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Reduced Iron Stores and Its Effect on Vasovagal Syncope (Simple Faint)

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Iron deficiency is extraordinarily common. Iron deficiency anemia is the single most common deficiency world-wide (1). Within the vascular compartment, iron is primarily contained in hemoglobin and in storage forms such as ferritin and hemosiderin (2). Iron is also present in tissue-specific forms such as myoglobin. Less commonly considered is iron's vital role in enzymes such as the respiratory cytochromes, cytochrome P-450, nitric oxide (NO) synthases, tyrosine hydroxylase providing for catecholamine synthesis, and carotid body oxygen sensors (2). These are present throughout the blood and body and are essential for life. Such "specialized" iron increases and decreases with the amount of iron storage forms and can precede overt iron deficiency (3). A decrease in iron stores usually precedes and predicts future overt iron deficiency anemia even as early as at birth where it relates to the level of maternal iron stores (4). Decreased ferritin is the usual perinatal predictor but its predictive ability is hampered by its role as an acute phase reactant (5). Thus, in this issue of *The Journal*, Baumann-Blackmore et al (6) have compared a newer tool for measuring iron status, Cord Blood Zinc Protoporphyrin/Heme Ratio, which is insensitive to inflammatory stimuli yet correlated with ferritin in the neonate without inflammation. Although the paper does not directly relate measures of neonatal iron stores to anemia or to diminished iron stores later in life, such relationships have already been established (7). The present observations offer an important and sensitive new tool to the assessment of iron stores in the neonatal period.

Once iron deficiency is present, what are its pathophysiological consequences? It is perhaps redundant to state that aerobic metabolism depends on the delivery of oxygenated blood to the tissues. Oxygen delivery depends on hemoglobin-oxygen carrying capacity, cardiac output and its distribution, and oxygen extraction at tissue level (8). Anemia enhances oxygen extraction through a variety of mechanisms including tissue-level hypoxia, lactate, acidosis, and CO_2 - mediated oxygen mobilization from hemoglobin as well as an increase in 2,3 DPG and a shift of the oxygen dissociation curve (9). Assuming distribution and utilization at the tissue level remains unimpaired or even enhanced in iron deficiency, the rate at which oxygen is delivered to the tissues becomes limiting.

The reduced hemoglobin-oxygen carrying capacity of iron deficiency anemia is compensated by an increase in cardiac output (10). How this is accomplished remains incompletely understood although metabolites such as lactate, adenosine, and hydrogen ions can produce an

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metaboreflex response that selectively increases sympathetic outflow to the heart increasing contractility (11). Peripheral vasoconstriction, largely the province of the arterial baroreflex, is essentially unaffected as is the peripheral sympathetic response to orthostasis (12). Increasing cardiac contractility by itself cannot produce much of an increase in cardiac output. Increased cardiac output in iron deficiency anemia is dependent on cardiac afterload and increased venous return to the heart. Reduced viscosity (13) due directly to decreased hematocrit cannot entirely account for the low systemic resistance observed in iron deficiency anemia.

In recent years it has been demonstrated that both non-autonomic vasodilation and structural remodeling (14) with increased arterial diameter are related to increased blood flow and shear stress. This is sustained by the elaboration of substances released from the vascular endothelium, specifically nitric oxide (NO) (15). NO production is increased by shear stress. However, of greater importance, hemoglobin is the preeminent scavenger of NO (16). Cell-free hemoglobin as might occur during hemolysis (17) functions as an almost bottomless sink for NO. However, under ordinary circumstances hemoglobin is encapsulated within red blood cells and therefore NO removal is constrained. Iron deficiency anemia can increase nitric oxide production in adolescents (18) and greatly reduce its removal by virtue of decreased hemoglobin. Iron stores also scavenge NO. Reducing iron stores by chelation also improves NO-related endothelial function (19). In particular, plasma ferritin concentrations relate directly to nitric oxide mediated vasodilation and endothelial function even in the absence of specific hemoglobin alterations (20,21).

Which brings us to consider the paper by Jarjour and Jarjour (22). They performed a retrospective study which demonstrated an association between decreased serum ferritin and simple vasovagal faint. Although the majority of their subjects were not overtly anemic (11% vs 0% of non-simple faint subjects), there was a significant increase in the prevalence of low iron storage (57% vs 17%) and marked reduction of serum ferritin (27 vs 46 μg/L). Observations of apparent efficacy of iron therapy in children with decreased iron stores and breath holding spells, which may be an infantile form of acute orthostatic intolerance, are entirely consistent with these observations. Also, erythropoietin has been used with success for years in the treatment of relatively refractory forms of orthostatic intolerance, autonomic dysfunction and simple faint (23). The current study suffers from the deficits of retrospection, and from the lack of healthy volunteer control subjects. Yet, it is a valuable observation, pointing to a potentially crucial and simple clinical relationship between iron deficiency and fainting and indicating a simple means by which patients with simple faint might be improved through iron supplementation. Currently, these conclusions remain speculative.

Scientific Significance – Simple Faint and Nitric Oxide?

Why is this observation scientifically important? To date, the pathophysiology of simple faint remains elusive (24). The authors suggest that low iron may affect the metabolism of catecholamines, or that peripheral vasodilation prevents compensatory orthostatic vasoconstriction. Neither possibility works well because resting and upright norepinephrine is proportionate to vasoconstriction in fainters (25) while epinephrine increases in response to hypotension (26). Anemia fails to prevent effective upright vasoconstriction (12).

I propose an alternate explanation: The splanchnic circulation is the single largest reservoir of blood in the body (27). Work from our laboratory (28) and others (29) have shown that splanchnic pooling caused by persistent and posturally resistant splanchnic vasodilation is strongly associated with orthostatic intolerance including vasovagal faint. Evidence suggests preferential splanchnic vasodilation in anemia (30), and NO is increased while nitric oxide synthesis is upregulated in simple faint (31) and in other forms of orthostatic intolerance (32). Seen in this context the dual effects of vasodilation and nitric oxide excess caused by

reduced iron stores with or without anemia are highly consistent with experimental observations on the nature of simple faint. The study by Jarjour and Jarjour comprises a vital connecting piece to our understanding of simple faint in otherwise “normal” adolescents.

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