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Case Report

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Diagnostic Quandary of Iron Overload

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Abstract

Serum iron, percentage total iron binding capacity/transferrin saturation (TIBC/TSAT) and ferritin are among routine tests commonly used to assess iron status. Elevation may suggest iron overload/haemochromatosis leading to liver damage and deranged LFT. Accepting at face value such explanation could be susceptible to misinterpretation and/or diagnostic misapplication in patients presented with hepatitis/liver injury.

The case described an 80 years old man who had atorvastatin causing autoimmune hepatitis which was also associated with elevation of all iron parameters. Withdrawal of the offending medication was associated with simultaneous normalisation of both LFT and all iron parameters.

The case highlights the quandary of interpreting iron parameters in the presence of hepatitis/liver injury and the need for careful interpretation of elevated iron parameters in patients with hepatitis/liver injury by other causes.

Keywords: Iron, TIBC/TSAT, ferritin, LFT, Hepatitis, flu vaccine, statin

Introduction

Serum iron, percentage total iron binding capacity/Transferrin saturation (TIBC/TSAT) and ferritin are among routine tests used to assess iron status [1,2]. Elevation of all three parameters may suggest iron overload/haemochromatosis which could cause liver injury leading to deranged LFTs [3,4]. However, the case described highlight that accepting at face value such explanation could be susceptible to misinterpretation and/or diagnostic misapplication in patients with hepatitis/liver injury from other causes. Furthermore, it may also lead to unnecessary and costly investigations including genetic testing for hereditary haemochromatosis [3]. Appreciating the impact of hepatitis/liver injury per se on iron parameters may help a more balanced diagnostic approach to such impasse.

Case Report

A previously well 80-year old male presented with progressive anorexia, weight loss, myalgia and fatigue approximately 14 days' post-flu jab. His previous medical history included a NSTEMI for which he was taking high dose atorvastatin (80 mg/day), aspirin (75 mg/day) and an OTC multivitamin -mineral tablet containing 20mg iron. Clinical examination was unremarkable but malignancy was considered in view of patient's age and loss of weight.

Follow-up investigations therefore included a CT scan and pelvic/abdominal MRI, FBC, U&E, HbA1C, LFT, bone profile, lipids, TFT and PSA. All were normal apart from abnormal LFTs with raised ALT (x15) and bilirubin (x4) but modest increase in ALP (x2), a biochemical profile consistent with hepatitis. The patient subsequently stopped all medications apart from aspirin. Further investigations included liver ultrasound, viral serology

(Hep A, C, CMV, and EBV), CRP, ESR and iron status. Apart from clear elevations of serum iron, TIBC saturation and ferritin, all others were normal/unremarkable. Autoantibodies screen was positive for vascular smooth muscle (staining not specific for F-actin interpreted as query viral hepatitis, query drug induced) and for ANA antibodies (homogenous pattern); ANA is non-organ specific autoantibody, present with high frequency in healthy elderly people).

Serial measurements of the LFTs and iron parameters showed a progressive and parallel improvement in both LFTs and iron parameters, returning to normal after 2 months. Genetic analysis for the most common mutations of C282Y HFE seen in hereditary hemochromatosis was negative (other less common gene mutations which could also cause iron overload such as H63D, non-HFE haemojuvelin (IIA), hepcidin (IIb), transferrin receptor 2 (III) and ferroportin 1 (IV) were not carried out). Subsequently, atorvastatin was re-introduced 20 mg daily (two weeks) before increasing to 40mg/day (one week); this triggered a prompt rise in ALT again (x3), establishing that the liver injury was drug-related. A year after substituting atorvastatin by plant sterols (1.6 g/day) coupled with reducing cholesterol intake, the patients remained fit, active and well, with totally normal LFTs, iron parameters and total cholesterol of 3.7 mmol/L.

Comments

The liver is the principle bidirectional regulator of iron circulating in blood through synthesis of transferrin, storage (ferritin) and iron mobilisation to meet physiological need. Iron overload is however pathological and among its potential adverse effect is liver injury. Almost all iron entering into the circulation from whatever source is bound to carrier proteins of which > 70% is transferrin. Non-bound iron in the circulation is virtually non-existent. There are daily physiological fluctuations in iron homeostasis which can result in substantial intra and inter-individual fluctuations (up to 30%) that may affect test interpretation. Iron levels are generally higher in fasting morning samples [5-11]. Iron may also be released from hepatocellular damage/necrosis. Secondly, high percentage saturation of TIBC is the earliest evidence of haemochromatosis; values greater than 60% in men and 50% in women are considered significant. Transferrin synthesis decreases in conditions causing liver injuries/hepatitis [12] which could reduce the overall iron binding capacity, potentially contribute to an increase in percentage saturation of TIBC and/or transferrin saturation (TSAT). Thirdly, serum ferritin is an accurate measure of the body's iron stores in patients without liver disease, malignancies or conditions causing chronic inflammation [13]. Ferritin concentrations independently decline when the iron stores are also reduced, irrespective of serum iron and TIBC/TSAT. Ferritin levels > twice the upper quoted normal range in men and postmenopausal women indicates iron overload [14] especially when associated with significant elevation in TIBC/TSAT saturation. However, because both ferritin and ALT are stored in hepatocytes' cytosol, damage to or necrosis of hepatocytes release both ferritin and ALT hence their significant correlation ($p < 0.01$) [15]. Despite initial elevation of all iron parameters in this case, iron overload did not exist.

The rise in ALT following resumption of atorvastatin has established a causative relationship. However autoimmune hepatitis to flu vaccine [16] per se is also known to occur and of all statins, simvastatin and atorvastatin are among the most immunogenic especially in the elderly on high doses [17-21]. Needless to say symptoms following flu vaccination are normally transient and include malaise, nausea, and myalgia, however the symptoms following vaccination in this case, their progression, persistent and severity were atypical. Flu jab formulation changes annually as prevalent viruses mutate each winter. For this reason, the WHO recommendation of vaccine formulation changes from year to year and for the year 2018-19 winter it was a surface inactivated multiple viral influenza strains namely influenza A strain H1N1 and H3N2 plus influenza B Colorado strain. In the UK, intramuscular flu shot given to those ages >65 yrs also contained four times the dose of the standard vaccine.

It may be important to emphasize that in the case described, the aetiological mechanism underpinning the adverse immune hepatitis remained speculative [21, 22]. Although small organic molecules (i.e. haptens) such as atorvastatin are themselves not immunogenic, they could become immunogenic when they bind by chance, with high affinity to a carrier macromolecule (undetermined in this case) such as proteins, environmental agent or viruses to form a complex [23]. Such complex could be immunogenic, eliciting an autoimmune response with cross-reactivity and toxicity in some genetically susceptible individuals. Interruption of complex-formation by removal of the hapten such as atorvastatin could cause the autoimmune response to subside but would be re-triggered on re-exposure as shown in this case.

Take home message

1. Hepatocytes damage/necrosis irrespective of the underlying causes could increase serum iron and ferritin concentrations; reduce transferrin synthesis, thus increasing percentage TSAT/TIBC saturation.
2. Ferritin may be better perceived as an additional LFT parameter rather than an index of iron stores in patients with hepatitis/liver injury in view of their parallel correlations.

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