Causes of Hyperferritinemia in Qatar

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Abstract:
To assess the causes of high serum ferritin (over 1000 nanogram/ml) the records were reviewed of 145 samples of blood with ferritin levels over 1000 ng/ml taken in 2004 at Hamad Medical Corporation. The most common causes of hyperferritinemia in Qatar were found to be: end-stage renal failure, thalassemia major and sickle cell disease.

Introduction:
Ferritin is a globular protein complex consisting of 24 protein subunits and is the main intracellular iron storage protein in both prokaryotes and eukaryotes, keeping the iron in a soluble and non-toxic form. Ferritin is found principally in the intestinal mucosa, spleen, and liver, functioning as the primary form of iron storage in the body.(1) Ferritin that is not combined with iron is called apoferritin. Ferritin behaves as an acute phase reactant in various disease states such as rheumatoid arthritis, both adult and juvenile Still's disease, infections, and systemic lupus erythematosus.(2) Ferritin levels are high in patients with hemochromatosis, other liver diseases, alcoholism, renal diseases, malignancies, in patients who have had multiple transfusions, infection, and Still's disease.(3)

We studied the files of all patients at our hospital who had high ferritin levels above 1000ng/ml during the year 2004.

Methods and Patients:
Laboratory records were used to produce a list of patients with ferritin levels at or above 1000ug/l and the medical records of those patients were reviewed. For outpatients the diagnosis at the time when the ferritin level was measured was considered as the diagnosis and for inpatients the diagnosis at discharge was considered as the diagnosis.

Results:
There were 145 blood samples (68 male; 77 female) with ferritin levels above 1000 ng/ml. Seventy-two patients (50%) had end-stage renal failure (ESRF) with ferritin levels ranging from 1011 to 3225 ng/ml and an average ferritin level of 1421 ng/ml. Forty-seven patients (33%) had thalassemia major with ferritin levels ranging from 1062 to 17992 ng/ml and an average ferritin level of 3662 ng/ml. Nine (6%) had sickle cell disease with ferritin levels ranging from 1391 to 5366 ng/ml. Sixteen patients (11%) had other diagnoses, including two with thyrotoxicosis (1044 ng/ml and 1061 ng/ml); four with myeloproliferative disorders (1346-5040 ng/ml; average 2853 ng/ml); two with chronic alcoholism (1236 ng/ml, 1140 ng/ml); three with Hodgkin's disease (14,667ng/ml, 2087ng/ml, 1223ng/ml); three with juvenile Still's disease (1382 ng/ml, 2756 ng/ml, 3590ng/ml; average 2570 ng/ml) and two with adult Still's disease (4360ng/ml, 37129ng/ml).

Discussion:
Serum ferritin levels are usually measured as part of an iron studies workup for anemia. Normal blood levels are 12-300 ng/ml for males and 12-150 ng/ml for females. The causes of markedly raised ferritin levels are multiple and tests to determine serum ferritin levels are frequently requested.

An increased ferritin level occurs in iron excess and in iron overload from hemochromatosis or hemosiderosis; oral or parenteral iron administration; inflammatory diseases; acute or chronic liver disease involving alcoholism; acute myeloblastic or lymphoblastic leukemia; other malignancies (Hodgkin's disease, breast carcinoma, malignant lymphoma); hyperthyroidism; hemolytic anemia, megaloblastic anemia, thalassemia.(1)

In a clinical setting not every patient with these diseases is tested for ferritin but when certain patients are tested the ferritin level will support the diagnosis or treatment.
Clinicians might not be aware of all the reasons for markedly elevated levels of ferritin and the relative frequencies of these different cases that vary in regions of the World and might miss a potentially important factor in diagnosis.

Different levels of ferritin have been used in different studies of the etiology of hyperferritinemia. Our study focused on the conditions in patients found to have a ferritin level above 1000 ng/ml; we did not look at initial indications for checking serum ferritin level but at the final diagnosis.

In contrast to other studies, we found the most common cause of a high ferritin level (50%) was end-stage renal failure. The ferritin levels in this group of patients ranged between 1011-3225 ng/ml. It is known that in patients undergoing regular hemodialysis the serum ferritin levels are higher than those of healthy people even in the absence of iron therapy other than blood transfusion and it provides useful estimates of bone marrow iron stores.

The second common cause (33%) was thalassemia major with a ferritin range of 1062-17992 ng/ml. Ferritin is frequently tested in thalassemic patients to monitor the status of iron overload secondary to repeated blood transfusion.

Patients with sickle cell disease accounted for six per cent of our patients with elevated ferritin while the remaining 11% included patients with thyrotoxicosis (two patients), malignancy (four patients with myeloproliferative disorders and three Hodgkin’s), alcohol intake (two patients) and five patients with Still’s disease; three juvenile and two adults.

The level of ferritin did not discriminate between the group of diseases; one patient with thalassemia had a ferritin level of 17,992 ng/ml and most patients with end-stage renal failure, malignancy and Still’s disease had ferritin levels between 1000-5000 ng/ml.

Hearnshaw et al examined the demographic and medical data for all patients over eight years of age who had serum ferritin levels recorded as >=1500 ng/mL during the period January to September 2002 in the teaching hospital in Newcastle-upon-Tyne (UK) and found that the most common single cause for a high ferritin level was alcoholic liver disease in the local population and renal failure was the most common single cause in the overall population.

LePage et al evaluated the causes of high ferritin in patients with a serum ferritin level higher than 600 ng/ml between 15 November 2003 and 15 January 2004; the causes were: non–HIV systemic infections (23.8%), hematological diseases (16.1%), alcoholism (11.2%) and malignancies (9.8%). Serum ferritin levels were between 600 and 1000 microg/l for 50 patients, between 1000 and 1500 microg/l for 24, and over 1500 microg/l for 24. There was no significant difference in the etiological distribution between the three groups.

A.Gilles et al reviewed retrospectively the medical charts of 1,111 consecutive patients at the University of Brussels Hospital; (M: 625; F:486; median age 58 y) with hyperferritinemia and/or a transferrin saturation (TfSat >45%). Of 1,111 patients 311 (38%) had SFL between 500 and 1000 ng/ml; most of them presented with metabolic syndrome, inflammatory processes and low grade tumors. SFL over 1500 ng/ml accounted for 5.3% (59 patients) and were mainly associated with infectious or inflammatory diseases or hepatic disorders. SFL over 1500 ng/ml were mainly associated with solid tumors (the more elevated the SFL the more extended the neoplasia).

Yenson PR et al did a retrospective case review of 80 patients of Asian ethnicity referred to three subspecialties in a tertiary care teaching hospital between January 1997 and March 2005 for assessment of hyperferritinemia. Only four patients (5%) had iron overload on liver biopsy or quantitative phlebotomy. Forty nine patients (61%) had liver disease; 16 of those patients also had viral hepatitis. Thirteen patients fulfilled the criteria for insulin resistant syndrome. Thirty four percent of the patients had unexplained hyperferritinemia.

The list of causes of high ferritin in our study may not reflect accurately the causes of hyperferritenemia at our hospital because not every patients with a disease that would be associated with hyperferritenemia had ferritin measured. Our study focused on the conditions found in patients with a ferritin level above 1000 ng/ml. We did not look at the initial indication for checking serum ferritin level but at the final diagnosis.

Conclusion:

We conclude that the most common cause of hyperferritenemia in Qatar is end-stage renal failure, followed by the thalassemia major and sickle cell disease. The level of hyperferritenemia does not discriminate between the different groups of diseases.

Table 1: The different causes for raised ferritin levels in Qatar

<table>
<thead>
<tr>
<th>Cause</th>
<th>Number of patients/%</th>
<th>Range of ferritin level</th>
<th>Average ferritin level</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-stage renal failure</td>
<td>72 (50%)</td>
<td>1011-3225 ng/ml</td>
<td>1421 ng/ml</td>
</tr>
<tr>
<td>Thalasemia</td>
<td>47 (33%)</td>
<td>1062-17992 ng/ml</td>
<td>3662 ng/ml</td>
</tr>
<tr>
<td>Sickle Cell</td>
<td>9 (6%)</td>
<td>1319-5366 ng/ml</td>
<td>3397 ng/ml</td>
</tr>
<tr>
<td>Still’s Disease</td>
<td>5 (3.5%)</td>
<td>1382-37129 ng/ml</td>
<td>9845 ng/ml</td>
</tr>
<tr>
<td>Malignancy</td>
<td>7 (5%)</td>
<td>1346-14667 ng/ml</td>
<td>5410 ng/ml</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>2 (1.5%)</td>
<td>1140-1236 ng/ml</td>
<td>1188 ng/ml</td>
</tr>
<tr>
<td>Thyrotoxicosis</td>
<td>2 (1.5%)</td>
<td>1044-1061 ng/ml</td>
<td>1053 ng/ml</td>
</tr>
</tbody>
</table>
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References:

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