Porotic hyperostosis and cribra orbitalia: the erythropoietic response to iron-deficiency anaemia

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Abstract A recent paper by Walker et al. (2009) states that iron-deficiency anaemia can no longer be regarded as being a cause of porotic hyperostosis (PH) or cribra orbitalia (CO). It is argued here that this conclusion is not supported by the current literature on iron-deficiency anaemia and associated haematopoietic responses or consequences to this condition. Indeed, iron-deficiency anaemia is still a plausible candidate in any differential diagnosis of lesions identified as PH and/or CO.

Key words: erythropoiesis, marrow hyperplasia, palaeopathology

Introduction

Walker et al. (2009) make the case that iron-deficiency anaemia cannot be regarded as a possible cause of cranial lesions often referred to as porotic hyperostosis (PH) and cribra orbitalia (CO). Their key assertion, and argument, is summarized as follows:

“The simple fact that iron-deficiency anaemia effectively decreases mature RBC [red blood cell] production means that it cannot possibly be responsible for the osseous expression of hemopoietic marrow expansion that paleopathologists recognize as porotic hyperostosis and cribra orbitalia.” (p. 112)

This assertion is repeated in various forms throughout the paper. The authors go on to contend that the most likely underlying cause of PH, as restricted to the cranial vault and excluding the orbital roofs, is one of the inherent haemolytic anaemias or an acquired megaloblastic anaemia due to B12 and/or folate deficiency. As for CO, they are consistent with recent literature on the aetiology of this condition in proposing a diverse differential diagnosis, including infectious disease, scurvy and B12 deficiency megaloblastic anaemia.

We support Walker et al.’s (2009) view regarding the diverse potential aetiologies of PH and CO, and agree that PH and CO may represent age-related responses to common underlying pathological conditions or, perhaps, differential remodelling schedules. What we do not support are some of their assertions regarding iron-deficiency, with our main contention being their statements regarding the relationship between iron-deficiency, anaemia, and erythropoiesis are not supported by the literature.

Results and Discussion

As we do not dispute the link between the dyserythropoietic anaemias, increased erythropoiesis, and subsequent marrow hyperplasia, we will restrict our discussion to those conditions where iron levels play a crucial role in disease outcomes; these include anaemia of chronic disease (ACD) and the focus of Walker et al.’s paper, iron-deficiency anaemia. Both ACD and iron-deficiency anaemia are microcytic, hypochromic conditions (Cavill, 2002; Orazi et al., 2006). In ACD the cytokine response to the underlying condition (e.g. infection, inflammation or malignancy) results, through the anti-erythroprotein effect of tissue necrosis factor α (TNFα), in suppressed mitotic activity in the erythroblasts of the marrow. At the same time, and for a variety of disputed reasons, iron supply to the marrow for haemoglobin synthesis is impaired. This results in the production of red cells with reduced haemoglobin content (hypochromia). This is not the result of storage iron-deficiency, indeed the iron stores are usually raised in this condition.

On the other hand, when the iron stores are diminished, iron supply will also be limited and hypochromic red cells will also be produced: this is iron-deficiency and it is a result of blood loss and/or a diet low in iron (Han et al., 2001). The functional difference between ACD and iron-deficiency anaemia is that in the former erythropoietic activity is suppressed, while in the latter it is increased. However, because the rate of iron supply to the stimulated red marrow is limited in iron-deficiency, there are too many erythroblasts chasing too little iron. The result of this is that an increasing proportion will fail to make sufficient haemoglobin in the time available to become functioning erythrocytes; these are destroyed within the marrow. In iron-deficiency anaemia there is a massive increase in this intra-medullary ineffective erythropoiesis.

In summary, ACD is unlikely to be associated with marrow hyperplasia erythropoiesis, whether effective or ineffective, being essentially suppressed and, indeed, we are unaware of any claims linking ACD to marrow hyperplasia erythropoiesis. A dominant characteristic of iron-deficiency
anaemia is “the massive degree of ineffective erythropoiesis that is associated with inadequate iron supply to the marrow” (Cavill, 2002: 404). Walker et al. cite recent literature supporting the view that RBC levels are depressed with iron-deficiency. Indeed, RBC levels have been used for some time in differentiating between iron-deficiency anaemia and thalassaemia (e.g. England and Fraser, 1973; and more recently Demir et al., 2002), with lower levels, 3.8–5.08 (×1012/l), seen in iron-deficiency anaemia compared to thalassaemia (4.47–6.43) (Demir et al., 2002: table 1), although the ranges overlap with each other and also with those of normal (non-anaemic) individuals (e.g. Yip et al., 1984: table 2). What is crucially important here is not the RBC level in and of itself, but rather the vastly increased level of ineffective erythropoietic activity that occurs as a response to the lack of available iron. Whether one of the haemolytic anaemias such as sickle cell anaemia, macrocytic anaemias such as megaloblastic forms, or iron-deficiency anaemia is being examined, in all cases an underlying issue is the defective erythroblast development which results in erythroid hyperplasia of the bone marrow (Orazi et al., 2006: 33).

While we have pointed out that a range of anaemias, including those caused by iron and B12 deficiencies, result in erythroid hyperplasia of the bone marrow, we caution against making the seemingly plausible leap to linking observed skeletal changes in these conditions, despite one of us having done just that in previous publications (e.g. Oxenham, 2006; Oxenham and Matsumura, 2007). It seems clear that inherited haemoglobinopathies, such as sickle-cell anaemia and thalassaemia, are associated with a broad suite of skeletal changes in subadults (Tunaci et al., 1999; Almeida and Roberts, 2005; Tyler et al., 2006). One of the observed changes, relevant here, is an expansion of the diploic bone and thinning of the outer table in the frontal and parietals in particular; the occipital is generally spared due to its relatively lower marrow content (Tyler et al., 2006). Such skeletal changes have also been apparently observed in the earlier literature with respect to iron-deficiency anaemia (e.g. Aksoy et al., 1966; Agarwal et al., 1970) and at face value appear to support an association between iron-deficiency anaemia and bony changes to the subadult cranium. Nonetheless, we would argue that much more research needs to be performed in order to refute or support this apparent relationship. In the adult human, at least, there is almost always room for the red marrow to accommodate increased erythropoietic activity without encroaching on the bony surrounds. Indeed, there is evidence, in adults, that increased erythropoiesis can be accommodated without the need for physical expansion (Al-Adhadh and Cavill, 1983) or changes in the fat ratio of the cells. The more extensive distribution of erythropoietic marrow in children would appear, as mentioned, to be less accommodating, although again, much more research is needed with respect to deficiency diseases in childhood (e.g. iron and B12) and associated skeletal changes.

Conclusions

The assertion by Walker et al. that iron-deficiency anaemia, with an associated reduction in mature RBC, cannot possibly cause skeletal lesions (PH and/or CO) is based on a misunderstanding of the clinical literature concerning the various anaemias and associated haematopoietic responses or consequences thereof. As far as we can tell, the only form of anaemia unlikely to lead to PH or CO, due to a characteristic suppression of erythropoietic activity, is ACD. Iron-deficiency anaemia, characterized by massively elevated erythropoietic activity, would appear to be a more than plausible inclusion in a differential diagnosis of PH and/or CO. While we suggest more research is needed to confirm the apparent association between iron-deficiency, and B12 and/or folate deficiency for that matter, anaemia and pathological changes to the cranial bones, it is becoming clear that bone remodelling and haematopoiesis are intimately related processes (Aguila and Rowe, 2005), with any pathological change in one impacting on the other.

References


