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The malformed Non-adult Human Skeletal Remains of the Anthropology Museum of Naples: reading the past writes the future

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Abstract. Human skeletal remains provide data to aid in the reconstruction of human evolution and allow researchers to study the lifestyle, culture and habits of ancient and modern populations. Bones and teeth retain traces of growth and aging processes and their morphology can be influenced by internal and external factors including metabolic, nutritional and infectious diseases or traumatic events. The skeleton therefore represents an interesting biological archive. In this study, by anthropometric and morphological analyses, we have examined the non-adult human skeletal remains of the Anthropology Museum of the University Federico II in Naples to derive information regarding the process of skull ossification and skeletal development during prenatal and neonatal life. Then we have crossed our results with those deriving from a bibliographic survey to determine if the observed anomalies met the criteria of any pathological diagnosis of genetic nature, possibly incompatible with survival. The research was conducted through a non-invasive method to safeguard the integrity of finds considering their rarity and historic importance.

Key words: craniosynostosis, malformations, non-adult human skeletal remains, anthropology museum

Introduction

The Collections of the Anthropology Museum of Naples constitute a cultural heritage of high historical value. They are divided in Osteological, Archaeological and Ethnographic Collections and consist of more than 26,000 finds kept by one of the first anthropological institutions that arose in Europe. The Museum was founded at the University of Naples in 1881. Its history lies in the intellectual landscape which saw Anthropology emerging as a young and fervent science. The Osteological Collection was realized for the most part by Giustiniano Nicolucci (1819-1904), first Director of the Neapolitan Museum, and by his pupil Abele De Blasio (1858-1945), both doctors and highly interested in the study of anthropological disciplines. The Collection was then enriched thanks to the efforts of subsequent Directors such as Vincenzo Giuffrida Ruggeri (1907-1921), Gioacchino Leo Sera (1927-1948), Mario Galgano (1950-1980).

The Osteological Collection, and in particular the craniological one (the *Cranioteca*) which represents the Museum's flagship, is constituted of about 2000 human skulls, mostly belonging to adults. It reflects the scientific interests of an era that identified human remains one of the main tools to analyse human variability.

Numerous specimens are affected by malformations, trauma and infectious, metabolic, congenital and neoplastic diseases attesting the presence in past populations of pathologies that still affect humanity. The study of some of these interesting finds was deepened by De Blasio between the late nineteenth and early twentieth century and more recently by us (1). According to Cesare Lombroso (1835-1909), De Blasio supported the theory that the physiognomy revealed the personality and cranial malformations were indicative

of clinical pathologies or atypical behaviours. Considering the documentary value of these finds, researchers today approach them using innovative tools and technologies such as biomolecular, radiological and structural investigations.

Among these specimens particularly interesting are some foetal skulls at different stages of development, one articulated neonatal human skeleton and different juvenile skulls. Unfortunately, no information is available regarding any studies conducted on these finds by ancient museum researchers and no historical-scientific publications have been found.

For several years now, the approach to the study of human remains and their presentation to the public has been a much debated issue for ethical reasons. We studied these malformed non-adult skeletal remains because they constitute an important cultural heritage to be enhanced. Indeed, they have not only an important historical value but also a high biological interest that makes them a rare archive from which to derive information regarding the process of skull ossification and skeletal development during prenatal and neonatal life.

The neurocranium is made up of eight bones that articulate with each other thanks to joints made of fibrous tissue, called sutures. It begins to form between the 23th and 26th gestation day from tissue deriving from the mesoderm and neural crests (2). The skull growth and development are strictly regulated by a process that occurs along the osteogenic interfaces of the sutures facilitating the skull development perpendicular to the suture and allowing the progressive expansion of the brain (2). In humans, unlike other mammals, gestation ends before significant brain maturity has been reached. Much of our brain growth occurs in the first 1-2 years of life during which we acquire the ability to walk, language skills and we develop all the unique potential of our kind (3). Between 3 and 19 months of life the metopic suture is the first to merge while the sagittal suture does not close completely until adolescence or even in adulthood (4, 5, 6). Premature fusion of the sutures during prenatal life determines the irregular development of the skull which is forced to grow in the direction in which it does not meet resistance causing craniosynostosis, malformations that also influence the normal expansion of the brain (7).

Craniosynostoses (Fig.1) are very heterogeneous cranial anomalies. They are distinct in simple or complex forms according to the type and number of sutures involved. Based on the presence or absence of other associated signs and symptoms (malformations in other regions of the body, developmental delay, etc.), craniosynostoses are also subdivided into syndromic or non-syndromic (isolated) forms. Simple forms are classified as plagiocephaly, scaphocephaly, brachycephaly and trigonocephaly (8). Regarding the complex forms, they can be caused by alterations of the chromosome structure or by genetic mutations. In fact, the formation of membranous bone is regulated by a complex series of genetic processes: during intrauterine life, when osteoblastic activity is upregulated, osteoclastic activity is reduced. Therefore not occurring apoptosis (cell death), excessive bone growth take place with consequent fusion of the sutures (9).

The oldest case of craniosynostosis dates back to 530,000 years ago and was found at the level of the lambdoid suture in the skull of a child of *Homo heidelbergensis*, nicknamed "Benjamina", found on the site of Sima de los Huesos in Atapuerca in Spain (10).

In this work, by morphological and morphometric investigations, we have analysed the non-adult human remains of the Osteological Collection of the Anthropology Museum of Naples to obtain information related to development. Furthermore, to establish whether the observed skeletal condition met the criteria for any genetical syndromes, we performed non-invasive investigations to maintain the integrity of specimens.

Materials and methods

We performed an inventory reconnaissance and a research in the archive documents on the non-adult human skeletal remains belonging to the Osteological Collection. Thirty-one finds in a good state of preservation were found in deposits. All the specimens were examined by a careful macroscopic inspection and then measured by digital and curved callipers.

The presumed development period and the biological age estimation were evaluated by comparing the cranial circumference, skeletal morphology and

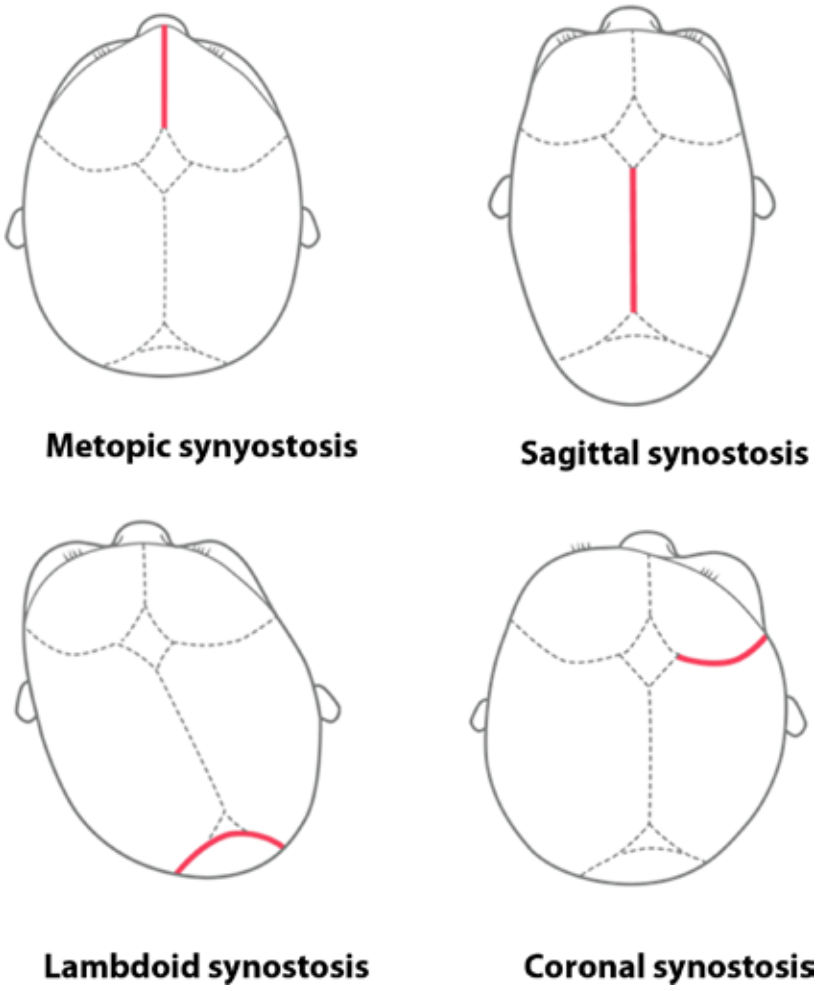

Figure1. Simple forms of craniosynostosis.

dentition with the growth tables and scientific literature (11).

Based on the available information and using current pathognomonic and dysmorphological features we also tried, for each specimen, to determine whether the observed skeletal morphology met the criteria for any genetic syndromes.

Results

In the non-adult human skeletal remains Collection present to the Anthropology Museum of Naples, we identified five foetal skulls, one articulated neonatal skeleton and twenty-five juvenile (7-15 years) skulls (12).

From the archival research carried out in museum documents it emerged that three foetal skulls were acquired by the Museum in 1907 during Francesco Saverio Monticelli's direction, likely due to the interest of Abele De Blasio. De Blasio presumably also coordinated the acquisition of the others two foetal skulls and neonatal skeleton. The juvenile skulls belong generally to the Nicolucci *Cranioteca*. It is plausible that the small collection was also used to educate medical students as there are some pencil marks found on the specimens.

Each find has been considered by us as case study (1 to 7).

Four of the five foetal skulls are sequentially numbered with a progressive number (from 1 to 4) written in pencil on the frontal bones. Only in one the

numerical sign was missing, so we decided to identify it as n.5.

All the foetal skulls are presumably of male biological sex as reported in pencil on the finds by researchers of early 1900s. Further, meninges-like formations are evident on the cranial vault of all the remains.

The morphometric analysis of Case 1 (Fig.2) reveals that the circumference of the skull is 24 cm and would correspond to a foetus of about 24 weeks (11). Closure of the metopic suture is evident (Fig. 2a) and the formation of a slight bone crest is also observed near the nasal bones. From the posterior view, bilateral fusion of the lambdoid suture also appears (Fig. 2b). From the superior view, it is interesting to note that the margins of the two parietal bones tend to overlap (Fig. 2c).

In the case 2 (Fig. 3) the circumference of the skull is of 30 cm and would correspond to a foetus of about 29 weeks (11). The morphological examination reveals an incomplete metopic synostosis mainly near the nasal bones (Fig. 3a,b). From the superior view, it is interesting to note that the margins of the two parietal bones tend to overlap (Fig. 3b). Posteriorly, bilateral lambdoid synostosis also is evident. Following the sagittal and lambdoid synostoses, an almost complete obliteration of the relative fontanel (lambdoid) is observed (Fig. 3c).

The case 3 (Fig. 4a) has a circumference of 31 cm and would correspond to a foetus of about 30 weeks (11). From the superior and posterior view, the closure of the sagittal and lambdoid suture with almost total

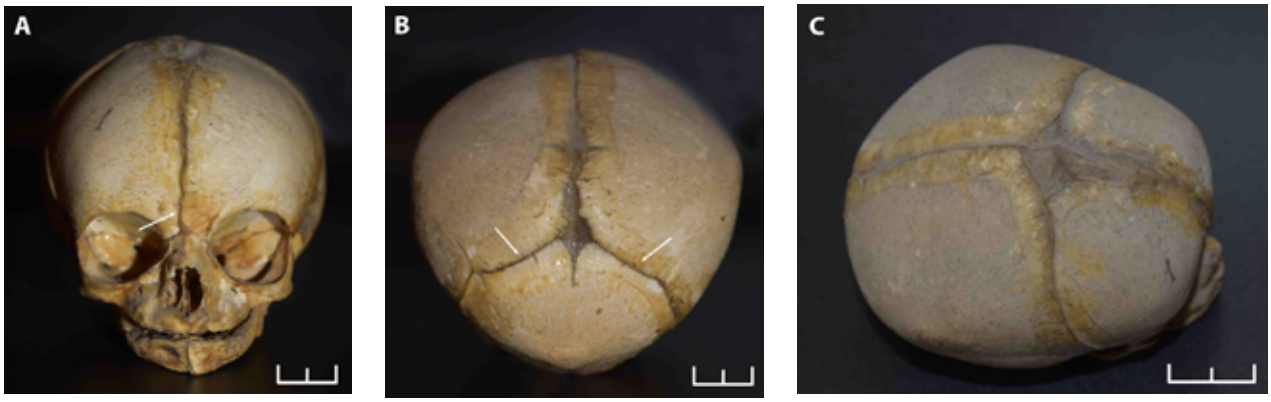

Figure 2. Case 1, foetal skull– a) frontal view, partial closure of metopic suture (arrow); b) posterior view, bilateral fusion of lambdoid suture (arrow); c) vertical view. The bar is 2 cm.

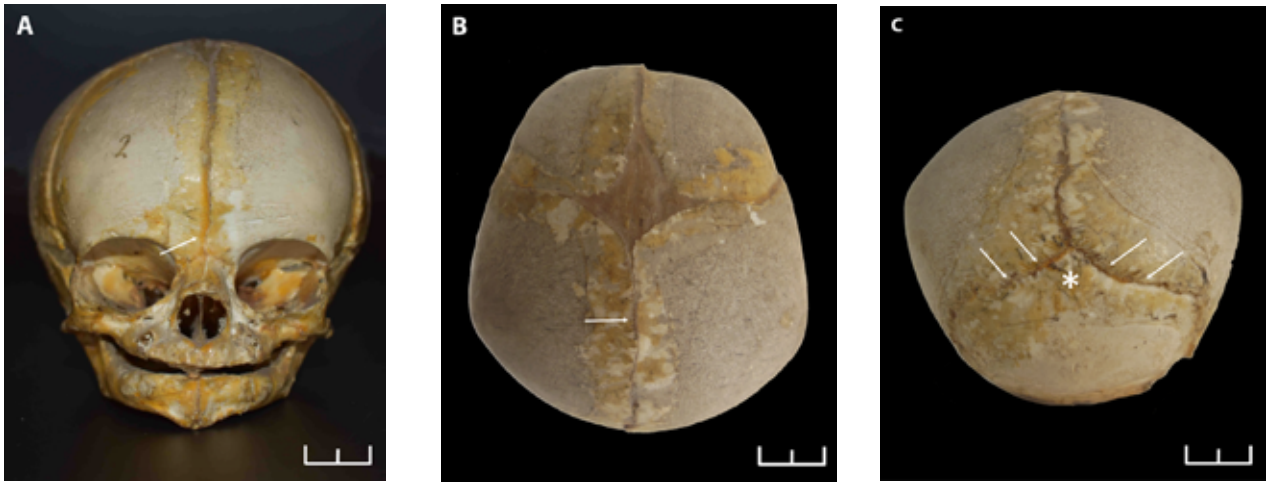

Figure 3. Case 2, foetal skull – a) frontal view, partial closure of metopic suture (arrow); b) vertical view, overlap of parietal bones (arrow); c) posterior view, bilateral fusion of lambdoid suture (arrows) and obliteration of fontanel (*). The bar is 2 cm.

obliteration of the relative fontanel (lambdoid) is observed (Fig. 4b, c).

Cases 4 and 5 have no mandible. The circumference is of 29 cm and would correspond to a foetus of 29 weeks (11). In the region proximal to the nasal bone, the metopic suture is partially fused (Fig. 5a). From the superior view, a crest resulting from the complete fusion of the sagittal suture is evident (Fig. 5b). A close connection of the upper margins of the occipital bones with the lower margins of each parietal is evident from the posterior norm. Both conditions have determined the obliteration of the lambdoid fontanel (Fig. 5b). Furthermore, the skull is particularly elongated and presents a narrow appearance. The presence of a bone crest at the sagittal suture that gives the head a shape reminiscent of the hull of a ship is interesting (Fig. 5 c).

The circumference of the case 5 (Fig.6) is of 31.2 cm and corresponds to a foetus of about 31 weeks (11). In several areas the partial overlapping of the cranial bones is observed as at level of the metopic and coronal sutures (Fig. 6a,b). From the posterior view this phenomenon is particularly evident: at level of the lambdoid sutures the posterior margins of the occipital bone are placed below the parietals (Fig. 6b). From the superior view the skull appears clearly plagiocephalus (Fig. 6c).

The gender of the skeleton (case 6; Fig. 7) is not reported. It is mounted on a metal rod with a wooden base to appear standing and facing the viewer. The head circumference and the skeleton height of about

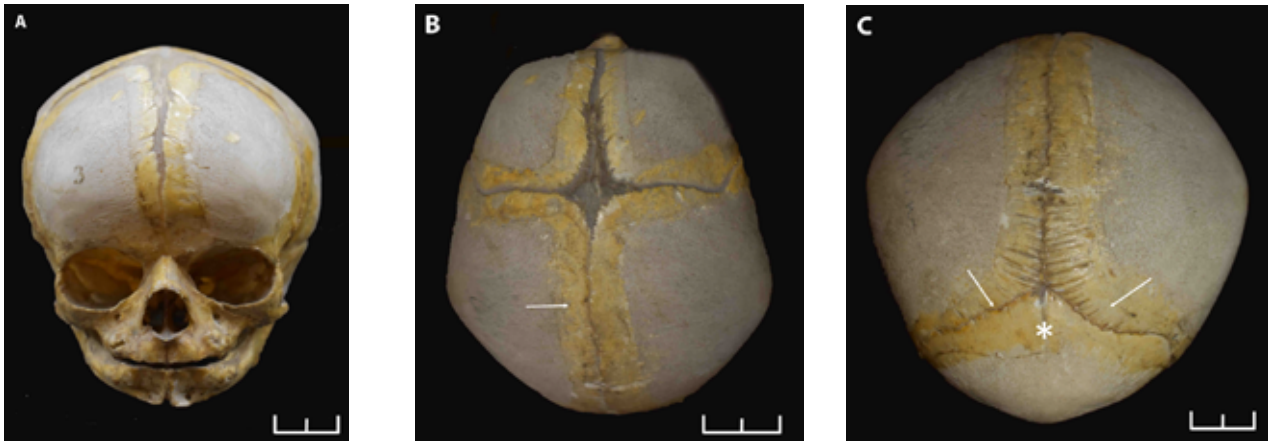

Figure 4. Case 3, foetal skull – a) frontal view; b) vertical view, overlap of parietal bones (arrow); c) posterior view bilateral fusion of lambdoid suture (arrow) and obliteration of fontanel (*).The bar is 2 cm.

Figure 5. Case 4, foetal skull – a) frontal view, closure of metopic suture (arrow); b) posterior view bilateral fusion with overlap of lambdoid suture (arrowhead); obliteration of fontanel (arrows); c) vertical view, sagittal crest (arrows). The bar is 2 cm.

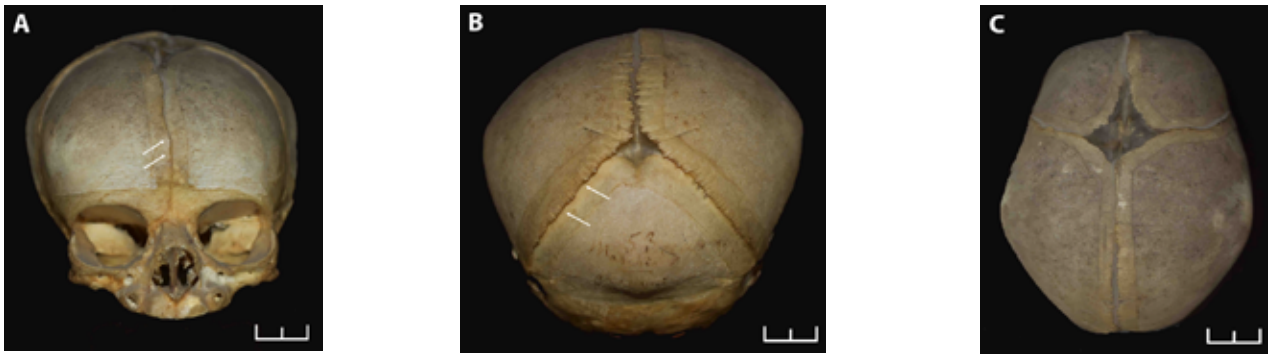

Figure 6. Case 5, foetal skull – a) frontal view, closure of metopic suture (arrows); b) posterior view bilateral fusion and overlap of lambdoid suture (arrows); c) vertical view. The bar is 2 cm.

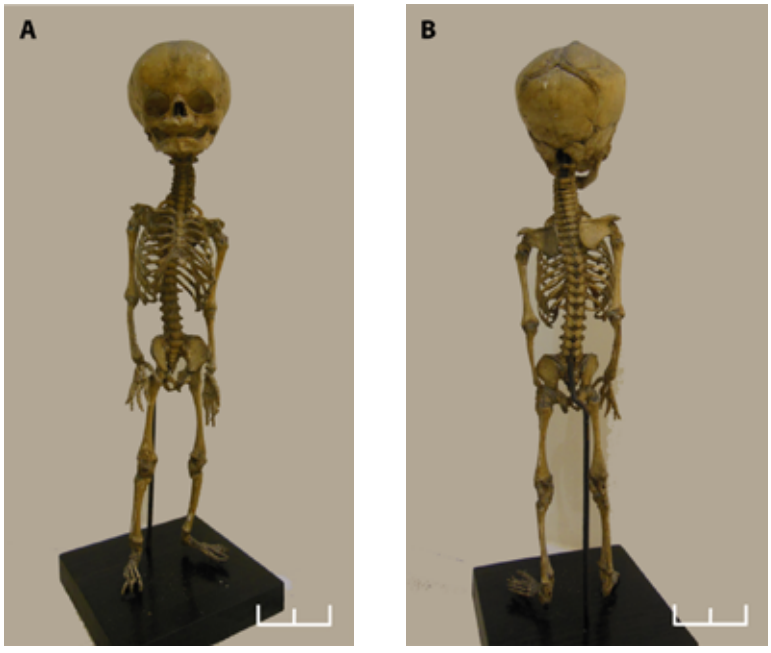

Figure 7. Case 6, neonatal skeleton – a) anterior view; b) posterior view. The bar is 2 cm.

32.5 and 42 cm respectively are compatible with a foetus of about 33 gestation weeks (11). Interesting to note that the femur length is about 8 cm corresponding to a foetus between 37 and 40 gestational weeks. The skull is large in particular on the posterior side and present a pronounced frontal bossing (Fig. 8a,b). Furthermore, all the sutures are closed. Particularly interesting is the appearance of the vertebral column which present a lumbar scoliosis with consequent pelvic dysmetria (Fig. 7,8c). In addition, the 11th rib is fused anteriorly with the 10th (Fig. 8d). The 12th rib is sketched (Fig. 8d).

Among the juvenile specimens we describe only one of the most emblematic. The skull in question (case 7; Fig. 9a,b) belongs to a small collection of finds from Lombardia (Italy) acquired on 1886 under the direction of Giustiniano Nicolucci. In the past, the skull was subjected to horizontal section, probably in order to carry out medical studies. This allowed us to make further observations on the endocranium.

From the physical external observation of the frontal view, the right orbit appears wider and slightly higher than the left one (Fig. 9a). Only the

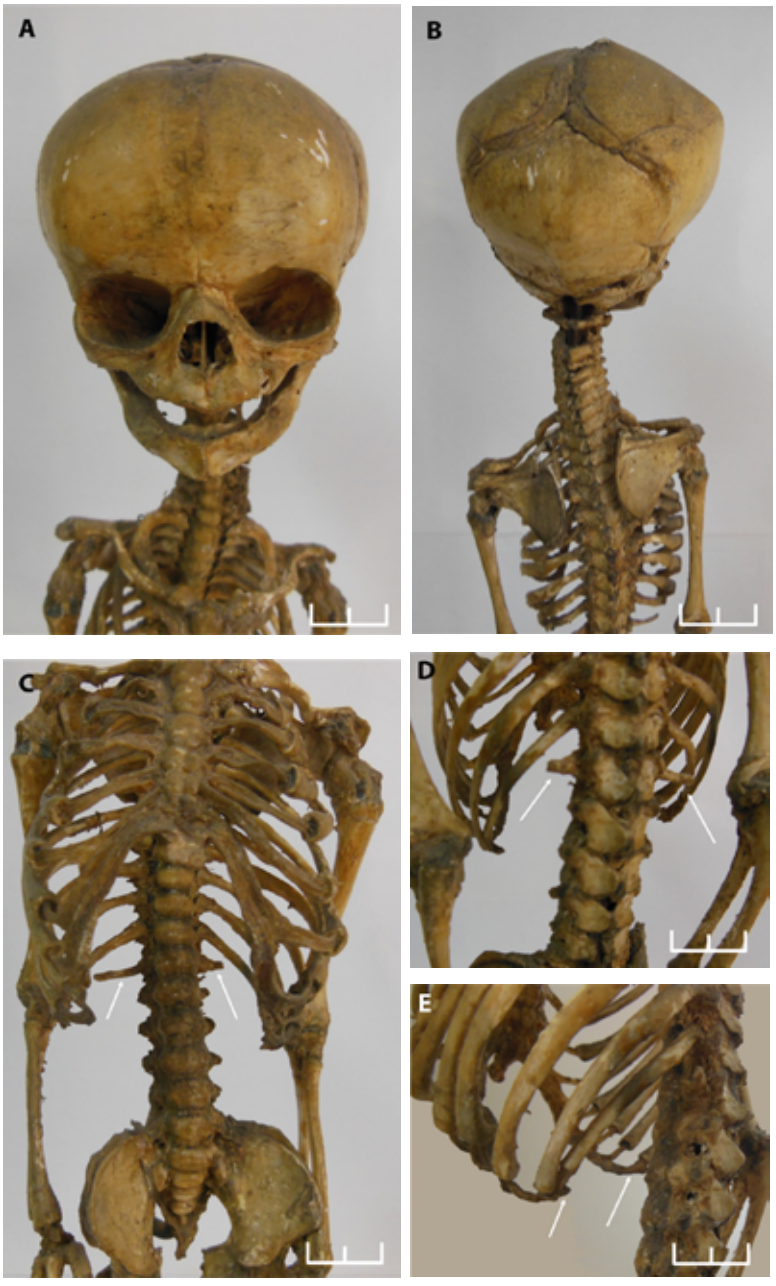

Figure 8. Case 6, neonatal skeleton – a) anterior view of the skull; b) posterior view of the skull; c,d) rib cage, note the sketch of the 12° ribs (arrows); e) 11° ribs merged with previous ones (arrows). The bar is 2 cm.

upper dentition is present with 12 erupted teeth belonging to both the primary and secondary dentition (Fig. 9a). Interestingly, both second molars have not yet erupted (Fig. 9d). It is also to noted that the skull presents parallelogram shape and the forehead slightly protrudes forward on the right side (Fig. 9c). Viewed from the bottom, it is evident that the mastoid bone and acoustic meatus of the right side are not symmetrical with the contralateral ones (Fig. 9d). From the examination of the inner surface of the skullcap, the imprint of the cerebral circumvolutions is particularly evident on the right side (Fig. 9e,f).

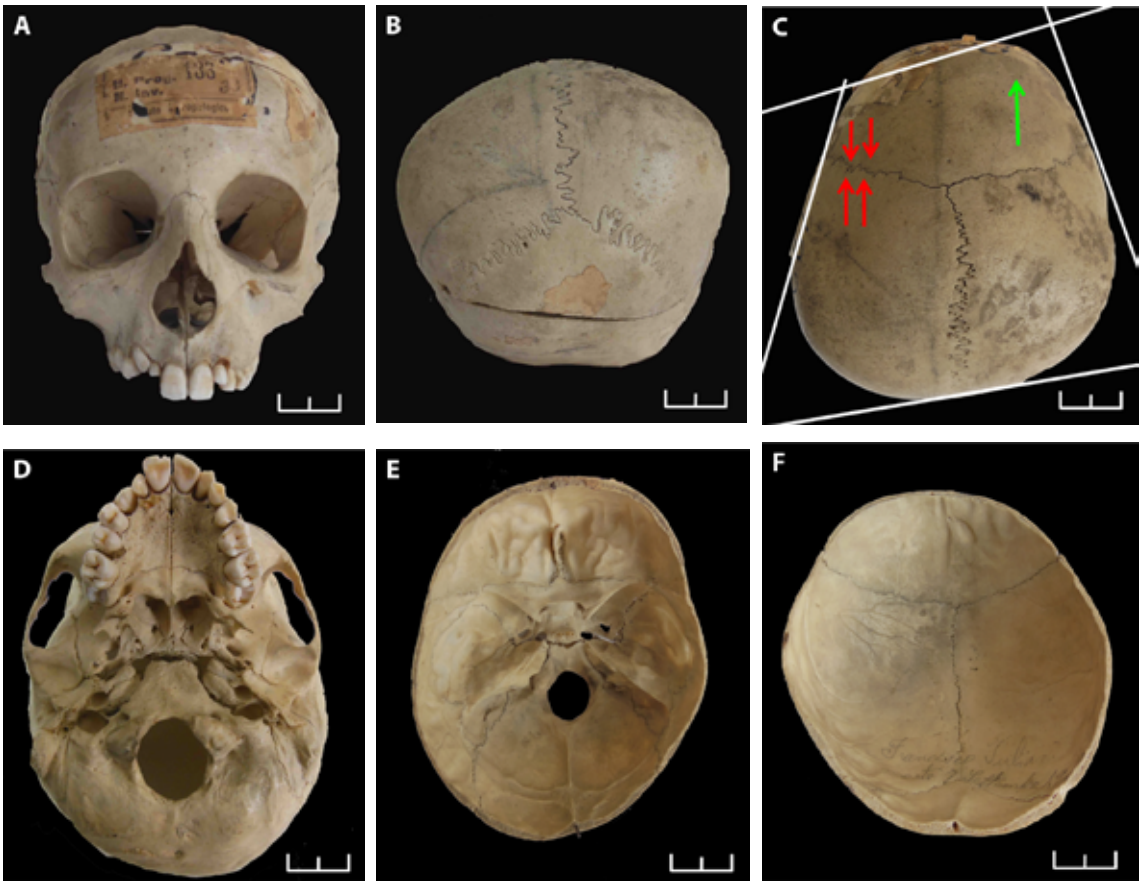

Figure 9. Case 7, juvenile skull – a) frontal view; b) posterior view, c) vertical view, note the parallelogram shape of the skull, left coronal synostosis (red arrows) and right protrusion (green arrow); c) bottom view, note acoustic meatus dysmetria and dental eruption; d,e) endocranium. The bar is 2 cm.

Discussion

Around the nineteenth century scientists were particularly interested in the study of the skull as the skeleton area that best characterized human physical attributes. From this perspective the craniological Collection of Giustiniano Nicolucci was born. Cesare Lombroso (1835-1909) and many other researchers, including Abele De Blasio, supported the theory that physiognomy revealed personality, furthermore, they believed that cranial malformations were indicative of clinical pathologies or atypical behaviours. Gradually during the 20th century the cause of congenital anomalies was debated and differently envisioned by researchers. In fact, topics as modern concepts of developmental biology were completely absent during the time in which these specimens were collected. Based on modern scientific knowledge, today the study of human skeletal remains stored by the museums can make an important contribution to the understanding of malformed diseases that still afflict humanity.

The malformed adult skulls of the Anthropology cabinet of the University of Naples have been described in particular by De Blasio (13). However, no historical notes on non-adult human skeletal remains have been found.

All the non-adult human skeletal remains of the Anthropology Museum examined in this study were affected by craniosynostoses and skeletal anomalies. This work provides a rare and interesting opportunity to observe disorders of the skeletal developmental process.

Furthermore, we carried out a preliminary bibliographic survey to determine whether the morphological anomalies observed by us in the findings were attributable to possible genetic pathologies not compatible with survival.

The foetal skulls represent a series in relation to the degree of development as it emerges from the progressive values of the cranial circumferences regardless of the estimated developmental age. In fact, it should also be borne in mind that the presumed age of development may be underestimated since the head circumference could undergo variations in relation to the observed synostoses (7). Further, the observed meninges-like formations, more evident with respect of the real development stage, are probably due to conservative interventions of tannization (a complex technique consisting in drying the specimens and injecting them with tannic acid for preserving anatomical specimens) according to the museum procedures in place between the end of the nineteenth and the beginning of the twentieth century, as suggested also by the unnatural bones colour (14).

From the morphological evidence of the case 1, the closure of metopic suture led us to hypothesize that the skull was affected by trigonocephaly (15). In particular, it is reported that this synostosis occurs during the gestational period or before 3 months of life determining a restriction of the frontal bone growth. Trigonocephaly currently has a prevalence at birth of about 1:15.000 with a predominance in the male sex (M:F = 3:1) (16, 17, 18). The skull also presents lambdoid bilateral craniosynostosis that results in the posterior cranial fossa reduction due to the lesser development of the occipital bone. This last condition might be attributable to Arnold-Chiari syndrome that, in severe forms, causes neurological problems such as cerebellar agenesis incompatible with life (19).

Case 2 and 3 are comparable as they present lambdoid and sagittal craniosynostosis. The early closure of sagittal suture may be responsible of the observed increase in the antero-posterior diameter of the skull with the subsequent presence of scaphocephaly (15). Scaphocephaly is the most frequent simple craniosynostosis with a predominance in the male sex (M: F = 3.5: 1) and a prevalence at birth of 1.9-2.3 per 10,000 live births (20).

Further, of particular interest are case 4 and 5: since all the cranial sutures are closed, we are faced with an exceptional case of pansynostosis. Pansynostosis, translates literally to mean "all one bone" or a complete fusion of all of the cranial sutures, is often associated with a genetic disease such as Kleeblattschädel syndrome or isolated cloverleaf skull syndrome, severe skeletal dysplasia, usually lethal, or with Crouzon and Pfeiffer syndromes, mostly caused by gene mutations of the fibroblast growth factor receptor (21, 22). It is possible that our finds 4 and 5 had suffered during their short life of one of these genetic pathologies.

Case 6 is unique. Based on femur length, it is a skeleton of an individual at the end of development. However, the skull circumference and the total height are compatible with a foetus of 33 weeks. This divergence could be due to an underestimation of the last two measures caused both from the cranial synostosis, that gives the skull a smaller circumference with the respect to real phase of development, both to the curvature of the vertebral column that impinges upon the skeleton height. It is also likely that the age prediction from the femur was underestimated, given the observed skeletal anomalies.

The physical analysis has revealed the presence of anomalies in different regions of the skeleton that could be attributable to a unique pathology. First the curvature of the spine suggests that the individual was affected by a lumbar scoliosis which was also responsible for pelvic dysmetria. Scoliosis is a complex structural deformity of the spinal column that usually occurs during adolescence. In 80% of cases, scoliosis is defined as idiopathic, that is, not attributable to an underlying cause. In 20% of cases, however, it is secondary scoliosis, caused by congenital malformations of the spine or thorax. Considered the simultaneous presence of malformations both in the spine and in the thorax, it is possible that the small individual was affected by secondary scoliosis. Further, suggestive is the hypothesis that the scoliosis observed on our skeleton may have been caused by dystrophic dwarfism. As described in literature, the dystrophic dwarfism could be correlate to a genetic alteration such as a mutation of a gene located on the long arm of chromosome 5 which causes the abnormal production of type IX collagen (23, 24). Achondroplastic dwarfism is a severe inhibition of cartilage proliferation limiting endochondral bone growth in all areas of the body and it is described in both the clinical and paleopathology literature (25). Today dystrophic dwarfism is not lethal but causes serious physical handicaps that require

aggressive treatments and prenatal diagnosis becomes a priority to give parents the opportunity to terminate pregnancy.

Additionally, it is interesting that in the thorax the 11th rib merged with the 10h. At this regard it is reported that the fusion and/or malformations of the ribs may be due to autosomal recessive spondylocostal dysostosis known also as Jarcho-Levin syndrome caused by pathogenic variants in DLL3, MESP2, LFNG, HES7 and RIPPLY2, all genes involved in the developmental processes regulated by Notch signalling pathway. Also, this disease causes an aspect similar to a dwarfism form and most affected infants do not survive the first year of life due to respiratory failure (26).

These data suggest that the infant might have dwarfism. To support this hypothesis, the external examination shows that the skull seems to be posteriorly deformed by increased intracranial pressure, as occurs in the hydrocephalus. At this regard, it is interest to note that also in achondroplastic dwarfism, the head circumference is abnormally large usually due to an excess of cerebrospinal fluid in the cortical subarachnoid space (27).

Concerning case 7, the dentition indicates that at the time of death the individual was about 12-13 years old since the second molar has not yet erupted. The peculiar trapezoid shape of the skull led us to surmise that the individual was affected by congenital plagiocephaly. In particular, the asymmetry of the forehead, the higher and wider ipsilateral orbit than the other, the nose deviation away from the side of the forehead flattening are the morphological characters that identify the plagiocephaly condition due to the coronal synostosis. Unilateral coronal craniosynostosis is present when one coronal suture closes before brain and skull growth are complete. In this condition the remaining cranial sutures must compensate with increased growth to continue to accommodate the growth of the brain. Since forehead is pushed forward on the right side, the skull is clearly affected by left coronal synostosis. This hypothesis is also supported by the evident imprint caused by the high pressure exerted by the brain abnormal growth over the right anterior side of the skullcap inner surface. A recurrent P250R mutation in fibroblast growth factor receptor 3 (encoded by the *FGFR3* gene, 4p16.3) was found to be responsible for the majority of these familial cases and for some of the sporadic cases of coronal synostosis (28, 29).

In conclusion, our morphological and morphometric observations made possible to highlight the presence of craniosynostosis and skeletal malformations in non-adult human remains of the Osteological Collection of the Anthropology Museum of Naples. The comparison of our findings with the data available in the literature has allowed us to describe, during different stages of development, various skeletal anomalies for which it was possible to hypothesize the probable genetic causes. This non-invasive approach was chosen not to damage the integrity of the specimens considered their historical value. Our research enriches the information relating to craniosynostosis and skeletal malformations not only in the developmental biology field but also in the paleopathological one.

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