Is Cribra Orbitalia Synonymous With Anemia? Analysis and Interpretation of Cranial Pathology in Sudan

Ulrike Wapler,1,2 Eric Crubezy,1* and Michael Schultz2

1UMR 8555 du CNRS, Universite Paul Sabatier, 31062 Toulouse, France
2Zentrum Anatomie, Georg-August-Universitaet, 37075 Goettingen, Germany

KEY WORDS paleopathology; histology; pseudopathology

ABSTRACT Cribra orbitalia is a porotic or sieve-like lesion in the bony orbital roof. Its cause has been the object of research and discussion since the end of the 19th century. Since about 1960, most scientists have started to agree on the hypothesis that the lesion is a result of hypertrophy of the red bone marrow, and therefore is proof of anemia. However, recent investigations showed that in some cases, the histologic bone structure does not support the diagnosis of anemia. The status of cribra orbitalia as an indicator then becomes uncertain. We carried out a histologic examination of thin-ground sections in polarized light to clarify the possible sources of orbital roof lesions in a Nubian population from Missiminia, northern Sudan (n = 333). In at least 56.5% of cribra orbitalia cases, there were no histologic features indicating changes due to anemia. Signs of other pathological conditions, such as inflammation or osteoporosis, as well as pseudopathological cases, were found. Am J Phys Anthropol 123:333–339, 2004. © 2004 Wiley-Liss, Inc.

Cribra orbitalia is identified on the basis of a porotic or sieve-like appearance of bony orbital roofs (Welcker, 1888). Research has focused on its origin, revealing vast geographical and temporal variability (Angel, 1966; Carlson et al., 1974; El-Najjar et al., 1976; Cybulski, 1977; Lallo et al., 1977; Germana and Ascenzi, 1980; Mensforth, 1985, 1991; Stuart-Macadam, 1985, 1987a, b; Fairgrieve and Molto, 2000; Ortner et al., 2001). The orbital lesions are generally considered to be a part or the initial stage of similar anomalies of the skull vault (porotic hyperostosis). This symptom has been associated with anemia since the 1960s (Angel, 1966; Stuart-Macadam, 1985, 1987a, b; Huss-Ashmore et al., 1982; Martin et al., 1985; Price et al., 1985; Palkovich, 1987; Tranco, 1987; Grauer, 1993; Mittler and van Gerven, 1994; Fairgrieve and Molto, 2000). Today, most authors (Huss-Ashmore et al., 1982; Martin et al., 1985; Price et al., 1985; Palkovich, 1987; Tranco, 1987; Götz, 1988; Grauer, 1993; Mittler and van Gerven, 1994; Stuart-Macadam, 1991, 1992; Fairgrieve and Molto, 2000) interpret the distribution of cribra orbitalia in relation to potential factors leading to anemia. The presence of lesions may be attributed to a high individual resistance potential to the causal agents (Stuart-Macadam, 1991, 1992), but the porosities are generally considered to be biological stress indicators (Huss-Ashmore et al., 1982; Martin et al., 1985; Price et al., 1985; Palkovich, 1987; Tranco, 1987; Mensforth, 1991; Grauer, 1993; Mittler and van Gerven, 1994).

Usually only surface morphological methods are used for lesion classification, to distinguish between healed and active cases, for instance. The importance of differential diagnosis in the study of cribra orbitalia was discussed by Stuart-Macadam (1982, 1985) and demonstrated by Schultz (1987, 1988a, 1993a, 2001) through histologic analysis. He described cases of cribra orbitalia lacking the histologic features of anemia (Schultz, 1993a, b). Instead, the thin-ground sections he used for investigation provided evidence of other conditions such as inflammation or rickets. Ensuing research confirmed that at least some cribra orbitalia cases exhibit traits indicating origins other than anemia (Schultz, 1987; Götz, 1988; Carli-Thiele, 1996; Kreutz, 1997; Carli-Thiele and Schultz, 1997). The indicator status of cribra orbitalia thus becomes uncertain. The aim of this study was to determine, among adults only, what percentage of morphological cribra orbitalia is associated with microscopic indicators of anemia.

MATERIALS AND METHODS

The skeletal sample of Missiminia, northern Sudan (2nd–6th centuries AD), was chosen for its ex-
TABLE 1. Distribution of cribra orbitalia in sample from Missiminia, northern Sudan

<table>
<thead>
<tr>
<th></th>
<th>Females</th>
<th>Males</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sample</td>
<td>161</td>
<td>172</td>
</tr>
<tr>
<td>Age at death ≤30 years</td>
<td>77</td>
<td>61</td>
</tr>
<tr>
<td>Cribra orbitalia present*</td>
<td>48%</td>
<td>25%</td>
</tr>
<tr>
<td>Age at death &gt;30 years</td>
<td>83</td>
<td>110</td>
</tr>
<tr>
<td>Cribra orbitalia present</td>
<td>24%</td>
<td>19%</td>
</tr>
</tbody>
</table>

* Difference is significant; G = 8.17, P < 0.01 (G-test after Weber, 1986).

Excellent conservation status, homogeneity, and size. The 333 skulls, which are currently housed at the Centre d’Anthropologie, Université Paul Sabatier, (Toulouse, France), belonged only to adults and adolescents attributed to three different cultural groups (Meroitic, Ballanean, and Christian periods). As demonstrated in previous investigations on the sample (Billy, 1985; Crubézy et al., 1999), the individuals are likely closely related from a biological point of view.

The individuals were divided into two age groups, namely age at death of greater than 30 years and age at death of less than or equal to 30 years (according to age determination by Billy, 1985), so as to allow a comparison between our frequencies and those of other publications (Table 1). There were no children in the sample. We relied on the sex determination carried out by Billy (1985).

The presence and macroscopic appearance of cribra orbitalia were determined for each orbit. Each orbit was examined by two of the authors. We described the orbital lesions and we noted the local distribution of lesions, dividing the orbital roof into 11 sections. In addition, we described the appearance of the holes, of the impressions of vascular activity and of the surface structure of the bone, using a description system developed by Schultz (Mensforth et al., 1978; Janssens, 1981; Götz, 1988; Trancho et al., 1991; Mittler and van Gerven, 1994; Wapler, 1998).

One bone sample from each skull presenting cribra orbitalia was taken from the affected orbital roof. The skull was then restored by filling the sample holes with pieces of plaster tightly adjusted. Some examples of lesions are shown in Figure 1. Several thin-ground sections (thickness, 50 μm) were prepared from each sample (Schultz and Droemer, 1983; Schultz, 1994). As demonstrated by Schultz (2001), other techniques are also appropriate. For example, micrography will permit the identification and classification of newly formed bone, such as subperiosteal layers caused by an inflammatory process. For the present study, we preferred microscopy using polarized light and a hilfsobject, because it gives more information about the structural features of macerated bone. Various features, such as orientation of collagen fibers and products of diagenesis like crystals or floral and faunal remains, are more easily observable (Schultz, 1988b, 2001).

Fig. 1. Cribra orbitalia in sample from Missiminia. A: Anemia, individual 2V6/89, female, Christian period. B: Anemia, individual 2V20/109/1, female, Meroitic period. C: Healing and/or chronic ostitis of orbital lamina and diploe, individual 2V20/168/2, male, Meroitic period. D: Postmortem destruction of orbital lamina, individual 2V20/204/2, female, Meroitic period.

Each section was examined by two of the authors in normal light, in polarized light, and in polarized light combined with a hilfsobject (red, first order, quartz) as compensator, using different magnifications (×10.5 up to ×360). The method of investigation makes use of the properties of the collagen fibers of bone. Collagen stands up well to decomposition after death, and is easily demonstrated in polarized light, which enables the study of lamellar orientation and identification of histologic structures and traces of bone reaction (Schultz, 1993a, 1994, 1997). For example:

1. Hypertrophy of the erythropoietic bone marrow, which is observed in severe cases of anemia (Diggs et al., 1937; Caffey, 1957; Eng, 1958; Powell et al., 1965; Aksoy et al., 1966; Moseley, 1966; Lanzkowsky, 1968; Agarval et al., 1970; Williams et al., 1975; Reimann and Celik, 1978), results in widened marrow spaces. The pressure may finally lead to an opening of the external lamina of the bone. These changes are visible in bone sections (Diggs et al., 1937; Williams et al., 1975; Schultz, 1993a; Carli-Thiele, 1996), but since thalassemia, deficiency anemia, and other anemic conditions may cause similar changes in bone (Eng, 1958; Powell et al., 1965; Aksoy et al., 1966; Moseley, 1966; Lanzkowsky, 1968; Agarval et al., 1970), it is generally impossible to determine the type of anemia by bone histology alone. Figure 2A shows the contours of thin-ground sections of an orbital roof. The marrow spaces are widened and the orbital lamina is opened. The remaining trabeculae lie almost at right angles to the orbital lamina.

2. The increased vascularization in periostitis results in impressions on the bone surface which can be observed even in archeological material. Transmission of the inflammation into the bone...
osteitis) may lead to extensive bone resorption. This process is characterized by increased osteoclast activity. Their cavities, the Howship lacunae, are visible in well-preserved bone (Fig. 2B). Remodeling (bone apposition) of these lesions is evidence of healing. The remodeling of the orbital lamina shown in Figure 2C indicates healing osteitis. The cement line between the lamellar and the newly woven bone is dentated by earlier Howship lacunae.

3. Alterations due to postmortem destruction are characterized by disintegration of the collagen fibers, with no features of bone reaction. The orbital lamina shown in Figure 2D apparently disintegrated from the exterior. A little pin separating the two holes has nearly broken off. The interior part of the table is still well-preserved.

RESULTS

Cribra orbitalia were present in 93 of 333 specimens. In the younger females (age at death ≤30 years), they were significantly (G-test, Weber, 1986) more frequent than in males (Table 1). However, this difference could also be due to sampling or to a difference in age distribution. Such possibilities cannot be ruled out.

The bone material of most samples was very well-preserved, and 85 cases were successfully examined. Lesions were bilateral in most skulls (96.3%). Figure 3 and Table 2 show the distribution of the assumed causes of cribra orbitalia according to the interpretation of the histologic patterns in the Missiminia sample. Table 3 shows the distribution in both age groups for comparison between the frequencies found in the present study and those of other publications.

Anemia

Characteristic features of bone changes due to hypertrophy of the bone marrow (Fig. 2A) were
found in 20 cases. Histologic analysis indicated that the condition had healed for 3 of these individuals. Possible traces of hypertrophy were observed in 17 additional cases, and here the cribra may also be related to anemia.

Opening of the orbital lamina in the living could not always be established. The thinned external lamina often showed at least postmortem enlargement of the holes.

Inflammation

Orbital lesions probably due to osteitis (Fig. 2B,C) were found in 15 individuals of the total sample (n = 85). In 7 cases (46.7%), the lesion had healed prior to death. Indications of inflammation of the orbital roof (osteitis) were present in 5 additional samples, but they were not so well-defined. Additional features of hypertrophy (anemia) were observed in 3 of these 20 samples. In 5 specimens, orbital lesions resulted from increased vascularization of the orbital lamina. The underlying cause was perhaps periostitis.

Other and undetermined causes

Features of other pathologic conditions were observed more rarely. Gentle local pressure on bone results in atrophy. Such a process may be related to the pressure of an enlarged organ, here perhaps the lacrimal gland, or to ophthalmic infections which are very common in the Nile Valley today. Traces resembling pressure atrophy were observed in two orbital roofs. One of these specimens also displayed signs of anemia.

Regular thinning of the bone, as seen in osteoporosis, was observed in 5 cases. In one of these, cribra orbitalia was due to this thinning, combined with postmortem erosion. The other samples also presented features of anemia (3 cases) or osteitis (1 case).

The structure did not seem to be normal in 7 samples, but the cause of the orbital lesion could not be attributed to a pathologic condition.

Postmortem erosion

The investigation also provided evidence of pseudopathology (Fig. 2D). We found that quite a considerable proportion (20%) of macroscopic cribra orbitalia cases presented only traces of postmortem erosion at histologic examination, and the specimens were considered to have normal orbital roofs.

DISCUSSION

Our study demonstrates that orbital lesions in adults are caused by a variety of factors. The etiology of cribra orbitalia was associated with anemia in 43.5% of cases. The remaining 56.5% displayed no features of anemia. This means that more than half of the individuals displaying cribra orbitalia were presumably not anemic, and thus that the lesions must not necessarily be identified with anemia. This clearly shows that the percentage of cribra orbitalia does not match the percentage of anemia. Comparing the distribution of cribra orbitalia between different samples can lead to misinterpretation because its frequency is not a reliable measure of the impact of diseases leading to anemia. In our sample, orbital porosity did not always represent pathologic changes, and a reliable distinction between ante-mortem changes and postmortem destruction was not possible by macroscopic analysis. In fact, the percentage of taphonomic alterations (very probably caused by desert sand erosion) in our sample was as high as 20%. Adequate microscopic methods are necessary, especially as pathologic lesions are often secondarily eroded. Consequently, fluctuations in cribra orbitalia frequencies may be related to the distribution of various diseases as well as to different impacts of erosion.

Anemia

In the Missiminia sample, 20 of 333 subjects (6%) displayed strong orbital evidence of marrow hypertrophy. These individuals had very probably suffered from severe anemia. This means that the minimum frequency of anemia stands at 6%. However, differential diagnosis in recent cases (Diggs et al., 1937; Eng, 1958; Caffey, 1957; Powell et al., 1965; Aksoy et al., 1966; Moseley, 1966; Lanzkowski, 1968; Agarval et al., 1970; Reimann and Celik, 1978) showed that only severe and chronic anemias are able to cause distinct changes in bone. Generally these alterations are most pronounced in thalassaemia major (Caffey, 1957; Moseley, 1966; Reimann and Celik, 1978). But swelling of the bones as well as the characteristic hair-on-end or onion-peel patterns are also present in thalassaemia minor (Caffey, 1957; Reimann and Celik, 1978), in sickle-cell disease (Diggs et al., 1937; Reimann and Celik, 1978), and in severe cases of deficiency anemia (Eng, 1958; Powell et al., 1965; Aksoy et al., 1966; Moseley, 1966; Lanzkowski, 1968; Agarval et al., 1970; Reimann and Celik, 1978). However, not every person suffering from severe anemia displays alterations recognizable with radiological techniques. Even in thalassaemia major, only a proportion of patients show these lesions (Moseley, 1966; Reimann and Celik, 1978), and hence the absence of bony alterations does not exclude a severe and
chronic anemic condition. Therefore, it could be suggested that a much larger proportion of the individuals of Missiminia might have been (severely!) anemic. Our percentage is a minimum value; the true proportion is unknown. The question of the validity of paleopathologic epidemiology was thoroughly discussed by Wood et al. (1992).

Accordingly, it must be noted that most studies on bone changes in anemic patients (Caffey, 1957; Eng, 1958; Powell et al., 1965; Aksoy et al., 1966; Mosley, 1966; Lanzkowski, 1968; Agarval et al., 1970; Reimann and Celik, 1978) were carried out using radiographic imaging. The marrow spaces of the skull (but not of the orbit) were examined in only a few necropsies (Diggs et al., 1937; Williams et al., 1975). The expansion of marrow spaces due to oppressive processes is directed distally because of the pressure on the endocranial part. But the outer lamina still exerts counterpressure through its thickness and its convex form. The orbital roof possesses, in contrast, only a very thin outer lamina. The concave shape of the roof may additionally promote a trabecular outgrowth in the socket whose soft content affords no resistance to bulging diploe. Because of these various static conditions, distinct features of marrow hypertrophy may occur more easily and more often in the orbit than in the skull vault. These alterations may have taken place while changes in the skull vault were still undetectable by radiology. This means that the number of undetected anemia cases is perhaps low.

Deficiency anemia is not likely to develop on account of poor nutrition only. The main reason for an anemic status in humans nowadays is still loss of blood. It is true that various factors increase the probability of blood loss, e.g., likelihood of accidents, menstruation and childbirth, vitamin C deficiency, and gastrointestinal ulcers. Malnutrition and anemia are often combined with parasitic infection among modern populations. Bloodsucking and hemolytic parasites are common in Nubia. Evidence that some of these animals, such as schistosoma, hookworm, and taenia, have long been present is provided by Egyptian mummies (Armelagos, 1977; Cockburn, 1977). Since intestinal parasites as well as malaria are still a major health problem in this region, it seems probable that large sections of the population also suffered from parasitic infection in ancient times. It is most unlikely that findings will be made from ancient remains of adults who suffered from thalassaemia major or sickle-cell anemia on account of the fatal outcome for homozygous individuals in childhood, although it is possible that some individuals were heterozygous for the thal allele. As there are few cases indicating healed anemia, it must be supposed that the condition was usually chronic and persisted throughout life, as far as our sample is concerned, but other results are sometimes found (Fairgrieve and Molto, 2000).

### Inflammation

Many inflammations in the head can lead to orbital involvement, including sinusitis, tooth abscesses and other oral infections, nasopharyngeal infections, and also suppurating skin inflammations. Several infectious diseases can cause dacryoadenitis and conjunctivitis. These inflammations may be transmitted into the periosteum and afterwards into the bone. The detection of an inflammatory process is generally limited to bone tissue as far as archaeological remains are concerned. Therefore, features of osteitis are the only evidence of inflammation in ancient human remains when no mummified tissue remains.

It has been shown that a considerable proportion of cribra orbitalia was caused by inflammation. Most of the skulls display bilateral lesions. For the greater part, the inflammatory process probably originated from the periosteum of the orbital roof and was transmitted into the bone. The primary focus is unknown. However, it does seem that in most cases, the inflammation arose from a focus in the socket. Conjunctivitis or dacryoadenitis are possible but speculative causes. Other infections might also have led to periostitis in the orbit and finally to osteitis in the orbital roof. However, it is important to bear in mind that we are dealing with archaeological bones, and that both parasites and humans have continually been developing their strategies of infection and immunity over time. It is probable that the parasites affecting the people of Missiminia were genetically different from their descendants living today. The defense reaction of humans to the pathogen may well have also changed with time, and the disease might be rare nowadays. But the lack of examples of bilateral inflammation in the orbital roof in recent material might also be related to a lesser interest in very slight or initial stages of bone disease (Schultz, 1993b). Thus these traces of infec-
tion may perhaps still exist today but have not been the subject of publications.

**Postmortem erosion**

Postmortem changes are not uncommon in the Missiminia sample in spite of the excellent conservation status. It seems possible that postmortem erosion may considerably increase the frequency of cribra orbitalia.

The orbit is prone to postmortem changes because of the thin orbital lamina. The thinner the outer cortex, the more marked these alterations, e.g., in remains of children or persons with osteoporosis. Because of normal individual variation (Süss, 1961; Lang, 1975; Lang and Brückner, 1981), the orbital roof may or may not contain diploe. Porosity would appear more easily in orbital roofs with a spongy layer and a thin orbital lamina. Consequently, populations with orbital roofs presenting spongiosa would be more prone to postmortem development of cribra orbitalia than others.

**Other causes**

Apart from marrow hypertrophy and inflammation, other pathologic conditions may cause porosity in the orbital roof. In our sample, we found histologic signs indicating atrophy by pressure and the regular thinning of the bone seen in osteoporosis.

The fact that hemorrhagic processes, caused for example by vitamin C deficiency, may produce porous bone surfaces has already been published (Carli-Thiele, 1996; Ortner et al., 2001). The sample of the present study did not reveal any such cases.

**CONCLUSIONS**

The frequency of cribra orbitalia in ancient populations does not necessarily reflect the frequency of anemia. However, microscopic examination of such lesions can in most cases differentiate between postmortem erosion, osteitis, anemia, and other pathologic conditions. In the case of Missiminia, northern Sudan (2nd–6th centuries AD), histologic investigation showed that at least 6% of the sample suffered from anemia. Features of inflammation in the orbital roof were found in at least 4.5%. Although the bones are in an excellent state of conservation, 20% of the cribra orbitalia cases are exclusively due to postmortem alterations. However, the present study deals with adults only, and so our conclusions have to be limited to this group. It would be interesting to complete our knowledge using a sample presenting known age cohorts, so as to study the origin of cribra orbitalia in different age groups.

Except for the pseudopathological cases, the presence of cribra orbitalia indicates that the individual experienced some kind of chronic health problem, although it may not have been anemia.

The present study indicates that histologic analysis is a valuable tool to establish a reliable etiology of cribra orbitalia. This result raises an important question, because in fact such examination is often impossible. We recognize that our study is exceptional because all cases displaying orbital lesions were sampled for thin-section analysis, which would be impossible for museum collections or similar collections. Further studies are required to clarify the etiology of cribra orbitalia with histologic diagnostic methods.

**ACKNOWLEDGMENTS**

We thank Professor B. Vandermeersch and UMR 5809 CNRS for their generous material support of this work, and M. Brandt and I. Hettwer-Steeeger (Zentrum Anatomie, Georg-August-Universität, Göttingen, Germany) for their assistance in ground-section preparation.

**LITERATURE CITED**


