

Congenital anomalies in a Sardinian population of 16th century (Italy)

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Abstract. The anthropological and paleopathological study of the 199 individuals from the Alghero cemetery, related to the plague epidemic that devastated the town in 1582-83, showed a high incidence of congenital anomalies in this population. In particular, a case of non-syndromic brachycephaly, consisting of a cranial malformation due to early closure of the coronal suture, was diagnosed in a subadult. As for the spine, anatomic variants of the atlanto-occipital junction have been observed: a case of posterior arch defect of the atlas occurred in a young male and a case of occipitalization of the atlas associated with other anomalies was observed in an adult male. Two adult males and one subadult had congenital fusion of two cervical vertebrae; in a subadult the fusion of C2 and C3 was accompanied by other anomalies such as supernumerary vertebrae, posterior arch defect of the atlas and L6, spina bifida occulta and bifurcation of a rib; these features permitted to identify a case of Klippel-Feil syndrome. Finally, the most interesting case is a sclerosing disease in an adult-mature male; differential diagnosis has led to a possible case of Camurati-Engelmann disease, a condition characterized by a thickening of the long bones and sclerosis of the cranial vault, of which only 200 cases are known in modern clinical literature. The high incidence of congenital anomalies observed may be attributable to the geographic isolation and the endogamy of the Sardinian population.

Key words: congenital diseases, craniostenosis, atlas occipitalization, posterior arch defect of atlas, Klippel-Feil syndrome, Camurati-Engelmann disease, Sardinia, Modern Age

Introduction

Modern medicine has classified a large number of congenital disorders which range from minor anomalies, generally asymptomatic, to severe abnormalities, some of which are incompatible with life. In osteoarchaeology it is possible to detect only the abnormalities involving the skeletal apparatus and, generally, the less severe conditions, which often allowed the individual to reach the adult age. Therefore, the total number of congenital malformations observed in paleopathology is largely underestimated; in fact, although congenital

defects have been reported in ancient human remains (1-3), it is still impossible to determine the range and incidence of congenital diseases in past populations.

Therefore, all reports are important, as they attest the presence of specific diseases in the past, and allow to observe the evolution up to adult age of many defects that today are corrected by surgery; they also allow to infer the social behavior of past societies towards impaired or deformed individuals. Here we report a summary of congenital diseases observed in the population of Alghero (Sardinia) dated back to the second half of the 16th century.

Materials and methods

During archaeological excavations carried out in Alghero (Sardinia) the skeletal remains of 199 individuals were brought to light (4, 5). This large cemetery has been attributed to the plague episode that devastated the town in 1582-1583, as demonstrated by the archaeological dating and by the burial modalities. In particular, the corpses are arranged in sixteen trenches containing the remains of 10 to 30 individuals, and 10 multiple burials with an average number of 6 skeletons. The use of trenches and multiple tombs are considered a reflex of catastrophic events, when a large number of individuals died in a short lapse of time and a quick and simultaneous interment was necessary. This important sample has been studied from the anthropological and paleopathological point of view; the analysis revealed a series of congenital abnormalities.

Sex and age determination were performed on the basis of the standard anthropological methods (6).

Results

The non-syndromic brachycephaly

The skull of a 9-10-year-old child (US 2762) showed the premature closure of the coronal suture, a condition defined as brachycephaly. As a result, the skull is deformed, with slight reduction of the antero-posterior diameter, an increase in the bi-parietal diameter and marked frontal and parietal bosses (Fig. 1). The presence of digitate impressions in the inner table indicates brain compression and probable neurological disturbances. As no other anomalies has been detected in the skeletal remains of this child, brachycephaly can be considered an isolated condition and not part of a more complex syndrome (7).

The anomalies of the atlanto-occipital junction

Two individuals presented anomalies of the atlas.

In a male aged 35-45 years old (US 5125) the first cervical vertebra resulted fused with the skull base, a condition defined as occipitalization of the atlas. In

particular, a complete fusion of the superior articular facets with the occipital condyles, and of the anterior arch with the anterior rim of the foramen magnum was seen. Furthermore, other anomalies were present: an open anterior left foramen transversarium and a posterior arch defect (Fig. 2a). Osteoarthritic changes were observed in the right temporo-mandibular joint, probably in consequence of the lateral slight inclination of the atlas toward the left side, resulting in an asymmetry (8).

In a male aged 20-30 years old (US 2219) the first cervical vertebra shows a defect of the posterior arch, which exhibit a failure of the midline fusion of the two hemiarches with a small gap (Fig. 2b). Ac-



Figure 1. Coronal craniosynostosis (superior view)

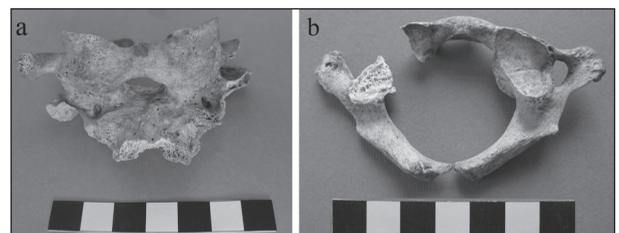


Figure 2. a) Occipitalization of the atlas (anterior view); b) type I posterior arch defect (superior view)

cording to the classification of Currarino et al. (9) this is a Type A arch defect (10).

The Klippel-Feil syndrome

Four individuals from Alghero showed fusion of two cervical vertebrae.

In a subadult aged 7-8 years (US 2291) C2 was fused with C3 through the posterior arches and the spinous processes (Fig. 3a). In addition, other anomalies were observed, including posterior arch defect of the atlas, supernumerary vertebrae in the thoracic (in number of 13) and lumbar (in number of 6) segments, posterior arch defect and unilateral dysplastic transverse left process of L6 (Fig. 3b), spina bifida occulta in the sacrum, and a bifurcated rib (Fig. 3c).

A male aged 35-45 years (US 2284) was affected by total fusion of C3 and C4, involving the margins of vertebral plates, the posterior vertebral arches and the zygoapophyseal joints.

An adult male aged 20-25 years (US 2309) presented fusion of C2 and C3 both by vertebral bodies, articular facets, posterior arches and spinal processes, with a slight inclination of the odontoid process on the left side.

Finally, in a subadult aged 9-10 years (US 2890) C3 was fused with C4 through the posterior arch with complete fusion of the right side and partial on the left one.

According to the classification of Andre Feil (11), skeleton 2291 represents a Type III of Klippel-Feil syndrome, consisting in fusion of two vertebrae accompanied by the presence of thoracic and lumbar spine anomalies, whereas the other three individuals could be affected by type II, that is fusion of two vertebrae without other anomalies. Nevertheless, for a

sure diagnosis of KFS in paleopathology, other skeletal anomalies should be associated to the fusion of cervical elements; therefore, for the skeletons 2284, 2309, 2890 the other possible diagnosis is that of congenital fusion of the cervical vertebrae, a congenital synostosis of one or more continuous segments of the cervical spine, due to embryological failure of normal spinal segmentation (12).

The Camurati-Engelmann disease

A mature male aged 45-55 years (US 2179), with a stature of about 165 cm, was affected by a sclerosing bone dysplasia, as the general thickening of several districts demonstrated. The skull bones are poorly preserved, but a severe thickening can be appreciated, whereas the mandible is normal. The long bones of upper and lower limbs are characterized by a hyperostosis of the diaphysis with increased and irregular cortical thickening, whereas the epiphyses are normal (Figs. 4a-4b-4c, 5a-5b-5c). The differential diagnosis allowed to diagnose a case of Camurati-Engelmann disease, a genetic disorder characterised by increased bone density (13).



Figure 3. a) Klippel-Feil syndrome: fusion of C2 and C3; b) posterior arch defect and unilateral dysplastic transverse left process of L6; c) bifurcated rib



Figure 4. a) Camurati-Engelmann disease: hyperostosis of the left humerus; b) left radius and ulna

Discussion and conclusions

A series of genetic abnormalities has been observed in the 16th century population of Alghero, including 199 individuals.

Unilateral/ bilateral coronal craniosynostoses represent the 20–30% of all non-syndromic craniosynostoses and are classified as rare genetic diseases (www.raredisease.org), with an estimated incidence of 0.6–0.7%, with a predilection for the female sex (14, 15). The aetiology of non-syndromic craniosynostoses seems multifactorial. However, recent molecular genetic studies have demonstrated that most of these disorders or syndromes have mutations in the fibroblast growth factor receptor genes. In particular, patients affected by coronal non-syndromic craniosynostosis show a P250R mutation in fibroblast growth factor receptor 3 (FGFR3) (16). In the population of Alghero this genetic condition was observed in 1 out of 133 individuals whose skull was in good conditions, corresponding to 0.67 %, a value correspondent to that currently observed.

The current incidence of occipitalization of the atlas is 0.67 to 3.63% in Asian populations (17) and 0.5 to 1 % in Caucasians (18). The aetiology is attributable to a failure of segmentation and separation of occipital and cervical sclerotomes in the third and fourth weeks of fetal life.

Type A arch defect of the atlas has a current incidence ranging from 2.6% (19) to 3.2 % (20). The pathogenesis of posterior arch defects has not been yet fully clarified; however, this anomaly is attributed to the defective or absent development of the cartilaginous preformation of the arch rather than a disturbance of the ossification (21).

The atlas in the Alghero population was observable in 119 individuals, therefore, the incidence of atlas occipitalization and of type I arch defect was 0.6 %, therefore within the current incidence the first condition and less frequent than today the second anomaly.

Klippel-Feil syndrome is a rare type of complex congenital condition, whose main feature is the fusion of two or more cervical vertebrae, accompanied by other possible skeletal anomalies, mostly affecting the spine (1). The current incidence varies from 0.0025% (22–24) to 0.5% (25); the syndrome results from an er-

ror in the segmentation of the axial skeleton of the embryo. The congenital fusion of the cervical vertebrae is a congenital synostosis of the cervical vertebrae again due to embryological failure of normal spinal segmentation, with a current incidence of 0.4% to 0.7% (26, 27).

Therefore, 4 out of 157 skeletons from the necropolis of Alghero, with at least some cervical vertebrae preserved, showed a vertebral fusion in the cervical spine, with a 3.1% incidence of this congenital anomaly. If we consider the diagnosis of Klippel-Feil, which is certain in only 1 individual, the incidence is of 0.79% in the entire sample examined; this incidence is slightly higher than that registered in modern clinical studies. As for the other three possible cases of congenital fusion of the cervical vertebrae the incidence is 3.1%, considerably higher than the current data.

Camurati-Engelmann disease is a very rare condition, whose current incidence is one in 1,000,000 (28); only approximately 200 cases have been reported in the English literature (29). It is an autosomal-dominant condition caused by mutations within the transforming growth factor- β 1 (TGFB β 1) gene on chromosome 19q13 (30). The case of Camurati-Engelmann disease is a *unicum* in the paleopathological literature, as no other cases have been reported. It was observed in 1 out to 93 adult individuals, with an incidence of 0.47; considering the rarity of the condition, this finding is exceptional.

The bioarchaeological study of the population of Alghero referring to the second half of 16th century allowed us to observe a series of congenital anomalies, including brachymetatarsia, occipitalization of the atlas, type I posterior arch defect, Klippel-Feil syndrome and Camurati-Engelmann disease. The incidence of these anomalies is similar to current clinical data, except for the Klippel-Feil syndrome and congenital fusion of cervical vertebrae, which is slightly more frequent in 16th century Alghero, and the Camurati-Engelmann disease, which is very rare today. Geographical isolation, high endogamy and inbreeding, which prevented a genetic differentiation, could be among the causes of this high incidence of genetic anomalies (31, 32).

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