

Approach to the diagnosis of unusual carpal ankylosis from Ancient Egypt

A. Isidro^{1,2}, I. Díez-Santacoloma¹, J. Méndez-López^{1,3}

¹Department of Orthopaedic Surgery and Traumatology, Hospital Universitari Sagrat Cor, Barcelona;

²Museu Egipci de Barcelona, Barcelona; ³Hand Unit, M.C. Mutual, Barcelona, Spain.

Abstract Objective

Carpal fusion is not an uncommon finding in archaeological bones. The majority of cases are due to inflammatory or infectious diseases and those are usually associated with other major alterations in the skeleton.

Methods

Two distinct individual cases, both adult females recovered from the Necropolis of Sharuna in the Middle Egypt from the Ptolemaic Period (IV to I BC) are presented in this study. Specimen 4323/1 shows a fusion of the scaphoid, lunate and triquetral bones in the right wrist. Specimen 4323/2 is a very rare fusion of a dysplastic lunate bone with the radius in the left wrist. In the proximal end of that left wrist, two possible remains of the flattened scaphoid and triquetral bones are also present.

Results

A differential diagnosis of both abnormalities as well as broad research into similar paleopathological cases were carried out: the most probable diagnosis for the specimen 4323/1 is an uncommon carpal coalition of three bones from the same row; the diagnosis of the specimen 4323/2 is more dubious with both rheumatoid arthritis and septic arthritis being strong candidates.

Conclusion

In archaeological remains, carpal fusion should be thoroughly studied in order to ensure an accurate differential diagnosis.

Key words

ancient history, articular disease, carpal coalition, Egypt, joint deformities, paleopathology, rheumatoid arthritis

Albert Isidro, MD, PhD
 Iván Díez-Santacoloma, MD
 José Méndez-López, MD

Please address correspondence to:
 Albert Isidro, MD,
 Department of Orthopedic Surgery,
 IDC Hospital Universitari Sagrat Cor,
 Viladomat 288,
 08029 Barcelona, Spain.
 E-mail: aisidro.cot@gmail.com

Received on March 24, 2014; accepted in
 revised form on July 29, 2014.

© Copyright CLINICAL AND
 EXPERIMENTAL RHEUMATOLOGY 2015.

Introduction

Fusions of the carpal bones usually have an infectious aetiology such as tuberculosis (TBC) or inflammatory conditions like rheumatoid arthritis (RA). A fusion that is present from birth is denominated a carpal coalition (CC).

In ancient times, infections (mainly TBC), inflammatory diseases and fracture sequelae may have led to an acquired fusion of the wrist bones. Cases of CC were uncommon.

Those secondary to systemic diseases such as RA and other seronegative arthropathies or TBC are often accompanied by skeletal disorders in other areas of the skeleton, while the isolated involvement of the wrist is rare. In this type of fusion, not only may the bones of the two carpal rows be affected but the metacarpals as well as the distal radius and ulna are involved from time to time.

Material

Here, two cases of a complex fusion of carpal bones in individuals (4323/1 and 4323/2) taken from the archaeological activities of the 7th joint campaign of the Museu Egipci of Barcelona (Spain) and the Eberhart-Karls University of Tübingen (Germany) are presented. They originate from the necropolis of the Kom el-Ahmar/Sharuna from Middle Egypt, dated by means of stratigraphy and grave goods from the Ptolemaic Period (IV-I BC). Unfortunately, *in situ* field radiology could not be performed during the excavation. Both individuals were found at the bottom of a 4 metre deep shaft (KAS.2012 / UE.4323) with another 5 specimens (total 7), three of which were subadults and children. As there was no strict anatomical connection, it was difficult to reconstruct the individuals in their entirety. Although the state of preservation of the bones was acceptable, the more distal parts of the hands and feet were not found or were the worst preserved. Thus, it was very hard ascribing them to any individual in particular. However, the conclusion was that both individuals were adult females after the *in situ* reconstruction of all the skeletons. This was determined after analysing the skeletal remains and applying pelvic as well as cranial sex determination criteria.

Part description 4323/1 (Figures 1 and 2)

This is an adult female whose age is estimated at between 35–45 years of age in which there is a right carpal anatomical specimen composed of the fused scaphoid, the lunate and triquetral. A dorsal prominence was present on the triquetral that was directed towards the radius, leading us to consider it a calcification of the extrinsic dorsal radiotriquetral ligament. Macroscopic observation of the piece shows that the anterior horn of the lunate is almost at the height of the distal pole of the scaphoid and of the carpal facet of the triquetral.

Part description 4323/2 (Figures 3 and 4)

This is an adult female whose age range is from 25–35 years old. Apart from a *post-mortem* loss of the radial styloid bone, a complex bone fusion that supports a link between the articular distal radial surface and the incomplete lunate can be seen in the left wrist. It is possible that the fusion with the radius came about through the volar radiolunar ligament. Moreover, an abnormal morphology of the lunate with a distal ovoid form, not presenting the usual crescent shape, can be observed. In the distal area of the lunate, flattened lateral bone masses are evident, which might correspond to the articulation with its scaphoid and triquetral, or parts of these bones. The aforementioned conditions a middle carpal joint with a concave morphology that is different from the usual convex facet articulation between the first and second rows of the carpus. It might be seen as a possible radiolunar fusion with some rudimentary fusion of the scaphoid and triquetral along with a type of biomechanical alteration in the joint between the first and the second row of carpus.

Results and discussion

Although the two carpals show bone fusions, their different morphologies lead one to think that they arise from two different etiologies. For the differential diagnosis, the fact that none of the 4 adult individuals showed other abnormalities that would justify more complex syndromes was relied upon.

Competing interests: none declared.

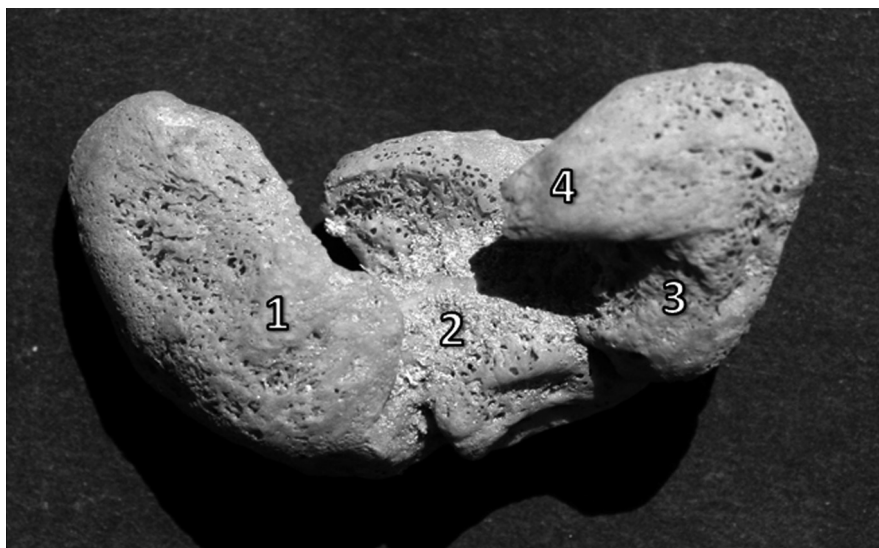


Fig. 1. Individual 4323/1. Dorsal view of the right carpal coalition. In this block the scaphoid (1), the lunate (2) and the triquetral (3) are involved. There is a prominence above the triquetral that could be a calcification of the radiotriquetral ligament (4).

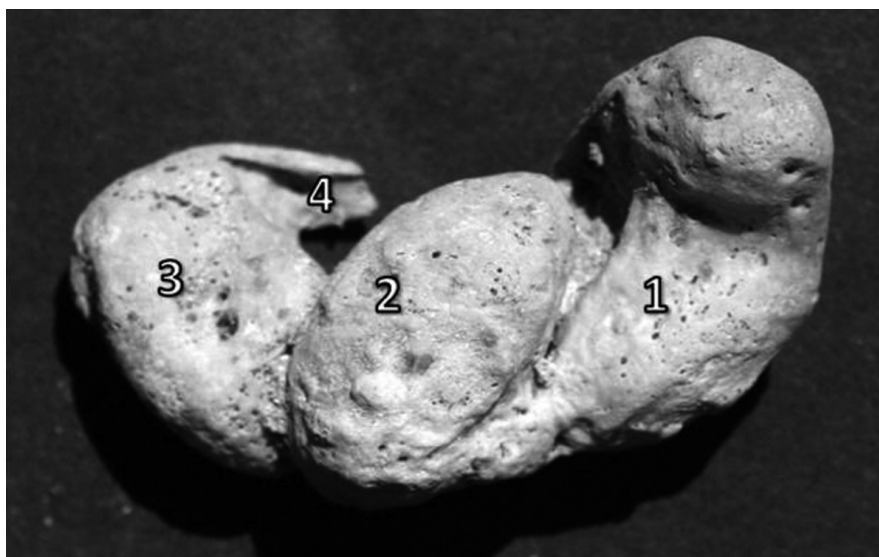


Fig. 2. Individual 4323/1. Ventral view of the carpal coalition with the scaphoid (1), the lunate (2), the triquetral (3) and the probable calcification of the radiotriquetral ligament (4).

In the case of part 4223/1, it is thought to be a complex CC. The first mention of carpal coalition was made by Sandifort (1) in 1779. Corson (2) described the second one 129 years later. The first large series studied was done by Minnaar (3) in 1952. It included 12 cases and resulted in the publication of the first classification based upon lunate-triquetral coalitions, the most common fusion. A carpal coalition is due, according to O'Rahilly (4), to a failure in the formation of the anlage that causes a persistent continuity of cartilage with subsequent condensation and poste-

rior ossification (5). This phase arises during the fourth to eighth week of gestation (6, 7). It draws attention to the consideration that, as above mentioned, the term fusion is a misnomer as the basis is a lack of separation or a segmentation error (8, 9).

CC incidence varies by geographic region. In Caucasians, it ranges from 0.1 to 0.5% (10, 11). It may reach up to 9% in some areas of West Africa (8, 10-12). The prevalence is 2:1 in terms of gender (female/ male) (13-15).

Some authors have argued for the theory of evolution from ape to man to explain

some CC based upon the fusion of the scaphoids and centrals in different species of African apes (16). These fusions enhance the stability for the pinch-grip and knuckle-walking. This theory has been challenged by others (17). Other scholars believe that two small ossicles are of interest in determining the origin of CC. They are the *os centrale* and the *os triangulare*, which disappear before birth. They are remains from the embryonic stage, from phylogenetic regressions as occurs in the foot (18).

CC is hereditary and transmitted as a Mendelian non-sex dominant factor (19). Amongst the genetic factors related to CC fusion, there are mutations in noggin (protein secreted by NOG gene [20] an antagonist member of the transforming growth factor-beta family that plays a significative role in joint morphogenesis) (21). These noggin associated changes make up a new genetic diagnosis: NOG-related-symphalangism spectrum disorders (NOG-SSD) (22), which include carpal fusion among other types of bone fusions.

Systemic carpal fusions due to systemic syndromes usually involve adjacent rows in front of the congenital ones in which only the bones belonging to the same row are fused. Nevertheless, isolated descriptions of CC involving two rows describes either those of two bones like the scaphoid-trapezium (23), pisiform-hamate (24) or bifocals like the capitate-hamate plus the lunate-triquetral (25) and an almost pan carpal coalition (a scaphoid-trapezium-trapezoid-capitate coalition) (26) and a total except the pisiform (27). More dubious could be the cases of a pan-carpal plus four metacarpal blocks as a CC (28).

The most frequent CC are: lunate-triquetral 0.1–0.5% in whites, to 6.9–9.5% in West Africans (29, 30); capitate-hamate, 0.25%–0.29% in whites; 0.4–0.8% in West Africans; capitate-trapezoid 0.1%. Much more unusual are those fusions that involve a complete row (31). The majority of the cases present a bilateral affection. The right side turns out to be the most frequently affected in those cases with a unilateral affection (3, 30, 32).

On the basis of the lunate-triquetral coalition, Minnaar (3) describes four

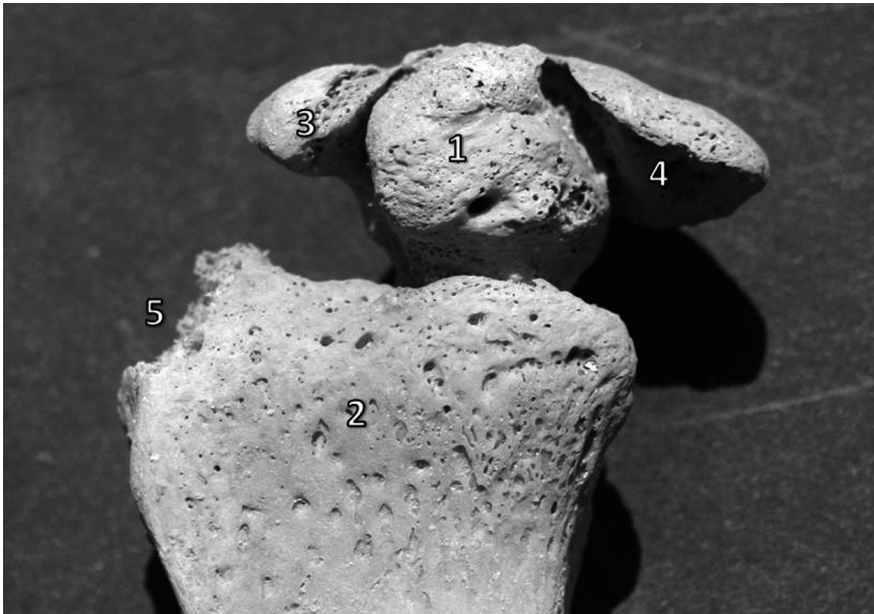


Fig. 3. Individual 4323/2. Ventral view of the left carpus that involves an ovoid-shape lunate (1) with the distal articular surface of the radius (2). Two flattened lateral bone masses might correspond to the scaphoid (3) and triquetral (4). The damage to the styloid radius is *post-mortem* (5).

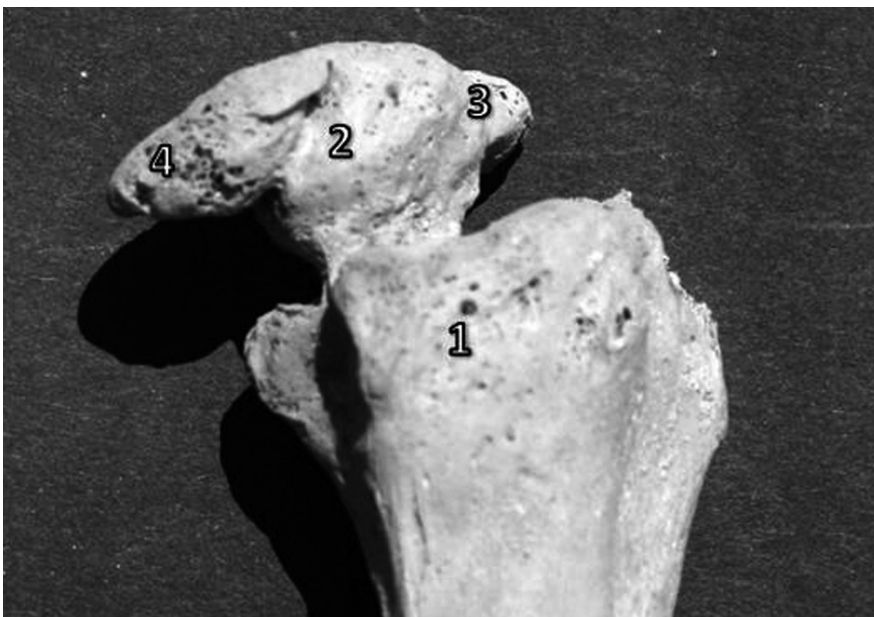


Fig. 4. Individual 4323/2. Dorsal view of the left radius (1) and carpus with the lunate (2), scaphoid (3) and triquetral (4).

types depending on the degree of fusion (Type I: proximal pseudoarthrosis, Type II: osseous bridge with notch, Type III: complete fusion and Type IV: fusion with other carpal anomalies). New classifications were made by Singh *et al.* in 2003 (29) and the last by Burnett in 2011 (33).

From a paleopathological point of view, it is worth noting that the most ancient case of CC in a Neanderthal individual

was described in 1989 (34). It is La Ferrière II from the Middle Paleolithic site in Dordogne, France. It has been dated at 74,000 to 68,000 years BP, which shows a lunate-triquetral synostosis in the left hand and is now stored in the Musée de l'Homme de Paris (France).

In the case of part 4223/2

The complex fusion and the morpho-

logical alteration that individual 2 presents might lead one to think that this is a destructive carpal aetiology caused by infection or, more probably, a rheumatic disease. In some archaeological cases, attribution to one aetiology or another is very difficult because the morphology is altered (Fig. 5).

The infectious diseases that most often cause ankylosis associated with partial destruction of the carpal bones are mainly granulomatous arthritis. In Paleopathology, there are some cases of carpal fusion in tuberculosis (35), being less frequent in the case of leprosy and anecdotal in other granulomatous infections such as brucellosis (36). In the location where the fused carpus under study was found, there were no vertebrae that might suggest the presence of Pott's disease in the spine. The remains of the phalanges studied showed no signs of alteration due to TBC or leprosy in his hands. On the other hand, fusions are usually total and include both the carpal bones like the radio/ulna and metacarpals in the case of TBC although we cannot rule out bacterial or fungal mono-arthritis. However, the most common cause of carpal bone fusion is currently rheumatoid arthritis (RA). This inflammatory disease causes the destruction and fusion of the carpal and tarsus bones with a predominance in females (3:1). It is generally symmetrical and, apparently, this destructive process might be an option to explain the fusion of this piece. The problem faced is that even today there is no consensus relative to the antiquity of RA. When you go back in the history of disease in order to determine its age, we are able to find historical and archaeological cases.

The Roman author Scribonius Largus, in the I-II century AD, wrote about a certain type of polyarthritis (37). Eight hundred years later, the Byzantine Emperor Constantine IX (AD 980–1055) was possibly the first ruler that suffered from something similar to RA. The description is owed to Michael Psellius (*Chronographia*) (38). Otherwise, evidence of RA could be seen in European paintings from the 14th to 16th centuries. It is mainly due to the work of Flemish masters like Jan Gossaert or Peter



Fig. 5. Destructive arthritis of the right carpus from the 16th century. (Courtesy of Dr Armando González).

Paul Rubens and the Italian Sandro Botticelli. In this context, attention is drawn to the case of two works, both entitled *Portrait of Siebrandus Sixtius II* (1538–1631), in which metacarpophalangeal and proximal interphalangeal joint swelling associated with ulnar deviation with flexion of the fingers (39) are clearly shown.

In 1676, Tomas Sydenham was the first to explain the differences between RA and gout (*Observationes Medicae*). In 1800, Augustine-Jacob Landrè-Beauvais went deep into the differential diagnosis after presenting his doctoral thesis. It might be the oldest unmistakable description in Europe. Finally, Sir Alfred Baring Garrod introduced the term rheumatoid arthritis (RA) to substitute rheumatic gout in 1859 (40). According to Garrod, “a new disease is not always one that has never been seen before. As a rule, a previously but unrecognised condition is the key”. A short time later, his son gave an opinion that began the debate about how old RA was; “the disease was not one of recent origin, and, of some epidemiologic importance, it did not arise because of any

recent change in man’s environment or manner of living” (41), contrary to the opinion of other scholars (40, 42). We must keep in mind that spondyloarthropathies were not distinguished from RA from much later than the beginning of the 20th century.

From a paleopathological point of view, we have to perfectly differentiate the probable cases compatible with RA from the New Continent from those that appear in Old World.

The earliest cases in the New World with the possible diagnosis of RA, based upon symmetric arthritis in the females, were identified in a Late Archaic Indian group (6500 to 4300 BP) in the area of the Green and Tennessee rivers. It might have arisen in reaction to the action of a new pathogen, possibly present in that area (43). Also in Mesoamerica, 8 cases belonging to the Pre-classic period at the site of Tlatilco, Mexico (1400–400 BC) are described (44).

In studies of human remains from ancient Egypt that encompass different eras, rheumatic diseases such as gout or ankylosing spondylitis have been

described, but no clear case of RA has been diagnosed (45). Nonetheless, the first paleopathological description of a possible RA is owed to Page May in 1897 on a Vth dynasty Egyptian mummy (46). In this regard, the diagnosis made of an individual from Kulubnarti in Sudanese Nubia, dated between 8th and 15th centuries, may be dubious (47). In the Old World, there are some examples which have been diagnosed as chronic aseptic polyarthritis. Among them, the oldest may be two skeletons from the Middle Neolithic Period of the Stone Age (2500–1900 BC) at Fridtorp, South Scandinavia (48).

The oldest cases with a presumed diagnosis of RA are found in northern Europe, as in the case of individual IB NM 12662-3 dating from the Early Bronze Age (period II) of Olmosehuse, Haraldsted (Denmark), which shows an incomplete fusion on the left hand (49). At the site of Pounbury (Dorset, England), nearly 1500 Roman British individuals were exhumed and 14 of them had cyst-like erosions in the carpus and metacarpal heads (50). This site is dated at from the 1st to the 5th century AD and another similar case diagnosed by x-ray study dated to 7th century AD (51). In the cemetery of Amiens, France (7th–9th century AD), there are another 3 cases with the same features as the previous ones (52).

One of the most striking theories that attempts to explain the rise of RA is related to the high levels of hygiene in developed countries, in which there is an increase of the autoimmune conditions associated with RA as opposed to the low prevalence in undeveloped ones (53, 54).

Back to specimen 2, this one presents associated injuries. There is osteochondritis in the distal ulna, in the radius head and in the medial epicondyle of the humerus in the right arm. There is a grade IV enthesopathy at the attachment of the costo-clavicle ligament on both sides which could be seen more in the side with a probable RA-like disease. No joint lesions appear in individual 1.

A few words about possible symptoms in antiquity. In ancient times, restricted mobility of the wrist after joint ankylo-

sis, either congenital or acquired, used to mean an overload on other joints of the upper extremity and might explain the presence, in individual 2, of the associated lesion in the arm. Anecdotally, such a restriction could be read about in ancient documents as in the example of Cardinal Carlo, son of Ferdinando I (1450–1609), 4th Great Duke of Tuscany. He was affected with bilateral wrist ankylosis, which he writes of in a letter: “Your Highness, please excuse me for not being able to sign in my own hand as my hand does not function” (55).

Acknowledgements

We would like to thank Ms M^a José Sánchez (Library Responsible Sagrat Cor University Hospital) for her invaluable technical support, the directors of the archaeological team in the field, Luis González and Mariangela Taule, as well as Eric L. Goode for his assistance in translating and correcting the text.

References

- SANDIFORT E: Observationum anatomico pathologicarum. *Batavia* 1779; 3: 136.
- CORSON ER: Fusion of the semilunar and cuneiform bones (os lunatum and os triquetrum) in both wrists of an adult male Negro- shown by the xray. *Anatomical Record* 1908; 2: 143.
- MINAAR AB. EV: Congenital fusion of lunate and triquetral in South African Bantu. *J Bone Joint Surg* 1952; 34B: 45-8.
- O'RAHILLY R: A survey of carpal and tarsal anomalies. *J Bone Joint Surg Am* 1953; 35A: 626-42.
- WEATHERMANN A: Die Entwicklungsstörungen der Extremitäten in Handbuch der Spez. *Pathology Anatomy Histology* 1952; 9: 319.
- MCCREDIE J: Congenital fusion of bones: radiology, embryology and pathogenesis. *Clin Radiol* 1975; 26: 47-51.
- MOORE HL: *The developing human*. 3rd ed. Philadelphia: WB Saunders, 1982: 356-8.
- COCKSHOTT WP: Carpal fusions. *Am J Roentgenol Radium Ther Nucl Med* 1963; 89: 1260-71.
- SILVERMAN FN: Note on os lunatotriquetum. *Am Jour Physc Anthropol* 1955; 13: 143-5.
- SZABOKY GT, MULLER J, MELNICK J, TAM-BURRO R: Anomalous fusion between the lunate and triquetrum. *J Bone Joint Surg Am* 1969; 51A: 1001-4.
- POZNANSKI AK, HOLT JF: The carpals in congenital malformation syndromes. *Am J Roentgenol Radium Ther Nucl Med* 1971; 112: 443-59.
- THAKKAR DH: Lunato-triquetral fusion and associated spinal abnormality. *Hand* 1982; 14: 89-96.
- HAMMOND G: Unilateral congenital synostosis of lunate and triangular bones. *Surgery* 1947; 22: 566-7.
- GARN SM, FRISANCHO AR, POZNANSKI AK et al.: Analysis of triquetral-lunate fusion. *Am J Phys Anthropol* 1971; 34: 431-3.
- SIMMONS BP, MCKENZIE WD: Symptomatic carpal coalition. *J Hand Surg Am* 1985; 10A: 190-3.
- KIVELL TL, BEGUN DR: Frequency and timing of scaphoid-central fusion in hominoids. *J Hum Evol* 2007; 52: 321-40.
- ROHDE RS, CRISCO JJ, WOLFE SW: The advantage of throwing the first stone: how understanding the evolutionary demands of Homo sapiens is helping us understand carpal motion. *J Am Acad Orthop Surg* 2010; 18: 51-8.
- ISIDRO A, VAZQUEZ MT: Phylogenetic and ontogenic parallelisms on talocalcaneal superposition. *The Foot* 2006; 16: 1-15.
- HENRY MB: Anomalous fusion of the scaphoid and the greater multangular bone. *Arch Surg* 1945; 50: 240-1.
- ZIMMERMAN LB, DE JESUS-ESCOBAR JM, HARLAND RM: The Spemann organizer signal noggin binds and inactivates bone morphogenetic protein 4. *Cell* 1996; 86: 599-606.
- DEBEER P, FRYNS JP, DEVRIENDT K, BATEN E, HUYSMANS C, VAN DE VEN WJ: A novel NOG mutation Pro37Arg in a family with tarsal and carpal synostoses. *Am J Med Genet A* 2004; 128A: 439-40.
- POTTI TA, PETTY EM, LESPERANCE MM: A comprehensive review of reported heritable noggin-associated syndromes and proposed clinical utility of one broadly inclusive diagnostic term: NOG-related symphalangism spectrum disorder (NOG-SSD). *Hum Mutat* 2011; 32: 877-86.
- HEY HW, TAN JJ, NG ZY, SZE CHONG AK: Unilateral isolated coalition of the scaphoid and trapezium a rare incidental finding. *J Hand Surg Am* 2013; 38: 207-8.
- ZEPLIN PH, JAKUBIETZ RG, SCHMIDT K: Symptomatic congenital pisiform hamate coalition. *Ann Plast Surg* 2010; 65: 396-7.
- KAHANE S, ISAAC SM, WILDIN C: A new type of carpal coalition. *J Hand Surg Eurl* 2012; 37: 581-2.
- INGRAM C, HALL RF, GONZALEZ M: Congenital fusion of the scaphoid, trapezium, trapezoid and capitate. *J Hand Surg Br* 1997; 22: 167-8.
- ARNANDER M, TOMARCHIO A, BECKER G: Symptomatic pan carpal coalition. *J Hand Surg Eur Vol* 2013; 38: 560-2.
- ETHNE BARNES: *Atlas of developmental field anomalies of the human skeleton: a paleopathology perspective*. 1st ed. New Jersey: Wiley-Blackwell; 2012: 142-4.
- SINGH P, TULI A, CHOUDHRY R et al.: Inter-carpal fusion – a review. *J Anat Soc India* 2003; 52: 183-8.
- DELANEY TJ, ESWAR S: Carpal coalitions. *J Hand Surg Am* 1992; 17A: 28-31.
- GÓMEZ-ROBLEDO J: An unusual carpal coalition associated with fifth ray anomalies in the hand. *J Hand Surg Br* 1998; 23: 537-8.
- SMITHAM JH: Some observations on certain congenital abnormalities of the hand in African natives. *Br J Radiol* 1948; 21: 513-8.
- BURNETT SE: Hamate-pisiform coalition: morphology, clinical significance, and a simplified classification scheme for carpal coalition. *Clin Anat* 2011; 24: 188-96.
- OBERLIN C, SAKKA M: The most ancient case of synostosis of the carpal bones: pyramido-lunate synostosis in La Ferrassie man. *Ann Chir Main* 1989; 8: 269-72.
- ISIDRO A, GONZÁLVIZ L, TAULÉ M et al.: Estudio preliminar de los restos humanos hallados en la Tumba U.20 de la Necrópolis de al Khom al Ahmar / Sharuna (VI dinastía) Campañas 2006-2007-2008. *Munibe* (Antropología-Arkeología) 2009; 60: 243-52.
- ISIDRO A., ETXEBERRIA F., ROCA C., GUIJO M. & MALGOSAA: Old skeletal brucellosis in Western-Europe Mediterranean countries. *J Bone Joint Surg (Br)* 2007; 91-B (Suppl. II): 299.
- COPEMAN WSC: A short history of gout and the rheumatic diseases. Berkeley, LA, University California Press, 1964: 145-6.
- CAUGHEY DE: The arthritis of Constantine IX. *Ann Rheum Dis* 1974; 33: 77-80.
- DEQUEKER J: Arthritis in Flemish paintings (1400-1700). *BMJ* 1977; 1: 1203-5.
- SNORRASON E: Landrè-Beauvais and his “goutte asthenique primitive”. *Acta Med Scan Suppl.* 226. 1952; 142: 115-8.
- SHORT CL: The antiquity of rheumatoid arthritis. *Arthritis Rheum* 1974; 17: 193-205.
- BOYLE JA, BUCHANAN WW: Clinical Rheumatology. Philadelphia, F.A.Davis Co., 1971, 71-72.
- ROTHSCHILD BM, WOODS RJ, ROTHSCCHILD C, SEBES JI: Geographical distribution of rheumatoid arthritis in ancient North America: implications for pathogenesis. *Semin Arthritis Rheum* 1992; 22: 181-7.
- ACEVES. AVILA FJ, MEDINA F, FRAGA A: The Antiquity of Rheumatoid Arthritis. *Jour Rheum* 2001; 28: 751-7.
- SMITH GE, JONES FW: The archaeological survey of Nubia. Report for 1907-1908. Vol 2. Report on the human remains. Cairo, National Printing Department, 1910.
- PAGE MAY W: Rheumatoid arthritis (osteitis deformans) affecting bones 5500 years old. *Br Med J* 1897; 2: 1631-2.
- KILGORE L: Possible case of Rheumatoid Arthritis from Sudanese Nubia. *Am Jour Physc Anthropol* 1989; 79: 177-83.
- LEDEN I, PERSSON E, PERSSON O: Aspects of the History of Rheumatoid Arthritis in the light of recent osteoarchaeological finds. *Sacn J Rheumatology* 1988; 17: 341-52.
- BENNIKE P: Paleopathology of Danish Skeletons. A comparative study of demography, disease and injury. Copenhagen: Akademisk Forlag 1985; 199-200.
- THOULD AK, THOULD BT: Arthritis in Roman Britain. *BMJ* 1983; 287: 1909-11.
- BROTHWELL D, MOLLER-CHISTENSEN V: Medico-historical aspects of a very early case of mutilation. *Danish Med Bull* 1963; 10: 21-5.
- CLAVEL G, GRADOS F, VIGER B et al.: Was rheumatoid arthritis existing in the Middle Ages? About 4 cases (Abstract). *Arthritis Rheum* 1999; 42 (Suppl.): S245.
- HALL L: Polyarthritis in Kenya. *East Afr Med J* 1966; 43: 161-70.
- MASON D: The roles of the hypothalamus and the gastrointestinal tract in the prevention of inflammatory autoimmune disease. *Clin Exp Immunol* 1994; 97: 339-41.
- GUIFFRA V, VITIELLO A, GUISIANI S et al.: Rheumatoid arthritis, Klippel-Feil syndrome and Pott's disease in Cardinal Carlo de' Medici (1595-1666). *Clin Exp Rheum* 2009; 27: 594-602.