M = F	All ages	Symmetrical	Axial + appendicular skeleton	Absent	Meta-, epiphyses,	Endosteal	Diffuse	Absent	Absent	Present	Present	transverse bands of osteosclerosis particularly at metacarpals, –tarsals, phalanges. "drumstick"-like metacarpals
Renal osteodystrophy (2)	M = F	All ages	Symmetrical	Axial + appendicular skeleton	Vault	Metaphyses	Endosteal	Diffuse	Absent	Absent	Present	Present (rugger-jersey-spine)	Osteosclerosis: cranium, ribs, pelvis, long bones, erosive lesions on phalanges, soft tissue calcifications

Key: 1) Resnick and Niwayama, 1989; 2) Freyschmidt, 2016; 3) Bollerslev, 1989; 4) Beighton et al., 1976; 5) Janssens et al., 2005; 6) Anderson et al., 1983; M = male, F = female, NHL = Non Hodgkin Lymphoma.
The grey shading indicates the similarities between the differential diagnosis and Osteopetrosis.

alone as evidence for osteopetrosis. Flaring of the metaphyses, particularly on the proximal humerus, distal femur, and proximal tibia is evidence of disrupted bone growth because the osteoclasts cannot follow osteoblastic activity (Beighton et al., 1977). The effect on the skull differs between ARO and ADO: in ADO a mild osteosclerosis of the skull base is initially visible, which can intensify and lead to a severe narrowing of the foramina of the cranial nerves. Furthermore, the facial bones can become dense, as well. In ARO, the changes to the skull are much more evident: in addition to osteosclerosis of the cranial base with narrowing of the cranial nerve foramina, macrocephaly, frontal bossing and hypertelorism are also observable (Loría-Cortés et al., 1977). Furthermore, dental development is delayed and defective (Elster et al., 1992). In ARO, retarded growth leads to short stature (Wu et al., 2017). Anemia, a non-specific condition associated with ARO, may induce a "hair-on-end" appearance on the cranial vault (Elster et al., 1992). Fractures are frequently found in ARO as well as in ADO. While appearing very dense, the bone lacks normal structural capacities and tends to break easily (Bollerslev and Andersen, 1989). The femur is most frequently affected (El-Tawil and Stoker, 1993), but fractures are possible in any long bone, as well as in the posterior arch of the vertebrae. Additional changes in ADO are scoliosis, hip osteoarthritis, and osteomyelitis, particularly affecting the mandible in association with dental abscesses or caries (Beighton and Cremin, 1980; Cameron and Dewar, 1977; Johnston et al., 1968).

2.1.2. *Radiographic characteristics*

Radiographically, a general finding is a diffuse sclerosis of the skull (especially the base) spine, pelvis and appendicular bones, evidenced by increased overall bone density, increased cortical thickening and loss of medullary cavity diameter (e.g., femoral block) (Bollerslev and Andersen, 1988; Resnick, 1981a). Apart from this, the specific findings are important for the diagnosis of osteopetrosis and occur in both ADO and ARO: bone-within-bone appearance, mainly in iliac wings, vertebrae, and phalanges is a very distinct feature (Andersen and Bollerslev, 1987; Resnick, 1981a). The spine shows sclerosis of the vertebral end plates, known as "sandwich" vertebrae and "rugger-jersey" spine (Andersen and Bollerslev, 1987; Resnick, 1981a). The enlarged, Erlenmeyer flask-shaped metaphysis, especially of the proximal humerus, distal femur, and proximal tibia show transverse bands of osteosclerosis, visible as alternating lucency between very dense and less dense bone apposition (El-Tawil and Stoker, 1993; Resnick, 1981a).

2.1.3. *Differential diagnosis*

Due to the pathophysiological process of the disease, the skeletal changes are quite predictable. As such, a skeleton with signs of osteopetrosis should be checked for all the features, especially for radiographically visible changes. The latter are crucial to exclude that the characteristic increased weight of the specimens might be caused by post-depositional processes, such as fossilization. Diffuse osteosclerosis alone is not enough to diagnose osteopetrosis. Highly characteristic features of osteopetrosis are the combination of metaphyseal flaring, transverse bands of alternating lucency in the metaphyses, and bone-within-bone. For detailed differential diagnosis see Table 2.

ADO and ARO, having similar skeletal changes, can be differentiated

by their age profile, as children with ARO die within the first decade of life, whereas ADO begins in adolescence (Beighton et al., 1977). The condition formerly known as ADO type I (Bollerslev, 1989) is characterized by a generalized osteosclerosis which, in contrast to ADO (where the cranial base is mainly affected), is most pronounced in the cranial vault and shows no increased fracture rate. This condition is due to an overactivity of osteoblasts and thus belongs to the category of hyperostoses rather than the osteopetrosis category characterized by osteoclast dysfunction (Schulz and Kornak, 2018). The symmetrical distribution of osteoscleorotic areas is essential for the diagnosis of osteopetrosis and excludes Paget's disease, myelofibrosis, and malignancies.

The specific location of osteosclerosis in the skeleton in osteopetrosis (axial and appendicular skeleton), as well as of the cranium (base), and within the affected long bones (dia- and metaphyses), can exclude several diseases like Melorheostosis and skeletal dysplasias. The type of osteosclerosis (cortical) and the distribution of osteosclerotic areas within the bones (generalized) differ from other diseases where it is periosteal or endosteal. The morphological changes of the medullary cavity (narrowed/obstructed) are another important criterion.

The occurrence of metaphyseal flaring, transverse bands of osteosclerosis and bone within bone is a very distinct combination for osteopetrosis. This same co-occurrence might only be shown in cases of poisoning by metals such as lead, bismuth, and beryllium (Resnick, 1981b). Yet, the latter can be excluded by the missing narrowing of the medullar cavity, as well as by taking into account the historical context, as the bio-uptake of high amounts of these materials is unlikely in pre-metal-processing periods.

The limits of the diagnostic criteria presented by Table 2 apply only to the distinction among the subgroups of ADO, which can be achieved exclusively by carrying out genetic testing.

2.2. Literature survey and online search

The literature survey aimed at formulating an assessment of the overall published evidence of osteopetrosis in the anthropological and paleopathological literature. The review was carried out in two steps: a literature survey and a wider ranging online search.

The literature survey targeted the last 45 years of publications within seven major bioarchaeological and paleopathological journals: American Journal of Physical Anthropology (AJPA), Journal of Paleopathology (JoP), International Journal of Paleopathology (IJPP), HOMO, Current Anthropology (CA), Journal of Archaeological Science (JAS), and the International Journal of Osteoarchaeology (IJO). For the same 45-year interval, our research extended to other relevant venues for the publication of the latest results in bioarchaeological research, although paleopathology is only a very small part of their scopes: PLOS One, the Proceedings of the National Academy of Sciences (PNAS) and the journals published by the editorial groups Nature and Science – American Association for the Advancement of Science (AAA). The literature survey was carried out within the framework of a larger bibliometric study aimed to provide a quantitative estimation of the representation of ARD in the scientific literature. The results are presented elsewhere in this issue (Gresky et al., 2021, in this issue).

The online search collected and cross-compared the data generated by the following keywords: (1) Osteopetrosis, Marble bone disease, Albers-Schönberg-Disease; (2) Paleopathology; (3) Bioarchaeology, Osteology, Osteoarchaeology. Other semantically broader keywords, e.g. Anthropology, Archaeology, Ancient and Past, were expected to produce a high number of non-relevant results and therefore they were not included. The queries were directed at the six most commonly used search engines globally: Google, Duckduckgo, Boardreader, Wiki.com, Yandex and Bing, using a non-biased user profile. Each search engine uses a different algorithm and some predominantly handle part of the search queries in different areas of the globe. Unlike the literature survey, the online search was not limited to a specific time span, although all the search hits refer to contributions published in the last 50 years. Despite the differences between the six search sites, the results show minimal and non-relevant differences and will be discussed below as a single dataset.

2.3. Neolithic individual from Palata 2 (Italy): case review

As part of the larger project on paleopathology of osteopetrosis presented here, the authors carried out a new analysis of the bones belonging to Individual 2, SU21, from the Neolithic settlement site of Palata 2 (Canosa di Puglia, Italy), which was first published by Favia and colleagues in 2010 as a case of autosomal dominant osteopetrosis (ADO). The individual was recovered in 2008 during excavations led by the Superintendence for the Archaeological Heritage of Apulia (Radina et al., 2010; De Nicola et al., 2010). The Neolithic occupation of this area is well documented by a large corpus of archaeological evidence and it plays a key role in the crucial changes leading to the formation of the first settled communities in this area between the 7th and the 6th mill. BC (Radina et al., 2011).

The individual was buried in a single grave pit that was dug into layers filling the moat that surrounded the settlement. Consistent with mortuary patterns noted at the site (Barbieri et al., 2017), the body was buried in a flexed position on its left side, with upper and lower limbs hyper-flexed. No grave goods were found in association with this individual. The skeleton was largely complete; only a small number of vertebrae, ribs, carpal and tarsal bones were missing (Fig. 1A). However, the preserved bones were heavily eroded and fragmented (Grade 3 according to Brickley and McKinley, 2004), and most of them were covered by a hardened layer of calcareous deposits. The osteological analyses published by Favia and colleagues (2010) determined that the bones belonged to a young adult (between 25 and 35 years old) male with a robust build and exhibiting skeletal changes consistent with a diagnosis of osteopetrosis. The results of the radiocarbon analysis, published by the same authors, date the individual to 6571 ± 50 BP, calibrated 2σ 5630−5460 BC (CEDAD, Università del Salento, Italy).

For the current study, a detailed macroscopic evaluation and documentation of the skeleton was undertaken, followed by radiographic and computed tomographic investigations carried out at the Unit of Radiodiagnostics of the University of Bari (Italy), led by Prof. A. Scardapane. The radiographic analyses were carried out using a remote-controlled Siemens Luminos with automatic exposure, while the computed tomographic investigations were carried out by an Aquilon One Toshiba 320 slice (0.6 mm thickness, kernel sharp, 120 kV, 200 mA).

3. Results

3.1. Literature survey and online search

The literature survey identified 24 published articles mentioning osteopetrosis; of them only two specifically refer to the condition and will be discussed below. The remaining 22 mention this condition along with others within a list of possible differential diagnoses and none of the cases present skeletal evidence for osteopetrosis.

Of the two articles specifically focused on osteopetrosis, one is a conference abstract with a major focus on diagnostic imaging techniques (McEwan, 2009) that mentions a tentative diagnosis of osteopetrosis in a medieval skeleton, diagnosed by means of dual energy X-ray absorptiometry (DXA) and plain radiography, along with bone histomorphometry. The author acknowledges the limits of providing a reliable diagnosis for such a largely unknown disease, but no more details are provided. The second article is a brief communication noting the presence of a case of osteopetrosis within the Swiss Galler Collection of human remains (Rühli et al., 2003). The article refers to one of 600 individuals diagnosed as osteopetrosis dating between the late 19th and early 20th centuries. No further documentation is presented for it.

The online search produced a number of relevant results that range

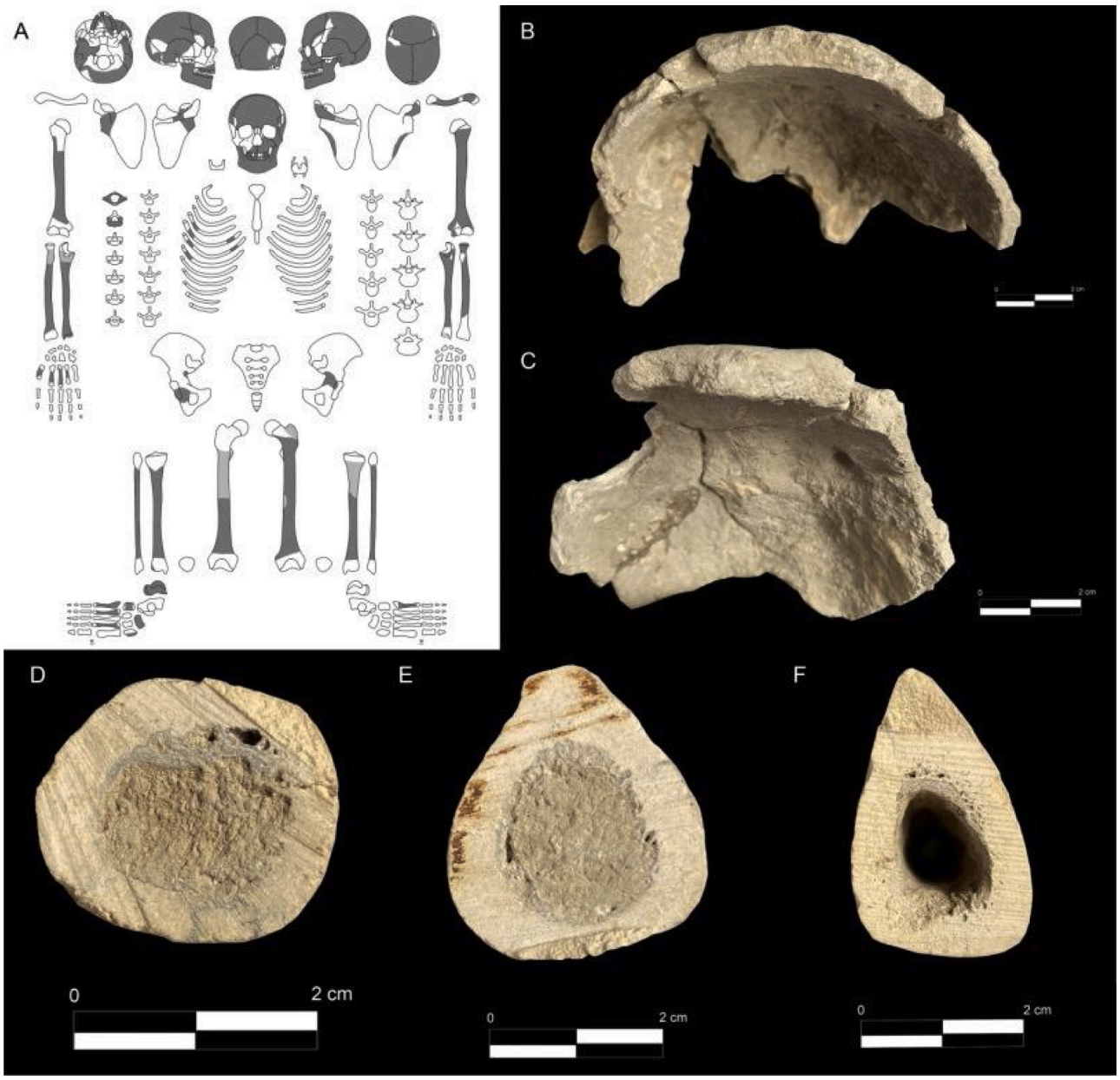

Fig. 1. Individual 2, SU21, from Palata 2. A: Skeletal inventory; well-preserved bones in dark gray, fragmentary bones in light gray, absent bone in white. B: Coronal suture of the frontal bone. C: Lambdoid suture of the occipital bone. D - F: Cross sections of long bones cut previously (Favia et al., 2010), showing the medullary cavity filled with soil. Middle of the diaphysis, D: Right humerus, E: Right femur and F: Left tibia.

from 118 to 139 hits, depending on the search engine used. Excluding overlapping data (i.e. different results for the same webpage), the highest number of hits resulted from the queries including "osteopetrosis" and "paleopathology" as combined keywords. According to the same selective criteria described above for the literature survey, between 25 and 32 search hits relate to articles mentioning osteopetrosis within a list of possible differential diagnoses, but without presenting skeletal evidence for this disease.

Of the remaining results (107 search hits - the highest number from all search engines combined), about 75 % (81 search hits) are manuals with a major focus on paleopathology that mention osteopetrosis, while about 15 % (16 search hits) are internet or social media pages announcing, mentioning or commenting on the 1st Workshop on Ancient Rare Diseases (1st W.A.R.D.), organized by our research group at the beginning of 2019. The high number of search hits generated for this meeting may be related to the recency of this event, as well as from the presence of a poster and a presentation about osteopetrosis hosted by it and, likely, from its website image, depicting a bone with changes due to the same condition.

Finally, about 10 % (10 search hits) of the online search results are contributions that actually discuss skeletal evidence for six cases of osteopetrosis (Table 3).

The first published case of osteopetrosis is an autosomal-recessive type (ARO) observed in a 3.5-year-old child from Late Antique Nubia (Nielsen and Alexandersen, 1971). The individual was represented only by the mandible; nevertheless, the description provided by the authors matches most of the changes expected for a case of subadult osteopetrosis (ARO). The mandible, defined as "unusually heavy", presented "heavy sclerosis of the bone, the cortex not being distinguishable from the spongiosa" (Nielsen and Alexandersen, 1971, 125). The radiological documentation confirms the osteosclerotic bone structure with obliteration of the trabecular bone and the presence of malpositioned teeth with misshaped roots.

The second published case of osteopetrosis is from Christ Church,

Table 3
Information about the six published cases of osteopetrosis in skeletons from archaeological contexts ordered according to their first publication.

Site	Date	Diagnosis	age at death, sex	Methods used	Type of work	References
Site 25: Nubia	350–550 AD	ARO	3.5 years, not available	macroscopy, radiology	journal article	Nielsen and Alexandersen (1971)
Spitalfields: London, Great Britain	18th–19th AD	ARO	three infants, not available	macroscopy, radiology	conference proceedings monograph chapter	Waldron et al. (1989) Molleson et al. (1993)
Abydos, Egypt	Intermediate period (2134–1797 BC)	likely ARO	infant, not available	not available	conference proceedings journal article	Baker (1999) Baker (2001)
Palata 2: Italy	5630–5460 BC	ADO	adult male	macroscopy, radiology, microscopy	conference proceedings conference proceedings	Favia et al. (2010) Favia et al. (2019)
Maliq, Albania	4620–4456 BC	ADO	adult male	macroscopy, radiology, computer-tomography, microscopy	conference proceedings journal article	Gresky and Petiti (2017) Gresky et al. (2020)
St. Stephen's monastery, Jerusalem	Byzantine period	possibly ADO	adult, not available	not available	monograph chapter	Sheridan (2018)

Spitalfields, England (Waldron et al., 1989). The presence of abnormal sclerosis in some areas of the skeleton detected by radiographic analyses suggested the diagnosis of osteopetrosis for three infants. In one of them "the base of the skull, lower limb bones, pelvis, and thoracic and lumbar vertebrae were sclerotic, but the upper limb bones, scapulae, and mandible were barely affected", while in a second one "the disease was widespread, the long bones, vertebrae, skull base, and mandible all being affected" and in the third "the disease was patchy, affecting the limb bones (which have radio-translucent zones at the proximal and distal ends), and the petrous temporal bones" (Waldron et al., 1989:4). After being published as a case of osteopetrosis (Waldron et al., 1989), the final review confirmed that the sclerosis visible on the bone radiographs was induced by high lead contamination from the coffins, which simulated the general dense appearance in the skeletons (Molleson et al., 1993).

The third case of osteopetrosis is an autosomal-dominant osteopetrosis from Neolithic Albania (Gresky and Petiti, 2017), confirmed by radiographic, computed tomographic, and microscopic diagnostics (Gresky et al., 2020). The fourth case of autosomal-dominant osteopetrosis is from Neolithic Palata 2, Italy (Favia et al., 2010) is discussed in detail below.

The publications of the remaining two cases of osteopetrosis make reference to, respectively, a case of ADO from St. Stephen's monastery, modern-day East Jerusalem (Sheridan, 2018), and a possible case of ARO from Abydos, Egypt (Baker, 1999, 2001). Two of these publications (Sheridan, 2018; Baker, 2001) briefly mention the affected individuals in the context of a broader osteological report. The third publication (Baker, 1999) is part of the proceedings of the Meeting of the Paleopathology Association and specifically refers to a presentation discussed by the author at the Roundtable Workshop on Congenital Disorders (Merbs et al., 1999). Therefore, none of them present detailed documentation and diagnostic results for these cases of osteopetrosis, as it would have been beyond the scope of either article.

Furthermore, a review of the cases of osteopetrosis would not be truly exhaustive without considering a further source of information that is available to any paleopathologist studying this disease: anatomical and medical collections. Most of them have been acquired within the course of the last two centuries and cannot be strictly considered archaeological. However, the archaeological evidence for osteopetrosis is so sparse that insights into disease pathophysiology provided by anatomical collections cannot be overlooked.

Besides the individual from the Swiss Galler Collection (Rühli et al., 2003) mentioned previously, a second case (WM S66.2 and S66.3 from 1932) is among the materials stored at the Royal College of Surgeons, London, England and was presented by Ortner (2003). Furthermore, the "osteopetrosis" section of the Fairbank collection of the Royal National Orthopaedic Hospital in London should also be mentioned here. The 22 cases originally classified as osteopetrosis and all dating back to the last century have been re-evaluated by Horan and Beighton (1978), who demonstrated that only 13 of them were associated with this condition (nine cases of ADO and four of ARO), while the remaining nine cases encompassed pyknodysostosis, atypical craniodiaphyseal dysplasia, and craniosclerosis with osteopathia striata.

3.2. *Re-analysis of osteopetrosis from Palata 2, Italy*

Upon macroscopic investigation, the skull of the Palata 2 individual showed a robust morphology, consistent with the postcranial skeleton. The cranium, fractured postmortem, showed a slightly increased thickness of the vault (Fig. 1B,C), particularly in the region of the frontal bone and the parietals close to lambda. The thickness of the cranial vault was recorded at the middle of the frontal bone (11 mm) and on the left parietal bone, slightly left of the sagittal suture in the region of the lambdoid area (12 mm). Most parts of the fractured surfaces of the cranial fragments were covered by adhering calcareous deposits. The removal of these sediments proved impossible without compromising the integrity of the bone. Their presence limited the collection of metric or visible structural data about the thickness of the external and internal lamina, as well as of the diploic bone. Yet, all recorded metric values including computed tomographic measurements, fall within non-pathological ranges and are consistent with the overall robust bone structure.

As for the postcranial elements, all bones are of robust appearance and heavy weight due to the soil lodged within the medullary cavities. However, no bony constriction of the medullary cavities was visible. The cross sections of the long bones, cut for the previously published analyses (Favia et al., 2010), have a dense surface appearance, probably due to the bone dust pressed into the bone tissue while cutting them (Fig. 1D–F). None of the bones showed any evidence of fracture or of any pathological changes to their morphology.

Plain radiographic analyses of the better-preserved bones that might show changes associated with osteopetrosis (Fig. 2) ruled out major pathological changes of the bone structure for both the cranial and postcranial skeleton. The postcranial bones show thickness values within non-pathological ranges, whereas the radiographic analyses suggested the presence of two radio-dense areas: a circular one (diameter approximately 12 mm) at the distal part of the diaphysis of the right femur (Fig. 2D) and an elongated one (maximum length approximately 10 mm) at the distal part of the diaphysis of the left tibia (Fig. 2E). Their limited extension, their fairly regular shape, and their asymmetric

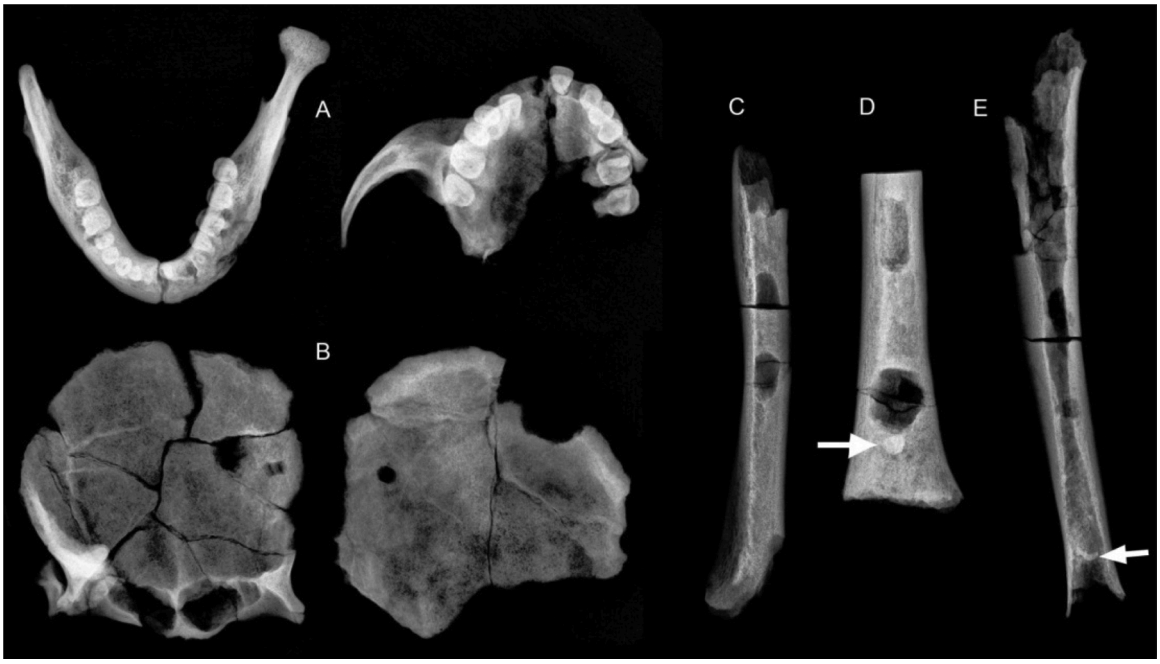

Fig. 2. Individual 2, SU21, from Palata 2, plain radiographic pictures (80kv and 5 min).
A: Mandible and maxilla in superior-inferior view. B: Frontal and occipital in posterior-anterior view. C: Right humerus in anterior-posterior view. D: Right femur in anterior-posterior view. Arrow points to radio-dense taphonomic inclusion into the medullary cavity. E: Left tibia in lateral view. Arrow points to radio-dense taphonomic inclusion into the medullary cavity.

position rules out the presence of pathological bone changes related to osteopetrosis as a possible cause, and instead points to taphonomic intrusions. All the results were further supported by subsequent computed tomographic investigations.

4. Discussion

This study presents the current state of research for the archaeological evidence of osteopetrosis, combining the results of a literature survey and an internet search. The literature survey targeted the last 45 years of publications by the main international journals with primary or secondary focus on bioarchaeology and paleopathology. The internet search combined eight different search queries using six of the most widely used search engines.

The results from the literature survey and the internet search were tested against an array of diagnostic criteria for osteopetrosis (see Table 1), also taking into account several differential diagnoses (Table 2).

Filtering out literature and online search hits that mention osteopetrosis as part of larger lists for differential diagnoses, our results highlight only ten publications referring to six cases of osteopetrosis in the archaeological record in the last 50 years: three for the ARO type and three for the ADO type.

As for the former three, one case was published but later retracted by the authors (Waldron et al., 1989; Molleson et al., 1993); in the second case, osteopetrosis is mentioned without further presentation of the osteological evidence (Baker, 1999, 2001). As such, the total count of published archaeological cases of ARO-type osteopetrosis is reduced to one (Nielsen and Alexandersen, 1971).

At the same time, the number of published archaeological cases must also be reduced to one for the ADO type (namely, Gresky et al., 2020). Of the two other cases, new analyses carried out on the Neolithic individual from Palata 2, Italy (Favia et al., 2010, 2019) now rule out such a diagnosis, while the third case (Sheridan, 2018) is mentioned in the publication without presenting any osteological evidence for it.

While the number of archaeological cases of osteopetrosis identified in this study is outstandingly low, the authors are aware that more cases may exist in the gray literature published outside of the academic and official distribution channels. While two published cases of osteopetrosis certainly do not constitute a large number, the disease may have occurred more frequently in the past, lying unidentified among a larger corpus of archaeological evidence or that is yet to be published, as the two previously mentioned cases from Egypt (Baker, 1999, 2001) and the Levant (Sheridan, 2018) seem to point out.

Also, from a more forward-looking perspective, the individuals in the three historical collections presented above, the Swiss Galler Collection, the Royal College of Surgeons, and the Fairbank collection, presents the opportunity to refine the standards needed for a comparative diagnostic approach to osteopetrosis. Individuals from anatomical collections have long served as reference material to set the standards for diagnostic procedures in paleopathology (e.g. Baker and Judd, 2012; Santos, 2015), as well as to critically review and refine them (e.g. Armelagos, 1997; Ortner, 2009; Grauer, 2018). Because of the fragmentary and incomplete nature of archaeological bones, as well as the required nuance in interpreting observed pathological changes, this process is difficult (Mays, 2018). However, this remains an indispensable step for the paleopathologist in order to better understand how the skeleton of an individual was affected by a rare disease, such as osteopetrosis. Furthermore, the medical literature for this disease (among others, see Weber et al., 2014; Del Fattore et al., 2008; Sobacchi et al., 2007) can provide insights into the pathophysiology of bone changes noted in the archaeological skeletons.

Finally, it must be highlighted that the combined literature survey and online search detected over 30 articles within the bioarchaeological field mentioning osteopetrosis, but most of these do not match the majority of the diagnostic criteria for osteopetrosis (see Table 1). Its inclusion among the potential differential diagnoses is only justified by the presence of an often-localized osteosclerosis. This often occurs when non-specific lesions, such as osteosclerosis or bone thickening, can be observed. This happens not only in paleopathological research, but is also well-known in clinical contexts (Whyte, 2016).

The disparity between this number and that of actual published cases

of osteopetrosis demonstrates how listing all potential diseases that might feature any form of osteosclerosis turns out to be misleading. Ultimately, it produces a sort of "hall of mirrors effect", inflating the number of times a disease, such osteopetrosis, is mentioned in search results. This means that a literature search for osteopetrosis produces a number of results that is much higher than the number of actual cases or possible cases. This kind of over-enumeration might obscure the specific pathological changes of a lesser-known disease such as osteopetrosis, eventually producing a sort of distortion of the condition and hindering the retrieval of its published bioarchaeological evidence. A wider bibliometric study of the bioarchaeological literature suggests that this problem is shared by most rare, or less well-known conditions (Gresky et al., 2021).

5. Conclusions

The research discussed above presents a critical appraisal of the paleopathological evidence for osteopetrosis, combining a literature survey with an extensive online keyword search and the direct analysis of archaeological skeletal remains from the Neolithic site of Palata 2. Of the six published archaeological cases of this disease, only two, one of ARO type (Nielsen and Alexandersen, 1971) and one of ADO type (Gresky et al., 2020), can be supported by osteological evidence so far.

These results not only indicate that this disease remains largely unknown in paleopathology, but highlight major caveats for future studies on rare conditions. Firstly, almost all cases of osteopetrosis were published as brief communications in the proceedings of specialized meetings, or briefly mentioned in monographs or articles describing the archaeological skeletal assemblage as a whole. This makes instances of this disease hard to track down and evaluate. Secondly, several of the search results generated in this study include osteopetrosis as a candidate for differential diagnoses, often without any evidence for the main characteristic features of this disease. As a result, the reader is confused as to whether a specific disease such as osteopetrosis might actually indicate a rather wide and not well-identifiable group of osteosclerotic changes. Lastly, this research calls for a more informed and evidence-based approach to osteopetrosis, and, more generally, to rare diseases in paleopathology including historical collections, as well as medical literature.

Acknowledgements

The authors would like to thank the Superintendence Archaeology, Fine Arts and Landscape for the Metropolitan City of Bari, Italy for granting them access to the osteological material from Palata 2 and to the Department of Medicine of the University of Bari for the technical support, J. Dorn for editing pictures, as well as S.D. Haddow for editing this manuscript.

References

Albers-Schönberg, H., 1904. Röntgenbilder einer seltenen Knochenerkrankung. Münch. Med. Wochenschr. 51, 365.
Andersen Jr., P.E., Bollerslev, J., 1987. Heterogeneity of autosomal dominant osteopetrosis. Radiology 164 (1), 223–225. https://doi.org/10.1148/radiology.164.1.3588909.
Anderson, D.E., Davidson, J.K., Catto, M.E., 1983. Primary hyperoxaluria. Case report 227. Skeletal Radiol. 9 (4), 266–271. https://doi.org/10.1007/BF00354130.
Armelagos, G.J., 1997. Palaeopathology. In: Spencer, F. (Ed.), The History of Physical Anthropology. Garland, New York, pp. 790–796.
Baker, B.J., 1999. A possible case of osteopetrosis in a neonate from the Abydos Settlement Site, Egypt. In: Presentation for the Roundtable Workshop on Congenital Disorders, Organized by Merbs, Ch.F. Scientific Program and Abstracts of the 26th Annual North American Meeting of the Paleopathology Association. Columbus, Ohio, 1999, 2.
Baker, B.J., 2001. Secrets in the skeletons. Archaeology 54 (3). https://archive.archaeology.org/0105/abstracts/abydos5.html.
Baker, B.J., Judd, M.A., 2012. Development of paleopathology in the Nile Valley. In: Buikstra, J., Roberts, C.A., Schreiner, S.M. (Eds.), History Of Paleopathology: Pioneers and Prospects. Oxford University Press, New York, pp. 209–234.
Barbieri, A., Bertini, E., Cappiello, M., et al., 2017. Studio antropologico delle antiche comunità di agricoltori del Neolitico pugliese. Studi di preistoria e Protostoria 4, 1–6.
Beighton, P., Cremin, B.J., 1980. Osteopetrosis. In: Beighton, P., Cremin, B.J. (Eds.), Sclerosing Bone Dysplasias. Springer, Berlin, Heidelberg, pp. 19–31.
Beighton, P., Cremin, B.J., Hamersma, H., 1976. The radiology of sclerosteosis. BJR 49, 934–939. https://doi.org/10.1259/0007-1285-49-587-934.
Beighton, P., Horan, F., Hamersma, H., 1977. A review of the osteopetroses. Postgrad. Med. J. 53 (622), 507–516. https://doi.org/10.1136/pgmj.53.622.507.
Blencowe, H., Moorthie, S., Petrou, M., et al., 2018. Rare single gene disorders: estimating baseline prevalence and outcomes worldwide. J. Commun. Genet. 9, 397–406. https://doi.org/10.1007/s12687-018-0376-2.
Bode, M., Peters, K.M., 2002. Osteopetrose. In: Peters, K.M. (Ed.), Knochenkrankheiten. Steinkopff, Heidelberg, pp. 6–8. https://doi.org/10.1007/978-3-642-57541-9_2.
Bollerslev, J., 1989. Autosomal dominant osteopetrosis: bone metabolism and epidemiological, clinical, and hormonal aspects. Endocr. Rev. 10, 45–67. https://doi.org/10.1210/edrv-10-1-45.
Bollerslev, J., Andersen Jr., P.E., 1988. Radiological, biochemical and hereditary evidence of two types of autosomal dominant osteopetrosis. Bone 9 (1), 7–13. https://doi.org/10.1016/8756-3282(88)90021-X.
Bollerslev, J., Andersen, P.E., 1989. Fracture patterns in two types of autosomal-dominant osteopetrosis. Acta Orthop. Scand. 60, 110–112. https://doi.org/10.3109/17453678909150106.
Bonafe, L., Cormier-Daire, V., Hall, C., et al., 2015. Nosology and classification of genetic skeletal disorders: 2015 revision. Am. J. Med. Genet. A 167A, 2869–2892.
Brickley, M., McKinley, J.I., 2004. Guidelines to the Standards for Recording Human Remains. IFA Paper No. 7. Reading.
Cameron, H.U., Dewar, F.P., 1977. Degenerative osteoarthritis associated with osteopetrosis. Clin. Orthop. Relat. Res. 127, 148–149.
De Nicola, L., Sublimi Saponetti, S., Scattarella, V., 2010. Bioarcheologia delle comunità preistoriche ofantine in località Salinelle e Palata (Canosa, Bari): dati preliminari. In: Bertoldi Lenoci, L. (Ed.), Canosa, Ricerche Storiche 2009. Edizioni pugliesi, Martina Franca, Taranto, pp. 239–258.
Del Fattore, A., Cappariello, A., Teti, A., 2008. Genetics, pathogenesis and complications of osteopetrosis. Bone 42 (1), 19–29. https://doi.org/10.1016/j.bone.2007.08.029.
Elster, A.D., Theros, E.G., Key, L.L., Chen, M.Y., 1992. Cranial imaging in autosomal recessive osteopetrosis. Part I. Facial bones and calvarium. Radiology 183, 129–135. https://doi.org/10.1148/radiology.183.1.1549658.
El-Tawil, T., Stoker, D.J., 1993. Benign osteopetrosis: a review of 42 cases showing two different patterns. Skeletal Radiol. 22, 587–593. https://doi.org/10.1007/BF00197140.
Enell, H., Pherson, M., 1958. Studies on osteopetrosis 1. Clinical report of three cases with genetic considerations. Acta Pediatr. Esp. 47, 279–287.
Favia, G., Scattarella, V., Sublimi Saponetti, S., et al., 2010. Osteopetrosis tarda in an adult Neolitic skeleton from Palata 2-Ofanto River Valley (Canosa-South Italy): radiological, histological and confocal laser microscopy study. In: Scientific Program and Abstracts of the 18th European Meeting of the Paleopathology Association. Vienna, Austria, pp. 51–52, 2010.
Favia, M., Ferorelli, D., Scattarella, V., et al., 2019. A probable case of Osteopetrosis tarda in an adult Neolithic skeleton from Palata 2-Ofanto river valley (Canosa-South Italy): radiological, histological and confocal laser microscopy study. In: First Workshop on Ancient Rare Diseases (1st W.A.R.D.). Berlin, 27.02-1.03.2019.
Freyschmidt, J., 2016. Skeletterkrankungen: klinisch-radiologische Diagnose und Differenzialdiagnose, 4th ed. Springer, Berlin, Heidelberg.
Gerritsen, E.J.A., Vossen, J.M., van Loo, I.H.C., et al., 1994. Autosomal recessive osteopetrosis: variability of findings at diagnosis and during the natural course. Pediatrics 93, 247–253.
Grauer, A.L., 2018. A century of paleopathology. Am. J. Phys. Anthropol. 165, 904–914. https://doi.org/10.1002/ajpa.23366.
Gresky, J., Petiti, E., 2017. Osteopetrosis and accompanied skeletal changes in a skeleton from Albania. In: Scientific Program and Abstracts of the 22nd European Meeting of the Paleopathology Association. Zagreb, Croatia, 2017, 31.
Gresky, J., Sokiranski, R., Witzmann, F., Petiti, E., 2020. The oldest case of osteopetrosis in a human skeleton: exploring the history of rare diseases. Lancet DE 8 (10), 806–808. https://doi.org/10.1016/S2213-8587(20)30307-7.
Gresky, J., Dorn, J., Teßmann, B., Petiti, E., 2021. How rare is rare? A literature survey of the last 45 years of paleopathological research on ancient rare diseases. Int. J. Paleopathol. 33, 94–102.
Horan, F.T., Beighton, P., 1978. Osteopetrosis in the Fairbank collection. J. Bone Jt. Surg. [Br] 60, 53–55.
Janssens, K., Vanhoenacker, F., Bonduelle, M., et al., 2005. Camurati-Engelmann disease: review of the clinical, radiological, and molecular data of 24 families and implications for diagnosis and treatment. J. Med. Genet. 43, 1–11. https://doi.org/10.1136/jmg.2005.033522.
Johnston Jr., C.C., Lavy, N., Lord, T., et al., 1968. Osteopetrosis: a clinical, genetic, metabolic, and morphologic study of the dominantly inherited, benign form. Medicine 47 (2), 149–167.
Köhler, S., Vasilevsky, N.A., Engelstad, M., et al., 2017. The human phenotype ontology in 2017. Nucleic Acids Res. 45 (D1), D865–D876. https://doi.org/10.1093/nar/gkw1039.
Loría-Cortés, R., Quesada-Calvo, E., Cordero-Chaverri, E., 1977. Osteopetrosis in children: a report of 26 cases. J. Pediatr. 91, 43–47.
Mays, S., 2018. How should we diagnose disease in palaeopathology? Some epistemological considerations. Int. J. Paleopathol. 20, 12–19. https://doi.org/10.1016/j.ijpp.2017.10.006.

McEwan, J., 2009. Diagnostic imaging techniques and skeletal remains: current trends. HOMO 60, 250. https://doi.org/10.1016/j.jchb.2009.02.020.
Merbs, Ch.F., Case, D.T., Burnett, S., 1999. Congenital and developmental abnormalities. In: Scientific Program and Abstracts of the 26th Meeting of the Paleopathology Association. Columbus, Ohio, 1999, 2.
Molleson, T., Cox, M., Waldron, H.A., Whittaker, D.K., 1993. The Spitalfields Project, Vol. 2, the Anthropology: the Middling Sort. CBA Research Report 86. Council for British Archaeology, York.
Nguengang Wakap, S., Lambert, D.M., Olry, A., et al., 2020. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. Eur. J. Hum. Genet. 28, 165–173. https://doi.org/10.1038/s41431-019-0508-0.
Nielsen, O.V., Alexandersen, V., 1971. Malignant osteopetrosis in ancient Nubia. A case from the period 350-550 A.D. Dan. Med. Bull. 18 (5), 125–128.
NORD, 2020 https://rarediseases.org/rare-diseases/osteopetrosis/ (Accessed on 19th December 2020).
ORPHANET, 2020 https://www.orpha.net/consor/cgi-bin/Education_AboutRareDiseases.php?lng=EN. (Accessed on 19th December 2020).
Ortner, D.J., 2003. Identification of Pathological Conditions in Human Skeletal Remains. Academic Press, Cambridge, MA.
Ortner, D.J., 2009. Issues in paleopathology and possible strategies for dealing with them. Anthropol. Anz. 67 (4), 323–340. https://doi.org/10.2307/29543064.
Radina, F., Sicolo, M., Sivilli, S., 2010. Le antiche vie dell'acqua. Insediamenti preistorici sulle sponde dell'Ofanto. Ricerche lungo il tracciato del nuovo Acquedotto del Locone. In: Bertoldi Lenoci, L. (Ed.), Canosa, Ricerche Storiche 2009. Edizioni pugliesi, Martina Franca, Taranto, pp. 25–51.
Radina, F., Sivilli, S., Alhaique, F., Fiorentino, G., D'Oronzo, C., 2011. L'insediamento neolitico nella media valle ofantina: l'area di Palata (Canosa di Puglia). Origini. Preistoria e protostoria delle civiltà antiche 33 (5), 107–156.
Resnick, D., 1981a. Additional congenital or heritable anomalies and syndromes. In: Resnick, D., Niwayama, G. (Eds.), Diagnosis of Bone and Joint Disorders Vol. 3: with Emphasis on Articular Abnormalities. Saunders, Philadelphia, London, Toronto, pp. 2548–2636.
Resnick, D., 1981b. Heavy metal poisoning. In: Resnick, D., Niwayama, G. (Eds.), Diagnosis of Bone and Joint Disorders Vol. 3: with Emphasis on Articular Abnormalities. Saunders, Philadelphia, London, Toronto, pp. 2369–2405.
Resnick, D., Niwayama, G., 1989. Diagnosis of Bone and Joint Disorders Vol. 3: with Emphasis on Articular Abnormalities. Saunders, Philadelphia, London, Toronto.
Rühli, F.J., Hotz, G., Böni, T., 2003. Brief communication: the Galler Collection: a little-known historic Swiss bone pathology reference series. Am. J. Phys. Anthropol. 121, 15–18.
Santos, A.L., 2015. Archives and skeletons: an interdisciplinary approach to the study of paleopathology of tuberculosis. Tuberculosis 95 (1), 109–111. https://doi.org/10.1016/j.tube.2015.02.014.
Schulz, A., Kornak, U., 2018. Osteopetrose: Eine heterogene Krankheit mit erhöhter Knochendichte. Osteologie 27, 222–228.
Sheridan, S., 2018. Mix 'n' match: the bioarchaeology of commingled remains. In: Yasur-Landau, A., Cline, E., Rowan, Y. (Eds.), The Social Archaeology of the Levant: From Prehistory to the Present. Cambridge University Press, Cambridge, pp. 199–223. https://doi.org/10.1017/9781316661468.013.
Sobacchi, C., Villa, A., Schulz, A., et al., 2007. CLCN7-related osteopetrosis. 2007 Feb 12 [Updated 2016 June 9]. In: Adam, M.P., Ardinger, H.H., Pagon, R.A. (Eds.), GeneReviews® [Internet]. University of Washington, Seattle (WA), pp. 1993–2020.
Waguespack, S.G., Hui, S.L., DiMeglio, L.A., Econs, M.J., 2007. Autosomal dominant osteopetrosis: clinical severity and natural history of 94 subjects with a chloride channel 7 gene mutation. J. Clin. Endocrinol. Metab. 92, 771–778. https://doi.org/10.1210/jc.2006-1986.
Waldron, T., Cox, M., Molleson, T., 1989. Osteopetrosis in an eighteenth century English family. In: Scientific Program and Abstracts of the 16th Annual North American Meeting of the Paleopathology Association. San Diego, CA. Paleopathology Newsletter 66, 4.
Weber, D., Econs, M., Levine, M., 2014. Osteopetrosis: pathogenesis, management and future directions for research. IBMS BoneKEy 11. https://doi.org/10.1038/bonekey.2014.15.
Whyte, M.P., 2016. Hereditary disorders of the skeleton. In: Jameson, J.L., De Groot, L. (Eds.), Endocrinology: Adult and Pediatric. Elsevier, pp. 1173–1183. https://doi.org/10.1016/B978-0-323-18907-1.00068-8 e4.
Wilson, C.J., Vellodi, A., 2000. Autosomal recessive osteopetrosis: diagnosis, management, and outcome. Arch. Dis. Childh. 83, 449–452.
Wu, C.C., Econs, M.J., DiMeglio, L.A., et al., 2017. Diagnosis and management of osteopetrosis: consensus guidelines from the osteopetrosis working group. J. Clin. Endocrinol. Metab. 102 (9), 3111–3123. https://doi.org/10.1210/jc.2017-01127.