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POROTIC HYPEROSTOSIS AS A MANIFESTATION OF IRON DEFICIENCY?

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Presence of porotic hyperostosis has been frequently used in the anthropologic literature as evidence of iron deficiency anemia. This perspective appears to represent a hypothesis that may not have been adequately tested. Any process which increases marrow activity (evidenced by porotic hyperostosis) increases consumption of basic nutrients. Iron stores, often low to begin with, are typically the most rapidly depleted. Thus, individuals with hemoglobinopathies or hemolytic anemia develop the "hair on end" phenomenon and only subsequently become deficient of iron. Even those clinical reports (which claim occurrence of diploic skull changes in patients with iron deficiency) report a very low frequency of the phenomenon. The only identified study of the frequency of skull changes in iron deficiency (Agarwal et al. 1970) revealed a frequency of only 0.68%! This certainly does not support iron deficiency as the explanation for the high frequency of porotic hyperostosis noted (approximating 50%) in some populations. There is also no relationship of degree of anemia or of iron deficiency to occurrence of the "hair on end" phenomenon of porotic hyperostosis. What then is the significance of porotic hyperostosis?. Ascribing high population frequency occurrence of porotic hyperostosis to iron deficiency anemia no longer seems tenable. Perhaps further exploration of presence of genetic hemolytic anemias, parasite exposure, hemoglobinopathies, and nutritional bases will prove enlightening.

Key words: Iron deficiency, porotic hyperostosis, hemolysis, parasitism.

La presencia de hiperostosis porótica ha sido usada frecuentemente en la literatura antropológica como evidencia de anemia debido a la deficiencia de fierro. Esta perspectiva parece representar una hipótesis que tal vez no fuera adecuadamente probada. Cualquier proceso que aumenta la actividad de la médula (evidenciada por hiperostosis porótica), aumenta el consumo de nutrientes básicos. Los depósitos de fierro, frecuentemente bajos, son típicamente agotados rápidamente. Así, individuos con hemoglobinopatías (e.g., thalassemia) o anemia hemolítica desarrollan el fenómeno de "pelo en punta", y sólo subsecuentemente llegan a ser deficientes de fierro. Aún los informes clínicos (que declaran la ocurrencia de cambios diploicos del cráneo en pacientes deficientes de fierro) reportan una frecuencia muy baja del fenómeno. El único estudio identificado sobre la frecuencia de cambios del cráneo en casos de deficiencia de fierro (Agarwal et al. 1970) reveló una frecuencia de sólo 0,68%. Esto ciertamente no apoya a la deficiencia de fierro cómo la explicación de la alta frecuencia de hiperostosis porótica notado (a casi 50%) en algunas poblaciones. Tampoco hay relación entre el grado de anemia o de deficiencia de fierro y la ocurrencia del fenómeno "pelo en punta" de hiperostosis porótica. ¿Cuál es entonces el significado de hiperostosis porótica? Quizá la exploración de la presencia de anemias hemolíticas genéticas, parásitos, hemoglobinopatías y bases nutricionales sea útil.

Palabras claves: *Deficiencia de hierro, hiperostosis porótica, hemólisis, parasitismo.*

Porotic hyperostosis is a frequently recognized archeologic phenomenon (Angel 1978; El-Najjar et al. 1975; Grmek 1989; Hill and Armelagos 1990; Von Endt and Ortner 1982) often attributed to iron deficiency. The pathophysiology has been explained as a marrow hyperplasia, which radiologically (in the skull) is recognized as a "hair on end" or "crew cut" phenomenon (Resnick and Niwayama 1988). If the above is blatantly obvious, why is it subject to continued discussion?

Historical Aspects

I have always been confused by attempts to attribute porotic hyperostosis to iron deficiency. In the past 25 years, I have seen hundreds of patients with iron deficiency. I have yet to see my first example of "hair on end" phenomenon, unless the patient had a concomitant cause of marrow hyperplasia.

Physiology

Any process which increases marrow activity increases consumption of basic nutrients (Fairbanks and Beutler 1972). Iron stores, often low to begin with, are typically the most rapidly depleted. Thus individuals with hemoglobinopathies [characterized by ineffective erythropoiesis (e.g., thalassemia)] or hemolytic anemia [who frequently (especially in thalassemia major) develop the "hair on end" phenomenon (Caffey 1957; Resnick and Niwayama 1988)] may become deficient of usable iron stores (Fairbanks and Beutler 1972).

I find problematic consideration of iron deficiency as a cause of hyperplastic marrow. If there is inadequate iron for blood cell production, the marrow may actually be hypo-regenerative (Fairbanks and Beutler 1972). The difficulty is identifying concomitant hemolytic anemia.

Recognition of Hemolytic Anemia

Several forms of hemolytic anemia are very difficult to diagnose. Any which occur as episodic events [e.g., fava bean-induced, when there is a deficiency of glucose-6-phosphate dehydrogenase (G6PD) activity] are especially problematic (Grmek 1989; Kattamis et al. 1969). The inheritance of G6PD function is not shared equally in all red blood cells. In G6PD deficiency, usually only one gene of a gene pair is defective in a given cell. Whether the active or ineffective gene is "turned on" in a given red blood cell determines that cell's response to the hemolytic agent. If a person is tested after a hemolytic episode, the blood is no longer sensitive to hemolysis (The sensitive cells are gone and there is insufficient time for their regeneration; (Dern et al. 1954; Kattamis et al. 1969). If iron deficiency is also present, regeneration is further impaired. Assays performed at this time will wrongly surmise that there is no hemolytic component to the anemia. Thus, hemolysis is often overlooked. Clinically reported cases of "hair on end" phenomenon in patients with iron deficiency do not appear to have adequately precluded (as compared with contemporary techniques) co-occurrence of a hemolytic process.

Iron Deficiency

Even those clinical reports (which claim occurrence of diploic skull changes in patients with iron deficiency) report a very low frequency of the phenomenon (Eng 1958; Lanzkowsky 1968). These certainly do not support iron deficiency as the explanation for the high frequency of porotic hyperostosis noted (approximating 50%) in some populations (Angel 1978; El-Najar et al. 1975). The first apparent report of diploic table thickening in iron deficiency anemia by Sheldon unfortunately did not assess for an associated hemolytic process. Only 16 cases of skull changes were added to the literature (from among thousands of individuals with iron deficiency) in the ensuing 32 years. Lanzkowsky (1968) concluded that "associated hemolysis was not ruled out with any certainty" even in these cases. A typical example was the claim of occurrence of "hair standing on end" (Eng 1958), in an individual who also had yaws. The presence of peripheral blood spherocytes and splenomegaly in that individual, however, suggests that another hemolytic process, spherocytosis (Young et al. 1951) was present.

Lanzkowsky's 1968 review of radiologic features of iron deficiency found only 15 candidate individuals among the substantial patient populations seen at the Cape Town and Red Cross War Memorial Children's Hospital in South Africa, where iron deficiency anemia was extremely common. Osmotic fragility tests in 8 of 14 individuals were abnormal, suggesting an associated hemolytic process. One test for hemolytic anemia is use of radionuclide-labeled red blood cells. Shortening of the normal red blood cell half-life is indicative of a hemolytic process. Chromium 51-labeled red blood cells had significantly shortened half-lives in all patients tested by Lanzkowsky (1968). Red blood cell half-life is not shortened in iron deficiency anemia (in the absence of a hemolytic process) (Kaplan and Zuelzer 1950; Temperley and Sharp 1962).

Six of the children reported by Lanzkowsky (1968) also had rickets. Lanzkowsky (1968) hastens to emphasize that rickets can cause these same skull changes (Silverman 1985). He emphasizes that previously reports attempting to suggest association of skull changes with iron deficiency anemia have failed to exclude rickets.

Porotic Hyperostosis

Attempts to relate porotic hyperostosis to severity of iron deficiency are also opposed by the clinical record (Lanzkowsky 1968). There was no relationship of degree of anemia or of iron deficiency to occurrence of the "hair on end" phenomenon of porotic hyperostosis. What then is the significance of porotic hyperostosis? The only identified study of the frequency of skull changes in iron deficiency (Agarwal et al. 1970) revealed a frequency of only 0.68%.

Marrow Hyperplasia

Marrow hyperplasia is the response to chemical stimulus to production of red blood cells. Loss of red blood cells through blood loss or destruction must be considered. Another stimulus to red blood cell production, hypoxia, has curiously not yet been associated. Destruction through a hemolytic process may be more pertinent in the Old World, but parasitic infections seem most appropriate to investigate in the New World. In addition to simple blood loss (e.g., from *Ancyclostoma*), consumption of vitamin B12 results in "ineffective erythropoiesis". In this anomalous form of anemia, the marrow keeps

producing cells, but they are not very effective in transporting oxygen. This has major implications, as the fish tapeworm, *Diphyllobothrium* consumes large quantities of vitamin B12. Correlation with fish consumption habits will be of interest.

Ascribing high population frequency occurrence of porotic hyperostosis to iron deficiency anemia no longer seems tenable. Perhaps further exploration of presence of genetic hemolytic anemias, hemoglobinopathies, parasitic infestations and nutritional bases will prove enlightening, as Grmek 1989; Hill and Armelagos (1990) and Mensforth et al. (1978) have suggested.

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