

**H**igh serum ferritin is a hallmark of genetic haemochromatosis and iron loading anaemias like haemoglobinopathies. Serum ferritin is also an acute phase protein and is raised in a number of other conditions, including inflammatory, autoimmune, malignant and liver disorders. In many such conditions, serum ferritin levels may rise up to several thousand/dl. There is paucity of data on correlation of level of serum ferritin and clinical conditions. In this study we analysed various degrees of high serum ferritin levels and correlated with a range of different clinical conditions. We found serum ferritin levels above 5,000mg/dl are mostly associated with malignancy and Still's disease.

Clinicians should therefore be alerted when such high levels of serum ferritin are reported.

### What is ferritin?

Ferritin is a soluble 450 kDa protein. It is a storage form of iron readily available and is found in high concentration in marrow macrophages, the spleen and the liver. Ferritin protects cells from iron-mediated free radical formation and toxicity due to reaction between free iron and hydrogen peroxide. Ferritin is composed of 24 monomer subunits that consist of either heavy (H) type (21kDa) or light (L) type (19kDa) polypeptide chains encoded by two different ferritin genes. A total of 24 subunits associate to form a hollow spherical particle that can store up to 4,000 iron atoms as  $FE^{3+}$  ions. The L

chains are found in liver and splenic tissue whereas ferritin in heart and red blood cells is composed of H subunits. Haemosiderin found in Fe-laden macrophages is an insoluble denatured ferritin from which iron is less readily available.

### Measurement of serum ferritin and normal ranges

Ferritin is measured using immunoassay, e.g. enzyme linked immunoabsorbant assay (ELISA), immunochemiluminescence assay or immunoturbidimetric assay. The assays are based on using antibodies against liver or splenic ferritin and are calibrated against third international recombinant standard for ferritin (National Institute for Biological Standards and Control code 94/572). Mean serum ferritin varies with age, ethnicity and gender. Mean serum ferritin is higher in blacks and Asians. It is also higher in adult males (60-80 $\mu$ g/L) than adult females (25-30 $\mu$ g/L). With age, serum ferritin levels may rise up to 400 $\mu$ g/L in males and up to 200 $\mu$ g/L in postmenopausal females.

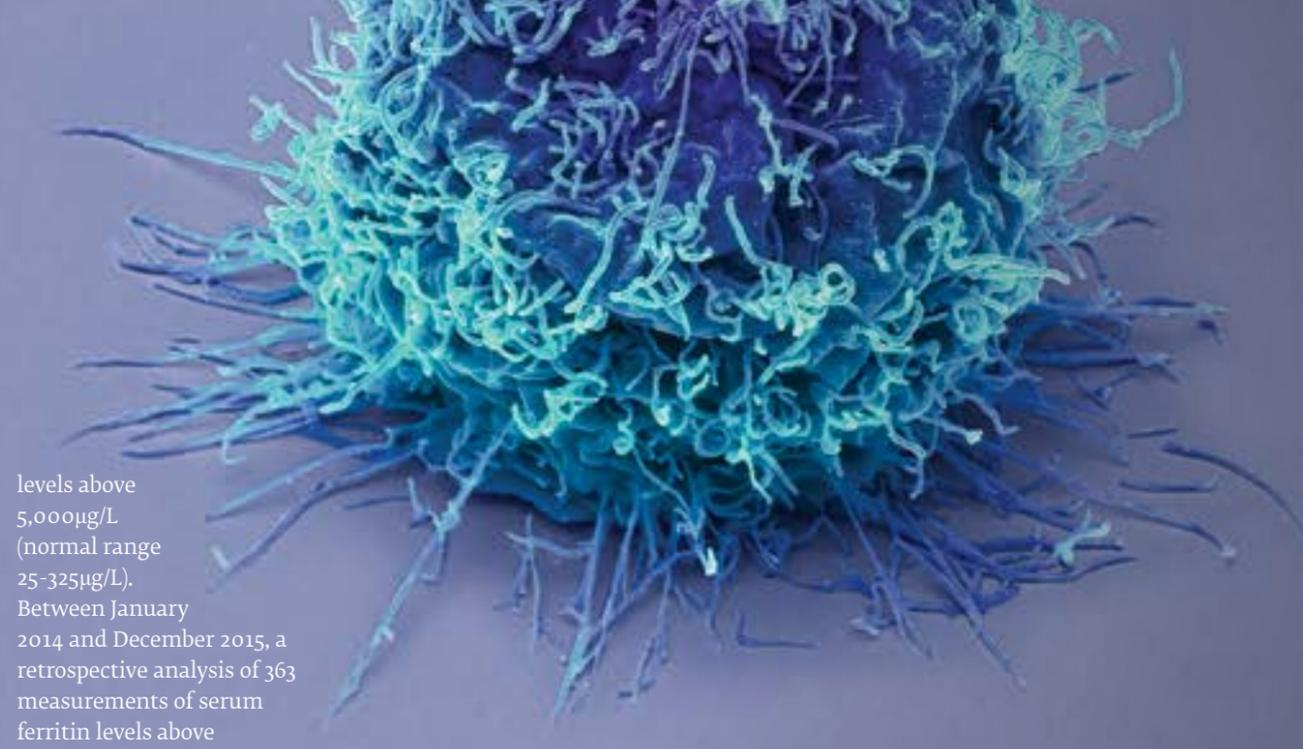
### Raised serum ferritin and its significance

Although the most common reason to request a serum ferritin assay is to rule out iron deficiency, many requests are made to diagnose iron overload and genetic haemochromatosis. The common causes of raised ferritin, however, are inflammatory disorders, malignancy, liver disease and alcohol consumption. The levels of serum ferritin in these disorders are variable (1,500-10,000 $\mu$ g/L). The levels can go up to 50,000 $\mu$ g/L in haematological malignancy, haemophagocytosis renal failure and liver disease.

### Current study

The aim of this study was to find if any particular level of raised serum ferritin is associated with specific clinical conditions. The researchers were mainly interested in looking at serum ferritin

Leukaemic (cancerous) T-lymphocyte white blood cell derived from a patient with acute T-cell leukaemia.



levels above 5,000 $\mu$ g/L (normal range 25-325 $\mu$ g/L). Between January 2014 and December 2015, a retrospective analysis of 363 measurements of serum ferritin levels above

5,000 $\mu$ g/L was carried out in the laboratory at Sandwell and West Birmingham Hospitals NHS Trust. This corresponded to 99 different patients over a two-year period. Clinical case notes and electronic records were then searched for 85 of the 99 patients and correlated with serum ferritin results. The most common cause of raised serum ferritin level above 5,000 $\mu$ g/L was transfusion-dependent anaemias (41%), then liver disease (17%), unexplained (15%), malignancy (13%), sepsis (08%), haemophagocytosis (3%), rheumatological conditions (2%) and haemochromatosis (1%) cases. Haematological malignancy and haemophagocytic syndrome were the only two conditions seen to be associated with median serum ferritin levels above 10,000ng/mL with some cases having levels up to 40,000ng/mL. C-reactive protein (CRP) tended to be higher in conditions with higher serum ferritin levels, but white cell count and serum ALT level did not show any correlation. Serum albumin, however, tended to be lower in all clinical conditions, with markedly raised serum ferritin suggesting some hepatic synthetic defect. This is an important observation and helped the researchers to guide clinicians in investigating patients

for such underlying disorders.

The findings are consistent with a number of previous observations. In 2007, Uppal *et al* described serum ferritin levels in a series of patients with adult onset Still's disease (characterised by fever, rash and arthritis), the majority of whom had ferritin levels five times above normal and some reaching as high as 50,000 $\mu$ g/L. In haemophagocytic lymphohistiocytosis (characterised by pancytopenia, hypertriglyceridemia, hyperferritinemia and multiorgan failure) serum ferritin levels are frequently above 10,000 $\mu$ g/L. In a study on 800 adults in three large US hospitals, Schram *et al* (2015) showed that markedly raised serum ferritin levels (above 10,000  $\mu$ g/L, small proportion had levels above 50,000 $\mu$ g/L) was associated with a variety of disorders such as renal failure (65%), liver disease (54%), infection (46%), haematological malignancy (32%), rheumatological conditions (18%) and haemophagocytic lymphohistiocytosis (17%).

### The message for clinicians

Raised serum ferritin levels are associated with multiple aetiologies, such as iron loading conditions such as primary (genetic) and secondary haemochromatosis due to thalassaemic

syndromes, but also due to non-iron loading conditions such as inflammatory, renal and liver disorders as well as malignancies. Serum transferrin saturation helps to differentiate between iron loading and non-iron loading conditions (transferrin saturations are high in the former disorders and normal in the latter).

Both this study and the published literature suggest that in cases of raised serum ferritin with normal transferrin saturations we should consider inflammatory disorders, renal and liver disease and malignancy. In situations with markedly raised serum ferritin levels (above 10,000 $\mu$ g/L) clinicians should specifically consider causes such as haematological malignancy, Still's disease, and haemophagocytic lymphohistiocytosis. The authors also direct readers to a recent review in the *British Journal of Haematology* by Cullis *et al* (2018) on investigations and management of a raised serum ferritin. 

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Honorary senior lecturer and consultant haematologist **Dr Farooq A Wandroo** and his colleagues ask, what is the clinical significance of a markedly elevated serum ferritin?

# RAISED SERUM FERRITIN