

Klippel-Feil Syndrome: morphological findings in a 19th-century musealized skull from Viana del Bollo (Orense, Spain)

Jesús Herrerín¹ (ORCID: 0000-0002-5175-4385), Enrique Dorado²
(ORCID: 0000-0002-1137-2016), Francesco M. Galassi^{3, 4, 5}
(ORCID: 0000-0001-8902-3142), Elena Varotto^{3, 4}
(ORCID: 0000-0001-6637-9402), Rosa Dinarès Solà⁶

¹ Universidad Autónoma de Madrid. Departamento de Biología.
Unidad de Antropología Física, Madrid, Spain

² Sección de Antropología Forense, Instituto de Medicina Legal de Madrid, Madrid, Spain

³ FAPAB Research Center, Avola (SR), Sicily, Italy

⁴ Archaeology, College of Humanities, Arts and Social Sciences, Flinders University,
Adelaide, SA, Australia

⁵ Department of Anthropology, Faculty of Biology and Environmental Protection,
University of Lodz, Lodz, Poland

⁶ Hospital General de Catalunya, Spain

ABSTRACT: The aim of this study is to show the cranial alterations that Klippel-Feil syndrome produced in a case older than 200 years. Few paleopathological case studies diagnosed as Klippel-Feil Syndrome are focused on cranial abnormalities. A skull numbered 778, belonging to the Federico Olóriz Aguilera collection (Spain, 19th century AD), *Universidad Complutense de Madrid*, belonging to a young man born in a town in the North of Spain, was investigated. This cranium was visually inspected, hence macroscopically and paleoradiologically studied, using the images obtained through conventional radiology and CT scan imaging. In addition to the vertebral fusion between the atlas (C1) and the axis (C2), atlanto-occipital fusion, basilar impression, obliteration of the sagittal suture, enlarged parietal foramina and significant craniofacial asymmetry affecting maxillary bones, sphenoid, orbits, nasal bones and both palatines were observed. Morphological findings make it possible to diagnose a Klippel-Feil syndrome, possibly type-II, although the lack of the rest of the spinal column renders it impossible to verify other spinal anomalies. As a limitation, only the cranium and two cervical vertebrae were preserved, hence the possible involvement of the rest of the skeleton cannot be verified.

KEY WORDS: Olóriz collection, Klippel-Feil syndrome, atlanto-occipital fusion, basilar impression, facial asymmetry, enlarged parietal foramina

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Introduction

Klippel-Feil syndrome (KFS) is characterized by the congenital fusion of a variable number of cervical vertebrae (Vujasinovic Stupar et al. 2015), in the majority of cases accompanied by other abnormalities in different apparatuses, including otorhinolaryngological and craniofacial ones (Clarke et al. 1998). The classic clinical KFS triad comprises a short neck, restricted neck mobility, and a low dorsal hairline (Gunderson et al. 1967; Fietti and Fielding 1976; Taylor-Martínez et al. 2019). In the modern clinical setting, in cases in which the condition presents asymptotically it can be discovered by chance, after a radiological examination in living patients. Although the etiology of KFS is not fully understood, some genetic involvement was postulated since mutations in the *GDF6*, *GDF 3*, and *MEOX1* genes were found in some families and an inheritance pattern was determined. For the first two, involved in bone formation and development, it is an autosomal dominant pattern, while for the third one, whose homeobox protein regulates vertebral separation, it is instead an autosomal recessive one (Manger et al. 2021). Before genetic correlations were found, families with KFS individuals within them were historically subjected to anthropological studies (Henneberg and Otocky 1974).

Several cases of KFS have been recorded in the paleopathological literature. Archaeological cases globally have been described since the Neolithic in Slovakia (site of Vráble-Velké Lehemby) and Late-Final Neolithic in Greece (Alepotrypa Cave, Peloponnese, 5000-2300 BC) (Papathanasiou 2005; Hukelová et al. 2021), the Chalcolithic Age in Peru

(MacCurdy 1923), North America (Jarcho 1965), Central America (Urunuela and Alvarez 1994), Ancient Egypt (Aufderheide and Rodriguez-Martin 1998) or Europe (Barnes 1994; Gladykowska-Rzeczycka 1997; González-Reimers et al. 2001; Herrerín, 2004, 2011; Pany and Teschler-Nicola 2007; Fernandes and Costa 2007; Giuffra et al. 2009; Macías-López 2020). In Italy, four cases of KFS from the 1582–1583 AD plague phase of the San Michele cemetery in Alghero (Sardinia) were identified among 199 individuals making this the archaeological site with more such finds also dating to the same historical period (Varotto et al. 2020).

In this study the case of a skull from the Olóriz collection is presented: this specimen shows some of the typical features of KFS, despite the sole preservation of two cervical vertebrae and not of the entire skeleton. The Olóriz collection was formed for research purposes – as the history of anatomy teaches (Papa et al. 2020) – from corpses collected by Federico Olóriz Aguilera (1855–1912), Professor of Anatomy at the University of Madrid, reaching a total of 2,250 skulls, almost entirely from Spain and dating to the 19th century. At present the collection is distributed among various Departments of the *Universidad Complutense de Madrid*, and although the written documentation is now missing, all the skulls are marked with black ink indicating their basic data about sex, age at death and geographic provenance. In addition, it must be underlined that the collection is dispersed and many specimens have disappeared from the register. However, it has been possible to verify that there is no similar case among those preserved, after a thorough review of all the preserved skulls.

Material and Methods

The analyzed skull (inventory number 778 – Olóriz collection) comes from Vi-ana del Bollo, in the Spanish province of Orense. Data about sex and age at death are labelled on the skull itself, but sex determination and age estimation were anyhow performed utilizing Ferembach et al.'s (1979), Masset's (1982) and Buikstra and Ubelaker's (1994) sets of methods. The skull was completely preserved, although the mandible is missing, and, as a result on the fusion, the atlas and axis are still present. Its state of preservation can be grossly assessed as good although no preservation indexes, more commonly used for bio-archaeological material originating from excavation sites – and, as yet, not for scientifically musealized anatomical specimens – were calculated. Together with the visual inspection and macroscopic examination of the skull, image analysis was carried out using conventional radiology and CT scan imaging [Equipment: HP 15.0; Parameters: 120kV/150mAs; 0.5/3.0mm].

Results

The information about sex and age at death was written on the right parietal bone by Dr. Olóriz himself (Fig. 1): the skull belongs to a 22-year-old male. Morphologically and anthropologically, the skull confirmed the above-stated information: male features and 20–25 years age range.

The following pathological findings were observed in skull 778.

Neurocranium:

1. Absence of sagittal suture;
2. Enlarged parietal foramina;
3. Basilar impression;

4. Atlanto-occipital fusion with a significant spinal canal synostosis.

Splanchnocranium:

5. Asymmetry of orbits and nasal region;
6. Asymmetry of nasal and palatal bones;
7. Displacement of maxillary massif.

Spinal column:

8. C1-C2 fusion.



Fig. 1. Lateral view of skull number 778 with information on sex, age at death and provenance labelled on the ectocranial surface of the right parietal bone.

In the superior view (Fig. 2a), the sagittal suture was totally missing and the coronal one showed no obliterated areas. In the frontal view, a significant lateral asymmetry was observed, with deviation of the nasal bones and nasal septum to the right (Fig. 2b). This asymmetry also affected the orbits, the left being more cranially located, taller and narrower than the right. In the posterior view (Fig. 2c), the asymmetry was also evident, with significant lateral displacement of the sagittal suture and the lambda craniometric point, while the lambdoid suture appeared visible and unobliterated. Additionally, two parietal enlarged foramina are present (Fig. 2c).

In the inferior view the skull showed asymmetry of the entire facial massif

(Fig. 3a, b), with a very significant displacement of the median sagittal plane (red and white lines). This asymmetry was very evident in the maxillary palatal processes and palatal bones, with smaller dimensions in the left hemicranium (Fig. 3c).

The palatal suture was asymmetrical in its course and length. Four teeth remained *in situ* (16, 17, 25 and 26) as well as two roots (18, 27), while the rest were lost *post-mortem*. The postero-inferior view (Fig. 4a) showed an atlanto-occipital fusion, with fusion of the lateral massif and a normal appearing posterior arch of the atlas. The axis was found to be fused with the atlas at its articular facets. The odontoid process was fused with the anterior arch and the right lateral mass of

the atlas. Part of the odontoid process had already been lost historically, torn off as a result of past manipulations performed to separate the skull from the spine at the time of its musealization (Fig. 4a+). On the other hand, the atlas was fused to the occipital but not symmetrically, leaving a space between the left postero-lateral edge of the foramen magnum and the left postero-lateral arch of the atlas (Fig. 4a*). The lower view (Fig. 4b) also showed the reduction in the antero-posterior diameter of the vertebral canal.

Conventional radiographic analysis showed a 4 mm basilar impression on McGregor's line (hard palate-occipital scale; red line; Fig. 5a). At the same time the CT study made it possible to



Fig. 2. Macroscopic examination. a) Superior view; b) Frontal view; c) Posterior view.

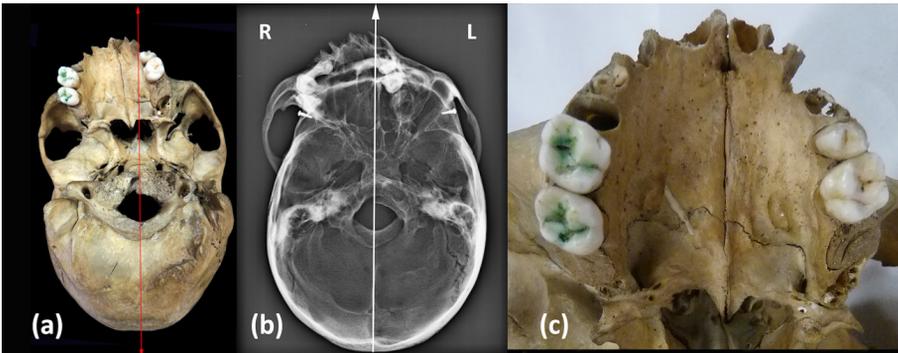


Fig. 3. a) Inferior view (red line, sagittal plane); b) Inferior view, X-Ray image (white line, sagittal plane); c) Maxillary and palatal bones, inferior view.

verify how the asymmetry also affected the sphenoid bone, with a marked shift towards the right side of its pterygoid processes (Fig. 5b), and likewise the maxillary bone and the nasal cavity (Fig. 5c).

Finally, the tomography verified the stenosis of the vertebral canal at the level of the foramen magnum (Fig. 5d, e), due to the fusion of the atlas in an asymmetric, rotated position.

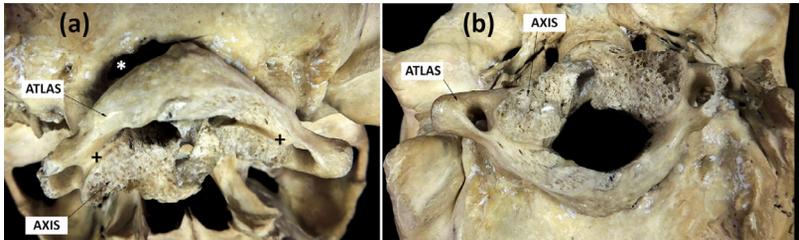


Fig. 4. Postero-inferior view. a) atlanto-occipital fusion + axis-atlas fusion. * Space between the left postero-lateral edge of the *foramen magnum* and the left postero-lateral arch of the atlas. b) Stenosis of the vertebral canal.

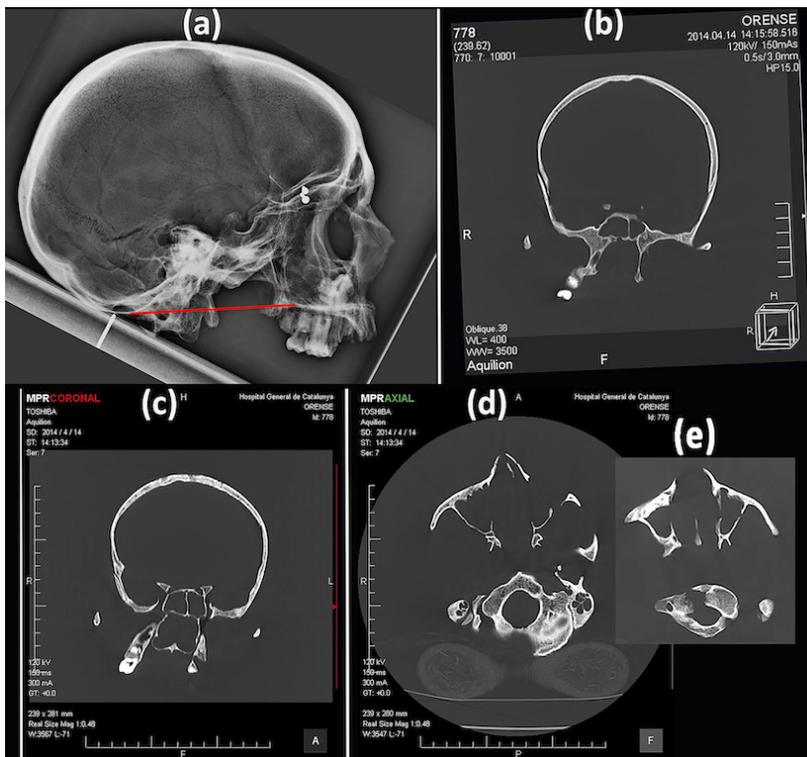


Fig. 5. a) Conventional radiographic image. McGregor's line (red line). b) CT image. Frontal view. Deviation of the pterygoid processes. c) CT image. Frontal view. Deviation of the maxillary bone and the nasal cavity d) and e) CT image. Inferior view. Stenosis of the vertebral canal at the level of the *foramen magnum*.

Discussion

KFS was first described in 1912 by Maurice Klippel and André Feil (1912) in a 46-year-old patient with a massive fusion of the cervical vertebrae, although the first clinical descriptions are attributed in 1745 to Haller and in 1746 to Morgagni (Gunderson et al. 1967).

Three different forms of KFS are defined (Barnes 1994; Pany and Teschler-Nicola 2007; Toker et al. 2009):

- Type I: with formation of a bony block of several cervical and upper thoracic vertebrae (three or more levels) often associated with more severe defects (Barnes 1994; Pany and Teschler-Nicola 2007).
- Type II: fusion of two or three vertebral segments. The second and third cervical vertebrae are the most frequently affected, followed by the fifth and sixth. When the thoracic vertebrae are affected, it is mainly between T2 and T5 (Barnes 1994). It can appear with an atlanto-occipital fusion, hemivertebrae and other anomalies. It is the most common form of KFS, although with minimal clinical symptoms (Barnes 1994; de Rubens-Figueroa et al. 2005; Pany and Teschler-Nicola 2007).
- Type III: fusion of the cervical block together with other anomalies in the lumbar and thoracic regions. Scoliosis is present in 60% of cases (Barnes 1994; Pany and Teschler-Nicola 2007; Toker et al. 2009).

Therefore, the cervical vertebrae are the most commonly affected, leading to the description, especially in old clinical textbooks, of a syndrome in which patients are characterized by a shortened or absent neck as the result of a complete cervical block.

The prevalence of KFS is estimated at 0.71% (Brown et al. 1964; Papagrigrakis

et al. 2003; Nouri et al. 2017) and the incidence of one case per 30,000–42,000 (de Rubens-Figueroa et al. 2005), with a female predilection (Jones 1997; Aufderheide and Rodríguez-Martin 1998; Martínez-Quintana and Rodríguez-González 2015; Sirico et al. 2015; Gruber et al. 2018).

The final cause of this vertebral fusion is found in a failure in spinal segmentation between the third and eighth weeks of embryogenesis (Fietti and Fielding 1976; Mahirogullari et al. 2006; Fernandes and Costa 2007). There is no unanimity of criteria on its genetic origin (Daum and Jones 1988; de Rubens-Figueroa et al. 2005; Pany and Teschler-Nicola 2007; Toker et al. 2009), with a genetic inheritance being proposed, dominant in Type II and recessive in Types I and III (Gunderson et al. 1967; Juberg and Gershanik 1976; Lowry et al. 2001).

Cervical fusions in KFS can remain asymptomatic, it being discovered accidentally after radiological analysis (Copley and Dormans 1998), although limitation of neck movement and its relationship with other abnormalities occurs in a high percentage of cases (Dietz 2001). On the other hand, atlanto-occipital fusion can lead to severe neurological symptoms after even minor trauma (Gray et al. 1964) due to the excessive mobility of the vertebral segments adjacent to the fused area (Strax TE, Baran E. 1975; Adeleye and Akinyemi 2010).

Multiple disorders associated with KFS have been described, such as kyphosis, spina bifida, cleft palate, atlanto-occipital fusion, basilar impression, scoliosis, supernumerary cervical vertebra, Sprengel's deformity, dwarfism, hypodontia, meningocele, renal and cardiac anomalies (Gunderson et al. 1967; Hensinger et al. 1974; Hensinger and MacEwen 1986; Daum and Jones 1988;

Tachdijian 1990; Barnes 1994; Copley and Dormans 1998; Herman and Piz-zutillo 1999; Warner 1998; Dietz 2001; Papagrigorakis et al. 2003; Narang and Goyal 2006; Pany and Teschler-Nicola 2007; Toker et al. 2009). Specifically, atlanto-occipital fusion is produced by a failure in the segmentation between the skull and the first cervical vertebra. It can be partial or complete, and it usually produces associated basilar impression (Boleaga-Durán et al. 2006). It can appear as an isolated sign or be part of different syndromes, among them (very frequently), type-II Klippel-Feil syndrome. With particular reference to the basilar impression or basilar invagination, it consists of an elevation of the floor of the posterior fossa, with displacement of the odontoid process towards the interior of the foramen magnum (Chamberlain 1939). The primary or malformative basilar impression is almost always associated with atlanto-occipital fusion and narrowing of the foramen magnum (List 1941). Among the many causes that can produce a basilar impression (osteomalacia, Paget's disease, Chiari malformation, syringomyelia, hydrocephalus, etc.), the Klippel-Feil syndrome is counted (Matson 1969). In skull 778, the radiographic analysis showed a light but obvious basilar impression (4 mm) on McGregor's line (hard palate-occipital scale; red line; Fig. 5a). Moreover, two enlarged parietal foramina (EPF) detected in the parietal bones are present. EPF are developmental defects characterized by variable intramembranous ossification, normally located on each side of the dorsal portion of the sagittal suture. They differ from normal parietal foramina, which are smaller (less than 1 mm in diameter) and considered anatomical variants. EPF can be associated with syndromic condition such as KFS

or Saethre-Chatzen syndrome (Thompson et al. 1984) or can be found isolated (Piagkou et al. 2013).

Differential diagnosis

A typical paleopathological diagnosis of KFS involves a morphological examination of the column and any other areas of the skeleton to determine if other anomalies may be present, a paleopathological and clinical comparison with the available scientific literature, and an imaging study (conventional X-ray and/or CT scan) in order to confirm the suspected skeletal condition ruling out other pathologies such as fusion caused by traumatic conditions like fractures. Occasionally, but not routinely (especially with historic remains in which invasive sampling is not always justified), a genetic test can be made to corroborate phenotypic observations with the discovery of a matching genotypic background. A sample may be taken and examined to see if there are mutations in genes like GDF3, GDF6, or MEOX1, which are known to be commonly affected in KFS (Mohamed et al. 2013). However, it must be stressed that, both clinically and paleopathologically, radiological analyses can be considered sufficient to make a substantiated diagnosis of KFS.

Differential diagnoses include Paget's disease, fibrous dysplasia, cleidocranial dysostosis, osteogenesis imperfecta, osteoporosis, rickets.

Paget's disease: Paget's disease of bone is a chronic bone disorder of unknown cause. It was first described by Sir James Paget (1814–1899) in 1877. There is an increase in osteoclast activity, resulting in increased bone resorption, the clinical expression of which is the lytic bone lesions observed in conventional radiography

(Resnik and Niwayama 1988; Bolland and Cundy 2013). In response, accelerated and chaotic bone formation occurs, resulting in sclerotic bone that is functionally weaker than normal bone without the characteristic laminar pattern (Menéndez-Bueyes and Soler-Fernández 2017). The clinical manifestations are usually expressed after years of evolution when bone deformity appears that leads to pain, osteoarthritis, and pathological fractures (Roodman and Windle 2005; Bolland and Cundy 2013; Corral-Gudino et al. 2013; Galson and Roodman 2014). The disease usually presents at an older age than 55 and its frequency increases with age (Resnik and Niwayama 1988; Bolland and Cundy 2013), with a slight predominance in males. The bones most frequently involved are the pelvis, femur, spine, skull, and tibia (Bolland and Cundy 2013). In the postcranial skeleton, thickening of the diaphyses of the limb bones are observed, which tend to deform laterally and fracture (in extreme affectations), with the femur and tibia being the most affected bones (Ortner 2003). The alteration in the cranium can cause a symmetrical or asymmetric growth of the parietal or frontal bones causing a greater size of the cephalic portion (Favus and Vokes 2005). This cranial expansion can narrow the diameter of the cranial foramina and cause neurological complications including hearing loss due to cochlear nerve damage caused by involvement of the temporal bone, cranial nerve palsy, and softening of the skull base with risk of compression of the brainstem. In the facial bones, a deformity and/or loss of teeth is caused (Aufderheide and Rodríguez-Martín 1998; Ortner 2003; Favus and Vokes 2005).

Of all the listed features, only platybasia is present in skull 778. But some fea-

tures of skull 778 may allow this disease to be ruled out, even though the vertebral column and the rest of the postcranial skeleton have not been preserved. First of all, age makes it possible to exclude this possibility. It would be extremely rare for a 22-year-old young adult to show signs of Paget's disease as advanced as the pathological changes shown in this case. Secondly, the widening of the diploe (hyperostosis of the cranial vault), the typical "cottony" radiological image of Paget's disease and circumscribed osteoporosis, do not appear in this case (Resnick and Kransdorf 2006; Herrerín et al. 2009). Third, CT images do not show involvement of the temporal bones, or stenosis of the auditory canal. And, lastly, teeth are not affected.

Fibrous dysplasia (FD): it is a bone development disorder in which the lesions form fibrous tissue and spicules of bone tissue (Ortner 2003). The spongy medullary bone is replaced by fibrous tissue. It can be monostotic (a single affected bone) or polyostotic (multiple lesions). The monostotic form is the most common (Herrerín et al. 2009). The monostotic forms mainly affect the long bones, ribs and radius. The polyostotic forms usually involve the proximal femur and the base of the skull (Parekh et al. 2004; Alonso and Muñoz-Torres 2009). The most frequently affected bone in fibrous dysplasia is the femur (44%) followed by the skull (38%), the pelvis (23%), the ribs (16%) and the spine (9%) (Benhamou et al., 2006). When the skull is affected, there is an expansion of the diploe associated with a reduction in the thickness of the internal and external tables of the cranial vault (Herrerín et al. 2009). Radiographic images are very similar to those obtained in Paget cases (*cottony* images). But computed tomography is more im-

portant in diagnosis, because it shows expansive focal areas with a homogeneous "ground glass" appearance (Herrerín et al. 2009; Raus and Coroiu 2016). Despite not having recovered the postcranial skeleton, we ruled out fibrous dysplasia because it does not show a widening of the diploe or the typical CT image in "thin glass" (Herrerín et al. 2009).

Cleidocranial dysostosis (CCD). The pathogenesis of CCD is currently unknown: it is probably caused by an ectodermal and mesodermal tissue disorder during the bone growth phase (Hernández et al., 1980). The difficulty in making a diagnosis of CCD lies in the variability of the alterations. The skull has the anthropometric characteristics of brachycephaly, protruding fronto-parietal fontanelle with large sutures and numerous small supernumerary (Wormian) bones (Herrerín 2011). Affected individuals show a slight hypertelorism and exophthalmos (Hernández et al., 1980; Ortner, 2003; Roberts et al., 2013; Russell, 2015; Lewis, 2019). In the dentition, skull 778 does not show supernumerary teeth or agenesis of premolars, which are also frequently seen signs in patients with CCD (Herrerín 2004; 2011).

Osteogenesis imperfecta (OI): OI are a group of inherited genetic pathologies of the connective tissue characterized by bone fragility and fractures (Jones 2006). They result from constitutional bone fragility (cortical bone thinning, trabecular bone rarefaction) but also from acquired bone fragility due to muscle wasting and immobilization. Wide fontanelles are a known symptom of OI. Typical radiographic signs are thinning of the cortical bone and excessive transparency of the trabecular bone. The main radiographic features are osteopenia, bone fractures and bone deformities

(Renaud et al. 2013). These signs do not appear on this skull.

Osteoporosis: there are no radiological osteopenic signs suggesting some form of osteoporosis (Resnick and Kransdorf 2006). The age of the individual (22 years) also makes this disease very unlikely.

Rickets: rickets is ruled out in the absence of cranial thickening and cranial porosity, frequent in the frontal and parietal bones of individuals affected by this disease (Resnick and Kransdorf 2006).

Among the various craniofacial anomalies associated with KFS, facial asymmetry occurs in 13% to 20% of cases (Martínez-Quintana and Rodríguez-González 2015; Naikmasur et al. 2011; Kerai and Saxena 2014; Jovankovičová et al. 2012). This facial asymmetry is very significant in skull 778, including the nasal area, where the part of piriform aperture and the nasal bones are asymmetrical, with the nasal septum laterally deviated from the sagittal plane. Both the displacement of the maxillary mass and the asymmetry of the orbits and nasal region may have their origin in genetic factors (as occurs in the case of hemifacial microsomia, multiple syndromes, craniosynostosis of the coronal suture or labio-palatal fissures) or in environmental and/or functional factors (such as intrauterine pressure, especially in multiple births, *ante-mortem* trauma with deficient fusion or even infections in the area during growth). In this skull we have not found any sign that would allow us to relate it to synostosis of the coronal suture, as this is the only synostosis that can present asymmetrical compensation of the cranial and facial bones. Neither have we detected, both in the conventional radiological study and in the CT scan, the presence of signs of any *ante-mortem* fracture nor any signs of infection.

These nasal features have also been described in other patients with KFS (Fragoso et al. 1982). The asymmetry of the palatine processes of the maxilla and palatine bones observed are also not unusual findings in KFS cases with facial asymmetry (Martínez-Quintana and Rodríguez-González 2015). Giuffra et al. (2009) describe the case of Cardinal Carlo de' Medici (1595–1666), who had a clear asymmetry of the nasal and maxillary bones, larger on the left side, together with a marked hypoplasia of the right hemimandible. All of these characters produced an easily recognizable facial asymmetry in the portrait that the artist Justus Sustermans (Galleria Palatina, Rome) made of the Cardinal.

Anomalies associated with KFS, such as atlanto-occipital fusion or basilar impression are also rarely mentioned in the paleopathological literature. The fusion of the atlas has been described in an individual of medieval chronology, in Portugal (13th–15th centuries), presenting partial atlanto-occipital fusion together in the skull with very slight differences in the outline of the nasal cavity (Fernandes and Costa 2007). Regarding the atlanto-occipital fusion, we have not found signs of infection, fracture or rheumatoid arthritis (subluxation, erosion, sclerosis, basilar impaction, etc.), which could indicate a different origin than congenital. In a juvenile individual from Gnadendorf (Hungary, 10th century AD), in addition to congenital fusion of several cervical and thoracic vertebrae, symmetric hypoplasia of the occipital bone, marked curvature of the occipital scale, basilar impression, and asymmetry of the occipital condyles have been described (Pany and Teschler-Nicola 2007). Such malformations are rarely described in the anthropological literature. In the presented

specimen, none of these signs are present. The age of the individual (22 years), together with the data provided by the analysis of the radiological images, has made it possible to rule out other cranial malformations with similar signs, such as Paget's disease, fibrous dysplasia, cleidocranial dysostosis, *osteogenesis imperfecta*, osteoporosis or rickets. Therefore, in skull 778, all the described findings are compatible with Type-II KFS, although, as only two cervical vertebrae are available, a completely accurate diagnostic assessment cannot be made. Type-II KFS corresponds to about 26% of all cases of this syndrome (McGaughan 2004), and usually includes atlanto-occipital fusion.

Conclusions

The pathological findings observed in skull 778 include the absence of sagittal suture, enlarged parietal foramina, basilar impression, atlanto-occipital fusion, asymmetry of orbits and nasal region, asymmetry of nasal and palatal bones, displacement of maxillary massif and C1-C2 fusion. This leads to the diagnosis of Type-II Klippel-Feil syndrome. X-rays and CT scans corroborate the morphological findings. Due to the absence of most of the vertebral column, in this article we have also paid a great of attention to other important skeletal alterations at the cranial level which are known to accompany this syndrome and, in this particular, have its detection more straightforward. This description also adds to the list, still under scrutiny, of previously reported KFS cases in the Spanish bioarchaeological record, covering a chronological span from the Bronze Age to the 19th century AD. As a final general note to this historical dissertation, it must be stressed how a careful analysis of cranial asymmetries and

splanchnocranial modifications should always constitute an important part of retrospective assessments of this condition.

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Authors contribution

J.H., E.D., R.D.S. = conceptualization, first draft, writing, data analysis and synthesis, diagnosis, palaeoradiological analysis;

F.M.G., E.V = writing, data analysis and synthesis, diagnosis, palaeoradiological analysis, literature review

Conflict of interest

The authors declare they have no conflict of interest.

Corresponding authors:

Jesús Herrerin, Departamento de Biología, Facultad de Biología, Universidad Autónoma de Madrid, Madrid 28049, Spain, E-mail: jesus.herrerin@uam.es or Francesco Maria Galassi, FAPAB Research Center, Pza Umberto I 5, 96012 Avola (SR) E-mail: francescom.galassi@flinders.edu.au

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