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ETIOLOGICAL STUDY OF MARKEDLY ELEVATED SERUM FERRITIN LEVELS IN A TERTIARY HEALTH CARE CENTRE

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BACKGROUND/INTRODUCTION:
Ferritin, a store of iron in soluble nontoxic form, reflects total body iron stores. It protects the cell from iron-mediated oxidation-reduction reactions. It plays a role as an acute-phase reactant and has long-standing association with rheumatologic diseases eg. adult-onset Still's disease, systemic juvenile idiopathic arthritis and hemophagocytic lymphohistiocytosis / macrophage activation syndrome.[1,2] The cause may be increased synthesis due to genetic or acquired effect usually seen in diseases like malignancies, hyperferritinemia-cataract syndrome. This may also be due to increased release from damaged cells eg. in acute myocardial infarction, liver disorders. However, making a definitive diagnostic link between a markedly elevated serum ferritin determination and a specific diagnosis, rheumatologic or otherwise, can be challenging as the manifestations of these diseases are often protean and can easily be mistaken for other conditions such as sepsis with multiple organ failure or malignancy. [2,3]
A markedly elevated serum ferritin level has been associated with inflammatory disorders, however, can also be caused by a wide variety of disparate conditions, often with impressively high serum levels.

OBJECTIVE:
The aim and objective of this research was to investigate the underlying aetiology of markedly elevated ferritin levels (≥1000 ng/ml) in a group of patients treated as outpatients or inpatients at a tertiary health care centre in eastern zone of India.

MATERIALS AND METHODS:
This was a retrospective observational study. The study was done at a tertiary health care centre in eastern zone of India. Data of all out and inpatients from January 2016 to December 2017 with at least 1 serum ferritin level greater than 1000 ng/ml were reviewed. If a patient had multiple

qualifying levels, the highest one was considered. For each case, the most likely cause of the elevated ferritin was assessed based on the available clinical data from medical record department. The ferritin was done by Electrochemiluminescence Immunoassay (ECLIA) method. The reference value is 10-200 ng/ml.

Results are expressed as percentage.

RESULTS:

In duration of two years of study, 944 patients were found to be investigated for serum ferritin levels out of which 114 patients had serum ferritin levels ≥ 1000 ng/ml. A total of 21 patients were in age of less than 16 years and 93 were ≥ 16 years (16–80 years). A total of 48(42.1%) were male whereas 66(57.9% female (Figure-1). Out of total 114 patients with higher ferritin levels, significant data was not found for 53 (46.49%). The high ferritin levels were noted with Chronic kidney disease (CKD)-29(25.43%), chronic liver disease-8(7%), thalassemia-6(5.26%), severe anemia-6(5.26%), cardiac failure-6(5.26%), infection 4(3.5%) and autoimmune disorders-2(1.75%) (Figure-2).

Figure-1: Percentage distribution of hyperferritinemia among male and female

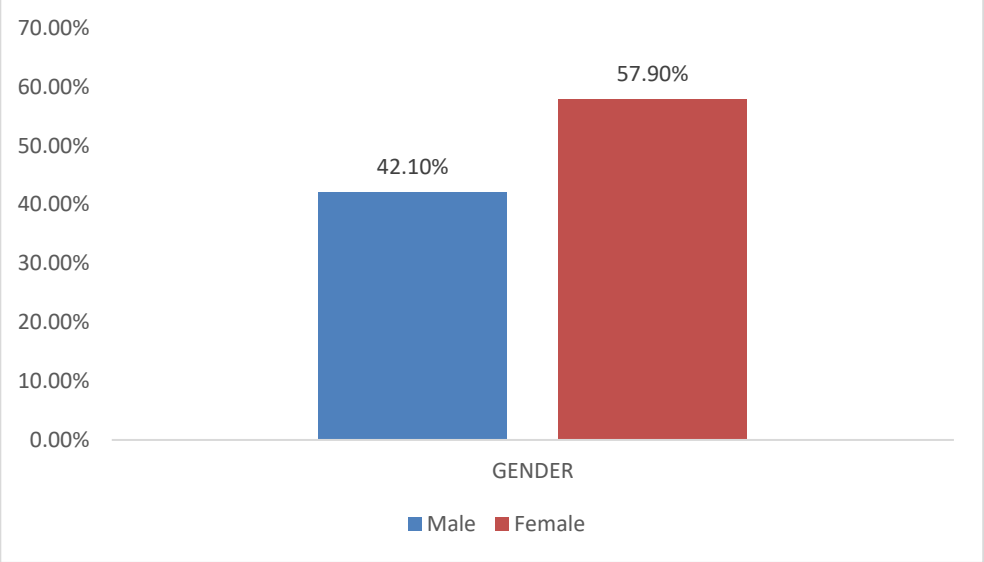
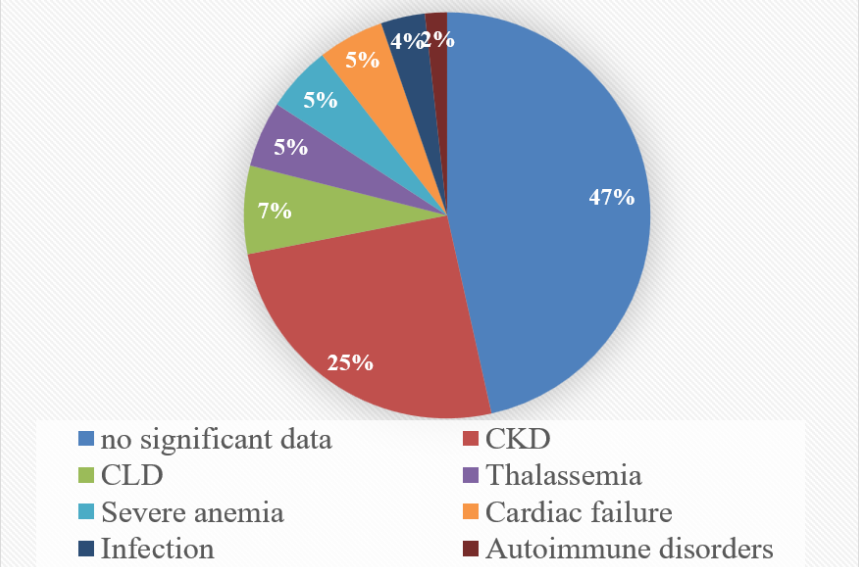


Figure-2: Percentage distribution of different disorders among patients with hyperferritinemia



DISCUSSION:

In current study presence of CKD was found 25% of patient with hyperferritinemia. In study by Hee-Taik Kang et al[2] higher prevalence risk of CKD in Korean males than females were noted. Reports of recent studies reveal association of oxidative stress and chronic inflammation in CKD [2]. Oxidative stress and inflammation act synergistically in development and progression of CKD. Inflammatory response in the form of chemokines and inflammatory markers like TNF- alpha is increased by oxidative stress like iron overload. On the other hand, the pro- inflammatory response results in further generation of oxidative stress.

Rosario et. al.; in 2013 [4] found markedly increased level of serum ferritin in rheumatological and inflammatory disorders and **Allen et. al**.; in 2008 [6] observed, statistically significant higher level of serum ferritin (>10 000 µg/l) in haemophagocytic lymphohistiocytosis (HLH) and inflammatory diseases. **Schram et. al; in 2015** [5] also found higher level of serum Ferritin > 10 000 µg/l in chronic kidney diseases (65%), hepatic cellular infections (54%), viral infection (46%) and haematological malignancy (32%).

Miriam Sandnes et. al.; in 2021, [7] reported the raised level of serum ferritin >500 µg/l in various disorders like unspecific infections (44.8 %), HIV infection (0.8 %), heamtological malignancy (12.0 %), Rheumatological/inflammatory disease (6.3 %), hepatocellular injury (20.3 %), renal failure (20.2 %), haemophagocytic lymphohistiocytosis (1.4 %) and serum ferritin level >1000 µg/l in various disorders of adult population like HIV infection (16.8 %), heamtological malignancy (17.9 %), hepatocellular injury (20.00 %), renal failure (17.9 %), haemophagocytic lymphohistiocytosis (10.5 %) and other cases (7.3 %) were found.

Lisa B. VanWagner and Richard M. Green in 2014 [8] observed >1000 µg/l level of serum ferritin in inflammatory disorders, liver injury and autoimmune diseases. Numerous Studies show that in patients with hereditary hemochromatosis, a ferritin level more than 1000 µg/L is linked to a significant prevalence (20%–45%) of severe fibrosis and cirrhosis.

Peng Cao et. al.; in 2020, [9] observed elevated serum ferritin level in severe disease (50%) and in liver injury (52.3 %) as compared to healthy subjects and p value was less than 0.05 which was statistically significant.

WeiLin Mao et. al.; in 2015,[10] reported elevated level of serum ferritin in liver cirrhosis and positive correlation with liver enzymes as compared to healthy individuals, which was statistically significant (p value <0.01). According to them serum ferritin is also associated with viral infection and inflammatory disorders.

Iron overload can result in lipid, protein, and nucleic acid peroxidation and in reactive oxygen species in the circulation decreases antioxidant activity, such as glutathione peroxidase, and increases lipid peroxidation, causing the oxidation of proteins and nucleic acids. Iron-related oxidative stress can catalyze the conversion of superoxide and hydrogen peroxide to more potent oxidants, such as hydroxyl radicals or ferryl or perferryl species, by Fenton-type reactions. The regulatory system of ferritin is sensitive to general oxidative status in addition to iron level. As ferritin is an acute phase protein, its level is elevated under acute and chronic inflammatory environments, independent of iron status. The H-ferritin gene is expressed by pro-inflammatory cytokines such as tumor necrosis factor-alpha and interferon-. Thus, ferritin can be used as a surrogate marker and connecting link between iron storage and inflammatory status. High ferritin level implicates iron overload, resulting in oxidative stress, and also reflects inflammation.

Higher iron levels are present not only in patients with hereditary hemochromatosis, but also in those with alcoholic liver disease, non-alcoholic fatty liver disease, and hepatitis C viral infection. The liver plays a critical role in the regulation of iron levels, particularly through production of

hepcidin. In patients with chronic liver disease, iron metabolism changes result in iron overload. This is believed to occur mostly due to low levels of hepcidin. Iron deposits .and NTBI are responsible for further damage to the liver by inflicting oxidative stress on hepatocytes

CONCLUSION:

Although extremely elevated ferritin levels may be associated with rheumatologic diseases, more often they are found in patients with other conditions such as malignancy or infection. In addition, extremely high ferritin levels can be found in patients with seemingly indolent disease or levels of chronic inflammation.

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