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Enrique Dorado, Jesús Herrerín,
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Klippel-Feil Syndrome in a Mudejar population: a sign of endogamy in a social minority

1. Introduction

The Municipality of Uceda is located in the Alta Campiña de Guadalajara, bordering the Northern Sierras of the Guadalajara and Madrid provinces, in the center of the Iberian Peninsula, on the Castilian Plateau (fig. 1A). In this village a Mudéjar cemetery with 116 individuals was found (fig. 1B). All the individuals were buried according to the Muslim funeral ritual (fig. 1C; Ramírez, Dorado 2020).

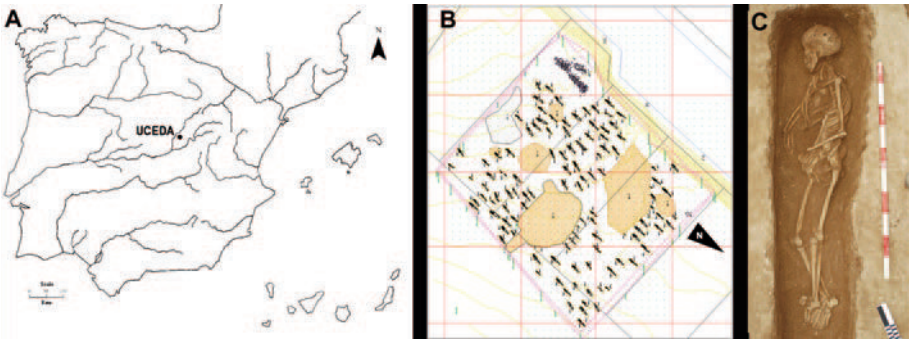

Fig. 1. (A) Location of Uceda (Guadalajara, Spain). (B) General planimetry of the cemetery. (C). Skeleton in situ.

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Uceda was founded by Fernando I, when he was fighting against the Muslims in the area of Buitrago and Lozoya, since it is mentioned in the second expedition in 1040.

In 1085 it was reconquered by Alfonso VI of Castile from the Muslims of the Kingdom of Toledo, and immediately incorporated into the domains of the archbishops of Toledo. The reconquest of Toledo took 374 years (711-1085), which caused the Mozarabic or Jewish population of this area to coexist with the Muslim population during all these years, since we can consider that it was as Iberian as before the Muslim conquest.

With the Christian reconquest, in the town of Uceda, as happened in most towns, there was a coexistence between Christians, *Conversos* Jews and *Moriscos*, but also with Jews and Mozarabs, who continued to maintain their religion, customs and rites. This went on for centuries, until the obsession to differentiate the "old Christians" from the "New ones" led to the publication of the statutes of "cleansing of blood" in the 15th century, in force until the middle of the 19th century.

From the moment of the reconquest (1085), the town was intensely repopulated: its castle was rebuilt and its entire wall and defenses were reinforced. During the Middle Ages, Uceda became a military stronghold, as well as a commercial and administrative centre of a wide region around the banks of Alto Jarama. Within the limits of its walls, it housed a population of about 2,500 inhabitants (Herrera-Casado 1985). From the Mudejar minority, we have the Church of Cubillo (12th-13th centuries), where we can observe typically Islamic decorative and construction elements, made by Muslim artists who lived in this area. This Chuch has an important historical value, because it demostrates the existence of an artisan Mudejar minority that would have lived in the area and that was respected and contracted for the construction of a building for religious purposes.

We can verify the respect for the customs and rites of this Mudéjar minority, in the fulfillment of the Muslim funeral rites in all the individuals exhumed in this necropolis (Ramírez, Dorado 2020), dated two centuries after the Christian reconquest.

2. Material and methods

Three skeletons are studied, coming from stratigraphic units 23, 41 and 124 of the Mudejar cemetery (13th-14th centuries) of Uceda (Spain), all corresponding to individual burials.

The chronology has been estimated by archaeological methods.

The evaluation of bone preservation has been based on the three-degree scale proposed by White (2008), with the following categories:

- Grade 1: bone surface in good condition and, although fragmentation is frequent, a lot of metric and non-metric information can be obtained.

- Grade 2: moderate degree of conservation, with frequent absence of the epiphyses, limiting the amount of information available.
- Grade 3: poor general preservation, with loss of bone surfaces, absence of numerous epiphyses and a high degree of fragmentation.

The degree of conservation has been calculated through the partial bone preservation indices, according to Safont (2003):

- IP1 (long bones) = ∑number of pieces / 12
- IP2 (long bones and pelvic and scapular girdles) = ∑number of pieces / 19
- IP3 (anterior pieces plus skull, maxilla and mandible) = ∑number of pieces / 22.

However, it is only an indicative index of recovered bones, without specifying to what degree, and they may be simple fragments.

In children and non-adult skeletons, age has been obtained through the length of the long bones (humerus, femur, tibia, radius; Scheuer, Black 2000), the degree of development and dental mineralization (AlQahtani *et al.* 2010; Smith 1991), and fusion of the epiphyses (Scheuer, Black, 2000).

Stature was estimated according to the length of the humerus and femur (Oliver 1969), and sex, in the EU23 skeleton through genetic DNA analysis (Gomes *et al.* 2015).

In the case of the adult skeleton, the age has been calculated based on the degree of wear of the tooth enamel (Lovejoy 1985; Brothwell 1987).

The stature was estimated according to the length of the tibia (Belmonte *et al.* 2011), and the sex by the skull and pelvis morphology and the metric values of the long bones (Ferembach *et al.* 1980).

X-ray images were taken with a Polyrad SE digital radiology equipment.

3. Results

UE124: Age was estimated in 5 years old (Infant II) and the stature in 116 mm. Although the morphological characteristics of the coxal bones and the lag between bone and dental age estimations could indicate the female sex, it is considered a very insecure data to be taken into account.

Although the number of bone elements recovered was high (19/22), their state of conservation was deficient (grades 2-3).

The cervical vertebrae C2 and C3 were fused by the right lamina, spinous process and right articular process (fig. 2).

Although the vertebral body, left articular process and left lamina are missing in C3, its state in C2 rules out its fusion at those levels. The rest of the vertebrae, all of which have been recovered in good condition except one cervical, appear unaltered. X-ray images show no traumatic signs in this vertebral block (fig. 2B).

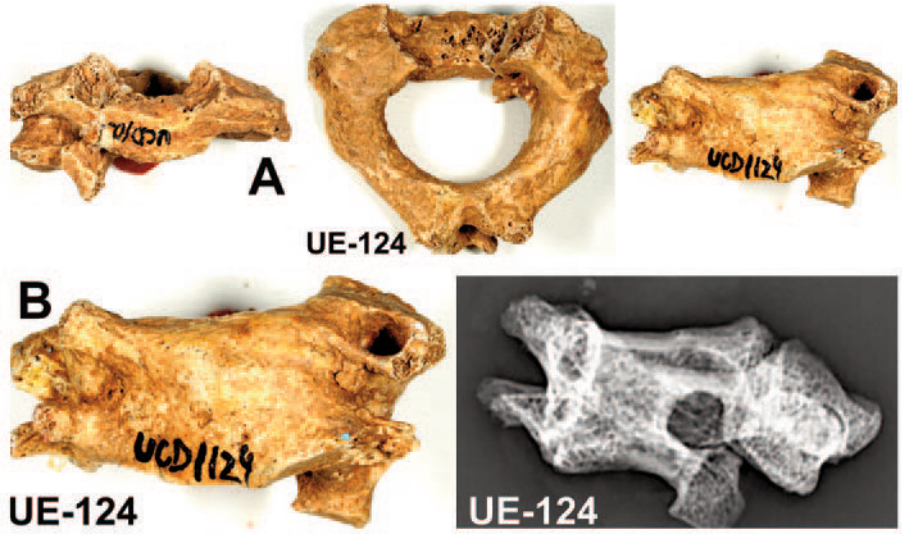

Fig. 2. UE 124. Fusion between C2 and C3. (A) Anterior, superior and posterior view. (B) Posterior view and AP X-rays.

There are no signs of *cribra orbitalia*. No other alterations are observed in the skeleton. The teeth show a normal morphology, without caries. There is no asymmetry in the long bone fragments. Due to the deterioration and fragmentation of the skull, cranium asymmetries cannot be assessed.

UE23: Sex estimation was male, age estimation around 14 years (subadult), and stature 159 +/- 1.58 cm.

All the bones were recovered (22/22), with a state of conservation of grade 2-3.

The individual shows vertebral fusion between C2 and C3 through the laminae, spinous and articular processes (fig. 3).

There is no fusion of the bodies (fig. 3B,C,D). X-ray images show no traumatic signs in this vertebral block (fig. 3B,D).

No other alterations were observed in the rest of the vertebrae and skeleton, except an area of minimal cortical erosion at the proximal end of the left tibial shaft, perhaps a secondary periosteal reaction to trauma. There are apparently no asymmetries in the esplacnocranium. Atlas occipitalization, unfused vertebral hemiarchs, or spina bifida were ruled out. Not dwarfism. In the preserved teeth there are no signs of caries.

UE41: Sex estimation was female, age estimation between 25 and 35 years old and approximately 155 cm tall. Complete preservation index (22/22) and conservation grades 2-3.

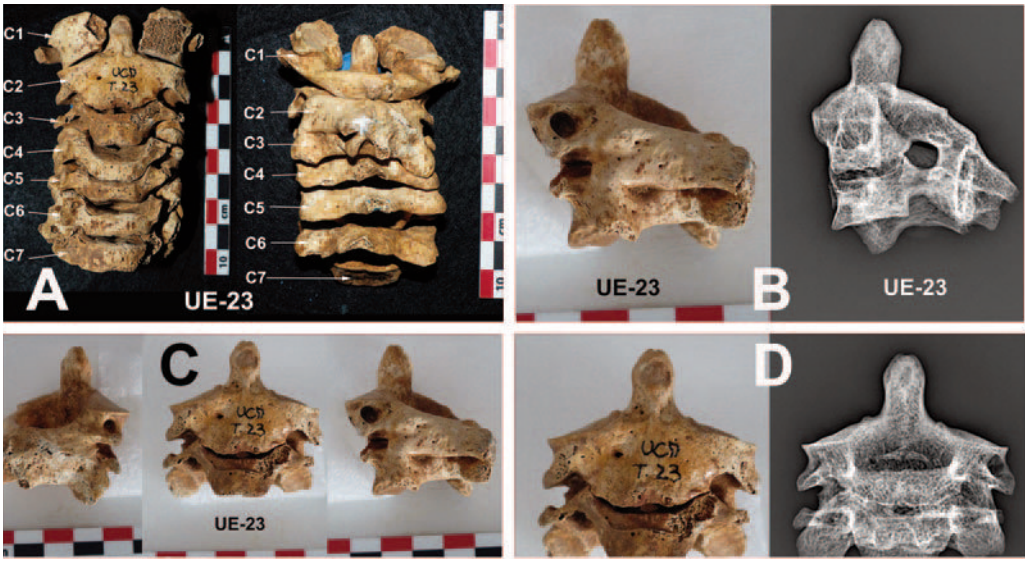

Fig. 3. UE 123. (A) Set of cervical vertebrae. Anterior and posterior view. (B) Fusion between C2 and C3. Lateral view and Lat. X-rays. (C) Posterior, anterior and lateral view. (D) Anterior view and AP X-rays.

This individual shows fusion of cervical vertebrae C6 and C7, through the body, laminae, spinous and articular processes (fig. 4).

There were no other vertebral fusions, vertebral hemiarchs, or spina bifida. X-ray images show no traumatic signs in this vertebral block (fig. 4B,C).

UE41 kept all vertebrae except the atlas. There were no asymmetries or other alterations in the skull. The anterior height of the cervical vertebral bodies was: 21.76 mm (C2), 12.06 mm (C3), 11 mm (C4), 10.4 (C5), 25.2 (C6 + C7). Wear of tooth enamel, with absence of caries. No other bone lesions except signs of joint wear in the right ulna, and left first metatarsal and first phalanx. Light marginal osteophytes in four dorsal and two lumbar vertebrae.

4. Discussion

Klippel Feil syndrome (KFS) was first described in 1912 by Maurice Klippel and André Feil, in a 46-year-old patient with multiple fusion of the cervical vertebrae (Klippel, Feil 1912). Although KFS was defined in the 20th century, descriptions of this anomaly have been known since the 16th century (Saker *et al.* 2016).

Since then, there has been no lack of discrepancies on the diagnosis of the syndrome (Lewis 2018), since any combination of fused vertebrae has been named in this way (Samartzis *et al.* 2006).

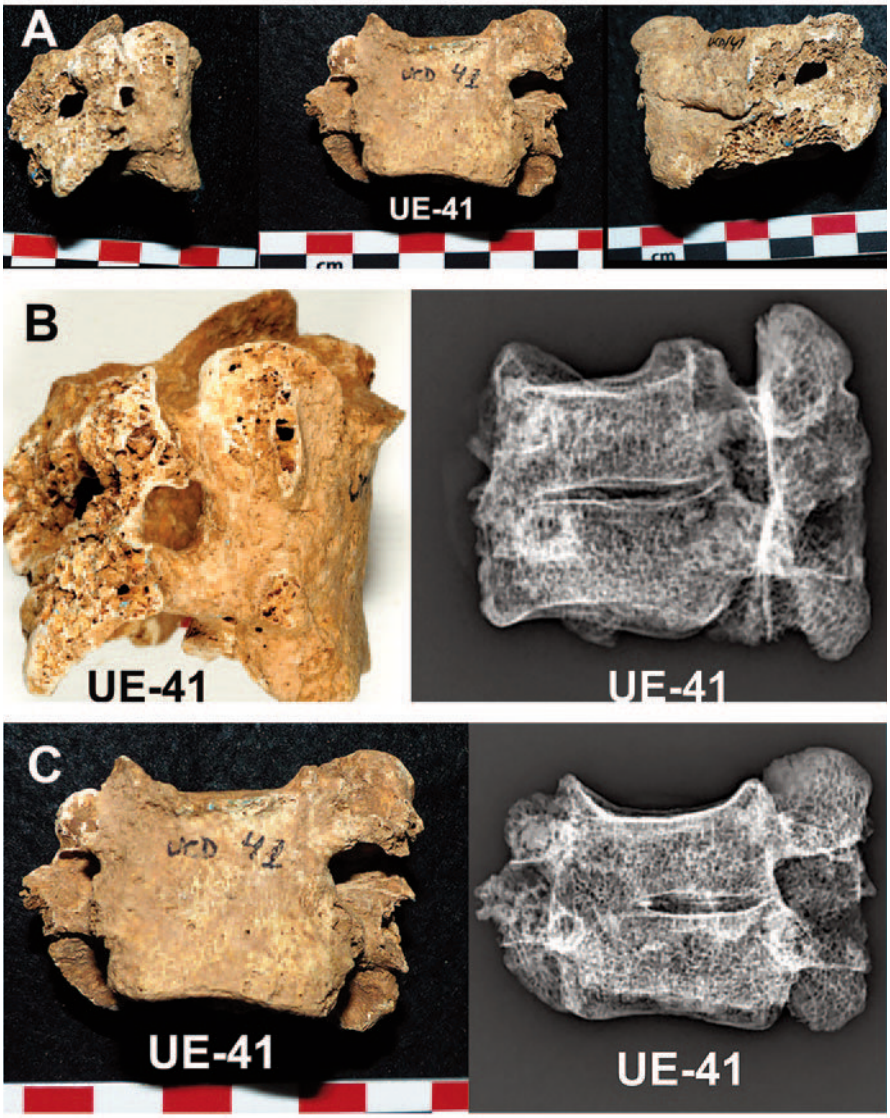

Fig. 4. UE 41. Fusion between C2 and C3. (A) Lateral and anterior view. (B) Lateral view and Lat. X-rays. (C) Anterior view and AP X-rays.

The original classification (Barnes 1994; Pany, Teschler-Nicola 2007; Toker *et al.* 2009; de Rubens-Figueroa *et al.* 2005) distinguishes three types of presentation:

- Type I: there is a bone block of several cervical and upper thoracic vertebrae (three or more levels). It is frequently associated with other more serious defects.
- Type II: fusion of two or three vertebral segments. It most often affects the second and third cervical vertebrae. When the thoracic vertebrae are affected, it is usually between T2 and T5. It is the most common form of KFS and usually has few clinical manifestations.
- Type III: characterized by the fusion of the cervical block together with other errors located in the lumbar and thoracic regions. It is associated with scoliosis in 60% of cases.

Samartzis *et al.* (2016) have proposed another classification of this syndrome, also widely used, which also differentiates three types. Type I for the merger of a single segment; Type II, for the fusion of several non-contiguous segments; and Type III for the fusion of several contiguous segments.

The three medieval archaeological cases from Uceda would be classified as Type II in the original KFS classification and Type I in the classification proposed by Samartzis.

An exhaustive macroscopic and radiological examination of the three cases was carried out. In none of them have suggestive signs of vertebral trauma, infection, rheumatoid arthritis, degenerative changes or other pathologies that allow to rule out a genetic origin.

In two of the cases (UE124 and UE23) the fusion takes place between the C2 and C3 vertebrae (fig. 2,3) while in the third skeleton (UE41) it is located between C6 and C7 (fig. 4). Different authors have indicated the C2-C3 level as the most frequently affected (Nouri *et al.* 2019; Moses *et al.* 2019).

The origin of this syndrome lies in a failure in the segmentation of the spine between the third and eighth weeks of embryogenesis (Fietti, Fielding 1976; Mahirogullari *et al.* 2006; Fernandes, Costa 2007), which has been related to alterations in the Pax1, HoxB / HoxD, Meox1, Cyp26b1 and GDF6 genes (Mardani *et al.* 2016). In GDF6 gene mutations, inheritance would be autosomal dominant, while alterations in the MEOX1 gene would have an autosomal recessive character.

The incidence of KFS is difficult to establish, as many cases remain undiagnosed because they are asymptomatic. At the other extreme, there are serious cases that go undiagnosed by causing premature death (Pany, Teschler-Nicola 2007).

In any case, the incidence of the syndrome has been estimated at around one case in every 30,000-40,000 (Aufderheide, Rodriguez-Martin 1998), with a

slight predilection for the female sex (Aufderheide, Rodriguez-Martin 1998; Nouri *et al.* 2019; Samartzis *et al.* 2006).

Regarding the prevalence of this syndrome, different values of 0.71%, 1.2%, 0.2 per thousand or 0.50 per thousand have been reported (Moses *et al.* 2019; Samartzis *et al.* 2016). In this Mudéjar cemetery, a total of 116 bodies have been exhumed (Ramírez, Dorado 2020), which implies a very high prevalence of the syndrome, 2.58%.

As we have previously mentioned, cervical fusions can remain asymptomatic, being discovered accidentally after a radiological analysis, without thus being diagnosed in current clinical settings (Copley, Dormans 1998). The classic triad of signs that characterize KFS (short neck, restriction of cervical movement, and low posterior hairline) is present in less than 50% of cases (Guapi, Martínez 2019; Vaidyanathan *et al.* 2002; Hensinger *et al.* 1974). In this regard, it has been pointed out that when the fusion affects less than three vertebrae or these are lower cervical, there is no impact on cervical mobility (Hensinger *et al.* 1974).

However, malformations of varying severity that may appear associated with this syndrome are not uncommon. Among them: small stature, limb hypoplasia, thoracic kyphoscoliosis, lumbar scoliosis, mild face asymmetry, high arched palate, rhinoscoliosis, high nasal bridge, inclined septi nasi, thin upper lip, spina bifida, as well as various neurological, cardiac, sensory and genitourinary malformations (Vujasinovic *et al.* 2015; Hensinger *et al.* 1974; Nouri *et al.* 2019; Vaidyanathan *et al.* 2002; Kena *et al.* 2018).

Samartzis Type III would imply a higher risk of suffering neurological, myelopathic or radiculopathic complications (Samartzis *et al.* 2016).

On the other hand, the hypermobility of the non-fused adjoining segments favors vertebral instability and degeneration due to wear of the segments adjacent to the fusion (Moses *et al.* 2019), which represents an increased risk of suffering spinal cord injuries caused even minor injuries (Adeleye, Akinyemi 2010; Vaidyanathan *et al.* 2002).

In this study, as they are skeletonized remains, the possible coexistence of cardiac, neurological or kidney damage, among others, cannot be verified. However, no other skeletal lesions have been observed, such as dismetria between long bones, assimilation of the atlas, short stature, hemivertebrae, spina bifida or the presence of cervical ribs. The deterioration and fragmentation of the skulls has made it impossible to rule out possible craniofacial asymmetries. Therefore, we do not have sufficient data to ensure how the malformation could have influenced the quality of life of these three individuals, or even death at such an early age in one of them, at 5 years of age.

The cases collected in the paleopathological literature are frequent, as in Peru (MacCurdy 1923), North America (Jarcho 1965), Central America (Urunuela, Alvarez 1994), Ancient Egypt (Aufderheide, Rodriguez-Martin 1998) or Europe (Herrerín 2004; 2008; Barnes 1994; Pany, Teschler-Nicola 2007; Fer-

nandes, Costa 2007; Giuffra *et al.* 2009; Gladykowska-Rzeczycka 1997; González-Reimers *et al.* 2006; Macías-López 2020).

In none of these studies was the prevalence of the disease as high as in the Uceda cemetery.

The data of the most important "*morerías*" (groups of people of Muslim religion) of the 14th-15th centuries in Castile, place the number of Muslims between 6.4 (Valladolid, Palencia and Medina del Campo) and 12.2% of the population (Ávila, Arévalo, Piedrahita and El Barco), according to various researchers (Andrés-Suárez 1995; Longás 1990). If, as Herrera-Casado (1985) points out, the population of Uceda was about 2,500 inhabitants, the Muslim minority could have between 150 and 300 inhabitants, although it was surely less, since Uceda was not a great economic capital like the cities aforementioned.

If we take into account the number of individuals exhumed (116), the time of use of the cemetery (two centuries), and the loss of information that usually occurs due to taphonomic reasons (alteration and disappearance of remains), cultural (possible selective burial in this exhumed area) and archaeological (loss of information due to partial or incomplete excavations of the funerary site), the number of exhumed individuals places us in a scenario with a very small human group during this historical period.

According to we know about daily life in Castile in the 13th-14th centuries, there was a clear separation between different religious groups. Always with the aim of preserving their own culture and rituals, these groups were very closed and the most effective way to achieve this objective was to limit marriages to "trusted" people, belonging to the same group.

In human populations, the panmictic model (total randomness in the search for a spouse) does not appear (Calderón 2000). The factors that cause this deviation are various and heterogeneous. Among them are geographical proximity, the couple's age difference, demographic sizes and, above all, socio-cultural factors, which are, without any doubt, the most important (Barral *et al.* 1962).

What is far from doubt is the number of undesirable effects of consanguineous marital behavior (Morton *et al.* 1956). It is interesting to note that marriages between first cousins are more desirable unions in populations that use inbreeding as a routine in the search for partners for young people (Calderón 2000). Specifically in Islamic countries, these marriages between patrilateral first cousins are especially favored. That is, the man is motivated to marry the daughter of his father's brother, while uncle-niece or aunt-nephew unions are prohibited by Koranic law (Calderón 2000).

Of the three major types of human populations (large populations without inbreeding, large populations with inbreeding due to a very low population density, and isolated populations), it is the latter where consanguinity is favored, not only because it is sought for cultural reasons, but also because the choice of the partner is also highly conditioned by the restriction of the potential partner (Bittles

1980; Barral *et al.* 1962). And they are the Islamic countries of the Maghreb and the Middle East where inbreeding has been estimated to be up to 20 times higher than western European populations, in current studies (Sutter, Goux 1962; Sutter, Tabah 1948).

Inbreeding and / or consanguineous matings increase the frequency of recessive genes that can cause malformations (Martínez-Frías 1998).

Regarding the prevalence of KFS in current clinic (between 0.02 and 1,2%), three individuals in a cemetery of 116 bodies (2.58%) is more than double the highest expected prevalence

On the island of La Gomera, in pre-Hispanic populations, two cases of KFS were found in a sample of 120 individuals (González-Reimers *et al.* 2006). In this case, insularity played a crucial role in this high prevalence (1.7%), and the possible kinship ties of the spouses (Maca-Meyer *et al.* 2004). It is known that aboriginal cultural customs in the pre-Hispanic Canary Islands favored group inbreeding (Espinosa 1980).

Therefore, the very high prevalence found in this small Mudéjar cemetery in Uceda can only be explained by the endogamous behavior of the group, favoring marriages between relatives. The small group size, the cultural / religious conditions that further limit the number of possible partners, and the coexistence within the same place of different religious confessions, with prohibited matings in order to preserve the culture, religion and rituals of each one of beliefs, it would be the main cause of the high prevalence of this anomaly of the cervical spine.

5. Conclusions

The presence of a hereditary anomaly that causes fusion of vertebral segments, called Klippel-Feil Syndrome, serves to highlight the need for multidisciplinary approaches in the study of historical necropolis. The knowledge of the societies of the past must be based on a comprehensive study that includes not only historical, artistic or archaeological elements, but also an essential knowledge of the health and way of life of the people who made up this group.

The high prevalence of this syndrome in a small human group with very specific characteristics (verified by a funeral rite common to all of them), allows us to conclude that this religious minority that lived in Uceda during the 13th-14th centuries, was a group with very high consanguinity.

The special historical conditions of this Castilian town of about 2,500 inhabitants, where three religious groups lived, would explain the need to carry out marriages between people of the same religion, increasing the consanguinity of these minorities and enabling the high prevalence of this syndrome, much higher than what could we expect.

Aknowledgements

This work is part of the doctoral thesis that the first author is completing at the University of Granada (Spain). We would like to thank Dr. Miguel Botella, Full Professor, for his collaboration.

Abstract

Klippel-Feil Syndrome (KFS) is a rare disease, a consequence of the congenital fusion of two or more cervical vertebrae, characterized by a short neck, decreased cervical mobility, and low hair implantation. In the Mudéjar cemetery of Uceda (Guadalajara, Spain), dated between the 13th and 14th centuries, 116 bodies have been exhumed, 3 of them presenting this syndrome, which implies a very high prevalence. Knowledge of this syndrome in archaeological necropolises has a double interest. On the one hand, it is very important knowing its incidence, taking into account its hereditary nature and foreseeable increase in closed populations. And on the other, to have a better knowledge of diseases in the population, given its possible association with other musculoskeletal, kidney, neurological or cardiac disorders, reflects the health status of this human group. In this case, the interest increases because it was a human group that formed a religious minority, the Mudejars of Uceda, within a population with a Christian majority. This high prevalence of this syndrome only can be explained with an important inbreeding carried out for several generations.
Keywords: paleopathology, Klippel-Feil Syndrome, inbreeding, Mudéjar, Middle Ages, Uceda.

La sindrome di Klippel-Feil è una malattia rara; conseguenza di una fusione congenita di due o più vertebre cervicali, è caratterizzata da collo corto, ridotta mobilità cervicale, attaccatura di capelli bassa. Nel cimitero Mudéjar di Uceda (Guadalajara, Spagna), datato al XIII-XIV secolo, sono stati scavati 116 individui, dei quali 3 presentavano questa sidrome, pari a un'alta incidenza. Il rinvenimento di questa sindrome in contesti archeologici è di duplice interesse. Da una parte, è importante conoscerne l'incidenza, considerando la sua natura ereditaria e il prevedibile aumento in popolazioni chiuse. Dall'altra parte, è utile per avere una migliore conoscenza delle patologie nella popolazione, data la sua possibile associazione con altri disordini muscolo-scheletrici, renali, neurologici o cardiaci, e dunque fornisce indizi sullo stato di salute delle popolazioni antiche. In questo caso, l'interesse è maggiore perché si tratta di un grouppo formato da una minoranza religiosa, is Mudejars di Uceda all'interno di una popolazione a maggioranza cristiana. Tale alta incidenza di questa sindrome può essere spiegata solo con rapporti endogamici portati avanti per parecchie generazioni.
***Parole chiave**: paleopatologia, sindrome di Klippel-Feil, rapporti endogamici, Mudéjar, Medioevo, Uceda.*

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