Serum ferritin concentration in sickle cell crisis

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SUMMARY Serum ferritin, aspartate aminotransferase (AST), alkaline phosphatase and hydroxybutyrate dehydrogenase (HBD) were studied during 21 vaso-occlusive crises in 12 adults with sickle cell disease (11 SS, 1 SβSP). The patients comprised three groups: those who had been untransfused (4), those who had received occasional exchange transfusion in crisis (3), and those who had been multiply transfused (5). Serum ferritin concentrations in crisis were compared with those of the steady state value.

Rises in serum ferritin concentrations occurred in all crises in all groups. Although AST, alkaline phosphatase, and HBD rose, there was no correlation between these and log ferritin concentrations. The clinical impression was that the degree of rise in ferritin related to the severity of the particular crisis, and the above results showed that haemolysis and liver damage were not causally related to this rise.

An estimate of serum ferritin cannot be used to assess the state of iron balance in sickle cell disease unless the patient is in the steady state. The considerable rise in serum ferritin concentration found in crisis, however, may be a useful marker of the extent of vaso-occlusion and tissue damage.

Traditional belief is that, as a result of increased gastrointestinal iron absorption due to chronic haemolysis and sporadic transfusion, patients with sickle cell anaemia develop iron overload.1,2 Some recent studies have shown that iron deficiency is not uncommon in sickle cell disease and that iron overload is only associated with hypertransfusion.3–7

The difficulty in assessing the state of iron balance in sickle cell anaemia has been shown: transferrin saturation, mean corpuscular volume, free erythrocyte protoporphyrin, and marrow iron stores have all been shown to have drawbacks.2,4,6,7 Low serum ferritin concentrations show iron deficiency, but conflicting results have been found in patients who have been transfused. Some groups found that serum ferritin concentrations correlated well with the number of units of blood transfused,2,4,6,7 and others did not find this to be the case.1 Several factors occurring in sickle cell anaemia may increase serum ferritin concentration. Liver disease and chronic infection or inflammation are well recognised associations.

We report a study of serum ferritin concentrations in the steady state of sickle cell disease and during vaso-occlusive crises. Aspartate aminotransferase (AST), alkaline phosphatase, and hydroxybutyrate dehydrogenase (HBD) were also measured in crisis in an attempt to estimate concurrent liver damage and the severity of haemolysis.

Material and methods

A prospective study of 21 vaso-occlusive crises in 12 adults with sickle cell disease (11 SS, 1 SβSP) was made. Serum taken on the same day was measured for ferritin, AST, alkaline phosphatase, and HBD. Steady state ferritin measurements were obtained from samples taken in the outpatient department when the patients were well and asymptomatic.

Serum ferritin was determined with Becton Dickinson radioimmunoassay kits, using a modification of the method described by Addison et al (1972).8 Aspartate aminotransferase, alkaline phosphatase, and hydroxybutyrate dehydrogenase were measured using standard Behringer Manheim Diagnostica reagents.

Coefficients of correlation were calculated using log ferritin values.

Results

In 12 patients with sickle cell disease 21 vaso-occlusive crises occurred. Of these 21 crises, 10 affected bones alone; six bone and chest; three bone, chest, and abdomen; and two bone and abdomen. There was considerable variation in the severity of
Rise in serum ferritin concentrations in crises from steady state in each group. Group I: patients who had been untransfused, group II: those who had occasionally been transfused, group III: those who had been hypertransfused.

these episodes.

The patients were divided into three groups: group I, four patients who had never been transfused; group II, three patients who had occasionally been exchange transfused in crisis; group III, five patients who had had numerous exchange transfusions in crisis, or who had had prolonged periods of hypertransfusion.

The Figure shows the ferritin increment in crisis in each patient. The three groups have been separated and log ferritin in steady state compared with the concentrations during the crises. A high rise in ferritin concentration is shown in each group. Two cases highlight this. A 17 year old girl in group II had a steady state ferritin of 109 µg/l that rose to 1979 µg/l during severe bony and chest crisis. A 23 year old man in group III had a steady state ferritin of 356 µg/l that rose to 2778 µg/l during a severe bone, abdominal, and chest crisis. During a less severe bony and abdominal episode in the same man the ferritin concentration reached 791 µg/l.

The rises in serum ferritin concentrations varied between crises in each patient, and the overall clinical impression was that the highest ferritin concentrations were associated with the most severe clinical states.

As raised ferritin concentrations are associated with liver disease and increased haemolysis, a simultaneous correlation between ferritin concentrations and AST, alkaline phosphatase, and HBD was sought. Although high values were invariably found, no correlation was found between ferritin and AST ($r = 0.0109$), alkaline phosphatase ($r = 0.183224$) or HBD ($r = 0.0404$). Thus neither liver damage nor haemolysis seemed to account for the severe rise in ferritin.

Discussion

Our results show that an increase in serum ferritin
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concentration occurs during sickle cell crisis. This is often of such a degree that the “crisis” ferritin concentration would suggest severe iron overload. It is therefore invalid to use ferritin as a “measure” of the state of iron balance in anything other than the steady state of sickle cell disease. Perhaps previous reports of iron overload in such patients have been overestimated, if samples have been taken during crises. Samples of ferritin taken during crises may in part explain the absent iron stores in the marrow associated with the raised serum ferritin concentrations found by Peterson et al. In three recent studies, in which the samples were stated to have been taken during the steady state, raised ferritin concentrations were not found in untransfused patients, and in transfused subjects the concentrations were lower than would be expected in similarly transfused thalassaemic patients.

Many patients with sickle cell disease have their state of iron balance assessed only in crisis when transfusion is anticipated and a “baseline” pre-transfusion ferritin value is desired. The above results invalidate this practice. If our clinical impression is correct—that is, the highest rises in ferritin concentration occur in the most severely ill patients—then measurement at this time is even more inappropriate. Assessment of the degree of iron overload and need for chelation treatment can be made only on the steady state values in combination with other procedures (such as liver biopsy, desferrioxamine excretion test, etc).

We found no correlation between the degree of haemolysis (as measured by HBD), or liver damage (AST and alkaline phosphatase) and ferritin concentrations. We cannot therefore assume that liver damage is the main cause of this rise in ferritin. Unfortunately, we were unable to measure isoferritins and so have no guide to the source of the ferritin measured. As these rises occur in vaso occlusive episodes in which bony pain, chest syndrome, and abdominal crises are all thought to have an ischaemic origin, it is not unreasonable to assume that the source of the ferritin is from tissue necrosis. Gregg et al showed that bone and marrow necrosis in rabbits caused a substantial rise in serum ferritin and suggested that this was due to marrow infarction. This would conform with our clinical observations. The severity of a sickle cell crisis is very often a subjective assessment. If ferritin concentration, or degree of rise above steady state, gave an objective measure of tissue damage it could be useful in the clinical assessment of individual patients.

Further studies are required to tabulate the pattern and time scale of the ferritin rise and fall, and studies of isoferritins are required to delineate the source of this phenomenon.

We conclude that ferritin concentration, which is one of the most useful tools in the measurement of the state of iron balance, rises considerably in sickle cell crisis. Measurements of ferritin to assess the state of this balance are only useful if performed in the steady state patient.

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References


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