



Opinion Article

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The Importance of Defining Anaemia

Sebastien Farnaud*

Research Centre for Health & Life Sciences, Coventry University, CV1 5FB, UK

***Corresponding author:** Sebastien Farnaud, Research Centre for Health & Life Sciences, Coventry University, CV1 5FB, UK

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Introduction

In a recent presentation on Iron metabolism, I started by asking the audience how they defined anaemia. Maybe not surprisingly, for quite a few attendees, the quick answer was "lack of iron". Of course, while iron deficiency remains the most common cause of anaemia, this definition is incorrect since not only other nutritional deficiencies, but also a number of other medical conditions can also be the cause of anemia.

Misdiagnosis is a major issue for correcting anaemia that in some cases can have some disastrous consequences. The importance of the correct diagnosis was already highlighted in the 19th century by Dr Armand Trousseau, a French doctor who is recognised for his work on iron metabolism, including his early description of iron-overload in 1865, although the term "hemochromatosis" was later coined by Friedrich Daniel von Recklinghausen in 1889. In an earlier lecture delivered at the Hotel-Dieu in Paris in 1868, [1] Trousseau presents what he called a False Case of Chlorosis, an early term used to describe iron-deficient anaemia (IDA) particularly in adolescents. In that lecture, Trousseau describes several cases including the following:

"A girl of fifteen fell into a state of anaemia, which I considered chlorosis. I administered ferruginous remedies, which rapidly restored her to florid health: and although there was nothing in the family history to lead me to fear the coming calamity, she was simultaneously seized with hemoptysis and menorrhagia, and died two months afterwards"... "Gentlemen, I am constrained to impute to iron some of the evil consequences which I had to deplore."

He later admits that what he had taken for IDA was in fact consumption, tuberculosis. We now understand that following the infection, in response to hepcidin activation and other mechanisms, the first line of defence of the body was iron sequestration to prevent the proliferation of the infectious agent, therefore resulting in anaemia despite repleted iron stock. Trousseau's incorrect diagnostic had led him to supply iron unknowingly to the infectious invader, promoting the infection in the young patient already weakened by her immune response, resulting in her rapid death. This case highlights the hidden face of anaemia and emphasises the need for a complete diagnostic approach to differentiate IDA from anaemia of inflammation (AI). Today, IDA and AI can be differentiated with key tests including Complete Blood Count (CBC), serum ferritin, to-

tal iron-binding capacity (TIBC), and also serum soluble transferrin receptor (sTfR). Generally, the ratio of sTfR to log of ferritin can be used to distinguish both conditions, where AI ratio would be below:

a) Whereas IDA ratio would be superior to

b) In addition to infection, AI also called anaemia of chronic disease (ACD), is also present in a number of conditions such as kidney disease, cancer, and rheumatoid arthritis, where a common factor between these otherwise apparently unrelated disorders is inflammation, which disrupts the normal processes of iron storage, utilisation, and red blood cell production, so with a level of anaemia expected.

Fortunately, not all anaemia misdiagnoses end up with a conclusion as catastrophic as the case described by Trousseau, but it is important to understand the true cause(s) of anaemia so that it can be corrected.

Although anaemias are generally divided in three groups based on the size of the red cells, microcytic, normocytic and macrocytic, around 400 types of anaemia have been defined [2], and maybe the complexity of some of the definitions is partly responsible for the confusion. Although a simple definition such as *"a condition characterised by a deficiency of functional red blood cells leading to reduced oxygen-carrying capacity"* could be enough, whichever definition is used, it rarely identifies all possible causes. As for all health disorders and diseases, identifying the cause is the best start towards correcting it, but in this case, a full understanding of iron metabolism, including Absorption, Distribution and Metabolism (ADM) is required. It can be noticed that whereas for most of active molecules the ADME includes Excretion, for iron the lack of a defined excretion pathway might simplify its pharmacological descriptive, but certainly not its metabolism.

Indeed, it is the absence of way-out that implies iron level regulation at the uptake, which in turn requires a very complex iron absorption mechanism, with a number of factors increasing the risk of failure that can translate into anaemia. Absorption is not the only issue, since iron Distribution through transferrin is also a very complex mechanism, while its Metabolism, which includes the production of both haemoglobin and red blood cells is also carefully regulated, primarily by the hormone erythropoietin (EPO), which is produced by the kidneys in response to low oxygen levels. So, undoubtedly anaemia is not always caused directly by iron deficiency, and several factors can also lead to the condition.

However, iron supplementation remains crucial, since it is estimated that IDA accounts for around 50% of all anaemia cases, which is thought to affect approximately 30% of the global population [3]. The overall iron uptake mechanism includes additional mineral and vitamins that plays a crucial role in helping the body absorb and utilise iron that should be considered in iron supple-

mentation. For example, Copper, an essential cofactor for a wide range of enzymes in various biological processes, is essential for the multicopper ferroxidase Ceruloplasmin and Hephaestin, which play a crucial role in iron absorption and metabolism. On the other hand, other metals such as Zinc are proposed to compete with Iron for absorption in the intestines. However, in regions where both Iron and Zinc deficiencies are prevalent, combined supplementation can be a convenient way to address both deficiencies simultaneously [4]. Some studies even conclude that combined iron and zinc supplementation can be effective in reducing the prevalence of anaemia and iron deficiency anaemia [5].

Deficiency in other factors such as Vitamins B6 and B12, can also lead to anaemia despite a suitable iron level, but because they both play a crucial role in red blood cell formation and can be involved [6,7]. In fact, pernicious anaemia, a low red blood cell count caused by the body's inability to absorb vitamin B12, which if left untreated can lead to serious complications including neurological damage, heart problems, and an increased risk of certain cancers, was also mentioned by Trousseau in the same publication in 1868 [1].

The list of enhancers and inhibitors is much longer than the few examples provided in this short article, but the message here is what can be called the Iron Paradox: iron might be the second most abundant metal in the earth's crust, but it is the world's most common nutritional deficiency; iron is the most used metal and the cheapest, but when it comes to life, iron is more precious than gold. Although a very simple element, its related disorder anaemia is far from being simple and needs to be considered very carefully.

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