Iron overload despite partial gastrectomy

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Summary
Iron overload was found in 3 patients who had undergone partial gastrectomy: a 61-year-old woman developed iron overload because she may have had idiopathic haemochromatosis and had also been given parenteral iron; in a 62-year-old man with thalassaemia minor, iron overload may have developed because of increased oral iron ingestion, low serum folate, increased, albeit ineffective, erythropoiesis and sideroblastic anaemia; a 74-year-old man with thalassaemia minor developed iron overload without exogenous therapy and died from a hepatoma. These cases illustrate that partial gastrectomy fails to protect patients from developing iron overload, particularly if given uncontrolled iron therapy.

Introduction
Iron deficiency anaemia is a common finding after gastric operations (Harkins and Nyhus, 1969). This may be due to defective diet (McLean Baird and Wilson, 1959), blood loss (McLean Baird and Sutton, 1972), and decreased absorption of food iron (Turnbull, 1965). Consequently, administration of prophylactic iron following partial or total gastrectomy has been justified (Dagg, 1974).

Iron overload may be acquired by absorption of inappropriate quantities of iron from the gut, excessive oral iron intake, or parenterally by blood or iron infusions. Three patients who underwent gastric surgery and later developed iron overload are described. Two patients had thalassaemia minor, one of whom had excessive iron treatment, and the third patient was given excessive parenteral iron.

Menstruation may protect females from developing haemochromatosis but does not always prevent its development (Sherlock, 1975). Similarly these cases illustrate that partial gastrectomy may fail to protect patients from developing iron overload, particularly if given uncontrolled iron therapy.

Case 1
A 61-year-old woman presented with 6 months’ history of tiredness, vagueness and loss of memory. Twenty-three years previously she had had a partial gastrectomy for uncomplicated duodenal ulceration. One year later she had been given 2 injections/week of iron dextran for some weeks, followed by one injection/week for more than one year. Then she was given intermittent oral iron treatment but no exact details were obtainable. Three years after surgery her menses stopped at the age of 41 years. They had been heavy and lasted for 4-5 days. She was infertile. She had never noticed any skin changes although her relatives had noticed her colour had changed about 10 years before admission.

She weighed 47·2 kg and had grey fine wrinkled skin. Her liver was firm and palpable 3 fingers below the costal margin.

Haemoglobin was 13·3 g/dl, MCV 101 fl, MCH 34·9 pg, WCC 6·6 × 109/l, platelets 200 × 109/l. Serum folate was 8·8 μg/l and B12 740 ng/l. Plasma iron was 37 μmol/l. Total iron-binding capacity (TIBC) was 38 μmol/l, and serum ferritin 3586 μg/l (normal, 15-250 μg/l). Total bilirubin was 10 μmol/l, prothrombin index 1·2 and aspartate transaminase 104 u./l. Plasma thyroxine, TSH and morning cortisol were normal, but the gonadotrophins were low, FSH being 0-4 u./l (normal range for amenorrhoea, 1-10 u./l) and luteinizing hormone 2 u./l (normal range for amenorrhoea, 1-21 u./l). The glucose tolerance test was diabetic (fasting blood sugar, 4·6 mmol/l; 1 hr, 12·5 mmol/l; 2 hr, 10·6 mmol/l). A liver biopsy showed that the liver architecture was destroyed with fibrous tissue breaking the liver into regenerative nodules. There was extensive free iron deposition in Kupffer cells, portal tract macrophages, liver cells and bile duct epithelium, Scheuer grade IV (Scheuer, Williams and Muir, 1962). The liver iron concentration was
32 μmol/100 mg dry tissue (mean normal liver iron concentration, 1-4 μmol/100 mg dry tissue). Her tissue type was A1,B17.

Her brother (64 years) had ischaemic heart disease, treated with oxprenolol. He was never a heavy drinker and had not had any iron treatment or transfusions. Haematological tests were normal. His plasma iron was 14 μmol/l, TIBC 51 μmol/l, saturation of transferrin, 28%, but serum ferritin was 800 μg/l. Liver biopsy showed iron deposition in parenchymal and Kupffer cells (Scheuer grade I) and his liver iron concentration was 66 μmol/100 mg dry tissue. His tissue type was A1, B17.

A3, --

Case 2

First admission

A 66-year-old retired painter was referred from another hospital with dyspnœa on exertion, fatigue, poor appetite and depression. He was English with no history of Mediterranean ancestors. Nineteen years previously he had developed a duodenal ulcer, which was treated medically. His haemoglobin (Hb) was 11·5 g/dl. Three years later exacerbation of the ulcer necessitated a Hofmeister/Pólya (medium high) partial gastrectomy. He was transfused with one pint of blood. Nine years before admission he had developed paraesthesiae in his hands and feet. His Hb was 9·5 g/dl, the blood film showing macrocytosis with hypochromia. He was given vitamin B12, folate, ascorbic acid and oral iron for 2 years with only partial response, then 50 ml of intravenous iron (ferriovenin), followed by 2 more years of oral iron and folate acid. Six years before admission his liver was felt 3 fingers’ breadth below the costal margin. His Hb was 11·7 g/dl. Target cells and hypochromic cells were seen on the blood film. Serum iron was 11 μmol/l and TIBC was 55 μmol/l.

Five years before his first admission to the London Hospital he developed acute cholecystitis. After this he ceased to attend out-patients and stopped taking his haematinsics. One month before admission he was admitted to another hospital with depression and fatigue. He was given oral iron, folic acid and parenteral vitamin B12.

He had smoked 20 cigarettes/day for the past 50 years and drank about 10–15 pints of beer/week. He shaved about once every 3 days.

The patient was thin and pale grey, with normal pubic and axillary hair. His liver was enlarged 4 fingers’ breadth below the costal margin and tender.

The Hb was 10·4 g/dl. Red cells showed anisocytosis, poikilocytosis and hypochromia. Target cells were noted. ESR was 10 mm/hr and WCC 4·1 × 10⁹/l. Reticulocyte count was 2·2%. Serum iron was 25 μmol/l, serum folate 2·7 μg/l, vitamin B12 180 ng/ml and vitamin C 1·8 mg/100 ml (normal).

The marrow aspirate showed active erythropoiesis with intermediate megaloblasts, frequent sideroblasts and some ring forms, and increased iron storage. Schilling test, liver function tests, urea and electrolytes, cholesterol, thyroid function tests, pituitary function tests and fat excretion were normal. Chest X-ray and pulmonary function tests confirmed the presence of chronic obstructive Airways disease. The patient was treated with ferrous gluconate, folic acid and pyridoxine and discharged.

Second admission (4 months later)

In the interim, the Hb was virtually unchanged. The patient was still tired and short of breath. There were no new signs.

The Hb was 10·3 g/dl and reticulocyte count 4%. Hb–A2 was 4% and Hb–F 4%. Serum iron was 12 μmol/l and TIBC 43 μmol/l. Liver biopsy showed marked haemosiderosis in Kupffer and parenchymal cells (Scheuer grade IV) without cirrhosis.

The urinary excretion of iron after one g of desferrioxamine i.m. was 2·3 mg in 24 hr (normal, <1 mg). Plasma iron turnover was 1·46 mg/day/100 ml blood (normal, 0·6 mg/day/100 ml blood ± 30%). At 14 days 51% of injected radio-iron was utilized (normal, 70–90%). In vivo counting showed a normal pattern of iron appearance in sacrum and liver but increased uptake in spleen from day one to 14.

All medication was stopped before his discharge. However, the patient did not attend out-patients. He died 2 years later with disseminated prostatic cancer. Permission for post-mortem was refused.

The diagnosis of β-thalassaemia minor was subsequently made in one son, one daughter and 4 grandchildren. One daughter and 5 grandchildren were normal.

Case 3

First admission (January 1975)

A 74-year-old retired docker was admitted with an acute exacerbation of his long-standing chronic bronchitis. Eighteen years previously he had had a Pólya gastrectomy for peptic ulcer. At no time did he receive oral iron or blood transfusion and he was not a heavy drinker. A distant ancestor was French.

He was grey, pale and weighed 46 kg. A smooth non-tender liver was palpable 2 fingers’ breadth below the costal margin.

Haemoglobin was 6·9 g/dl, MCV, 87 fl and MCH, 26 pg. The blood film showed moderate anisocytosis, poikilocytosis and hypochromia with many schistocytes and target cells. Hb–A2 was 4% and Hb F 4·2%. Serum folate was 0·6 μg/l and vitamin B12 110 ng/l. The bone marrow revealed megaloblastic...
erythropoiesis. The anaemia was attributed to nutritional deficiency related to partial gastrectomy and thalassaemia minor. Serum iron was 37 \( \mu \text{mol/l} \) and total iron binding capacity 40 \( \mu \text{mol/l} \). Liver biopsy demonstrated normal architecture with severe iron deposition (Scheuer grade IV). Treatment included transfusion of 6 units of blood, parenteral vitamin B\(_{12}\) and folic acid.

Three of the patients’ 4 children and 6 grandchildren had thalassaemia minor with microcytosis and raised Hb-A\(_{2}\).

Second admission (November 1976)

He presented with continuous sharp right upper quadrant pain of one month’s duration. He weighed 42 kg and was icteric. The liver had enlarged into the right lower quadrant and was hard, knobbly and tender.

Haemoglobin was 12-6 g/dl, MCV 61 fl, MCH 22 pg and MCHC 34g/dl. Serum iron was 19 \( \mu \text{mol/l} \), folate 5-4 \( \mu \text{g/l} \) and vitamin B\(_{12}\) 1320 ng/l. Ferritin was high at 3593 \( \mu \text{g/l} \). Total bilirubin was 40 \( \mu \text{mol/l} \), direct bilirubin 19 \( \mu \text{mol/l} \), aspartate transaminase was 69 u/l and alkaline phosphatase 271 u/l. Prothrombin ratio was 1-2. Australia antigen was not detected. Alpha-fetoprotein test was positive.

Liver scan revealed multiple filling defects. Liver biopsy showed both severe iron overload (Scheuer grade IV) in Kupffer and parenchymal cells, without cirrhosis, and hepatocellular carcinoma. Liver iron was 9-83 \( \mu \text{mol/100 mg dry weight} \) (mean normal liver iron 1-4 \( \mu \text{mol/100 mg} \)) and hepatoma iron 0-9 \( \mu \text{mol/100 mg} \).

The patient died of bronchopneumonia 3 weeks later.

Post-mortem. The liver weighed 3050 g; the parenchyma was largely replaced by nodules of tumour up to 15 cm diameter, some of which were necrotic. There was a dramatic blue colouration of parenchyma with potassium ferrocyanide. Microscopy confirmed the biopsy findings. Hepatoma had invaded the hepatic vein and deposited in lung parenchyma. Tumour emboli were found in the pulmonary artery and left ventricular wall. Large amounts of iron were present in the pancreas, spleen and marrow. The bone marrow was widened and contained red marrow throughout its length.

Discussion

These 3 patients show that partial gastrectomy, despite its association with iron deficiency anaemia (Harkins and Nyhus, 1969), fails to protect patients from developing iron overload.

Case 1 probably had idiopathic haemochromatosis because her brother had early iron overload without obvious cause. The genetic tendency to iron overload was exacerbated by exogenous iron therapy but not prevented by menstruation or partial gastrectomy. Simon et al. (1977) suggested that HLA typing in families with haemochromatosis could provide a means of early detection of subjects at risk before the appearance of any sign of iron overload, because there was a significant association between the presence of haemochromatosis and the possession of the same 2 HLA haplotypes. In the present instance one of the patient’s haplotypes is different from those of her brother.

Iron overload is a frequent complication of homozygous thalassaemia but is not usually a feature of thalassaemia minor, as occurred in the second and third cases. Case 2 was unusual in that the patient was an Englishman with thalassaemia minor, who developed iron overload, which was exacerbated by exogenous iron therapy, but not prevented by partial gastrectomy. The absorption of iron given as ferrous sulphate, with the patient fasting, is not altered by partial gastrectomy (McLean Baird and Wilson, 1959). Furthermore, the impaired absorption of iron, when taken with a meal, is not observed in all patients who have had a partial gastrectomy (Turnbull, 1965; Kimber, Patterson and Weintraub, 1967) and is more common when a duodenal blind loop is present (Hanngren, Hedenstedt and Reizenstein, 1967). While it is reasonable to conclude that absorption of iron was not impaired in the 3 patients, inappropriate absorption of iron has not been demonstrated in thalassaemia minor (Weatherall and Clegg, 1972). However, patients with thalassaemia may continue to absorb iron even when iron laden (Bannerman et al., 1964).

The increased plasma iron turnover and reduced utilization of radio-iron are consistent with increased erythropoiesis, much of it ineffective, as has been seen in thalassaemia minor (Pearson, McFarland and King, 1960). Several case reports of an association between cirrhosis with iron overload and folic acid deficiency have suggested that such deficiency may be responsible for increased absorption and hepatic deposition of iron (Greenberg and Grace, 1970). Folic acid deficiency has been described in thalassaemia minor and has been detected in 12\% of one series of randomly selected patients after partial gastrectomy, although usually in association with iron deficiency (Deller, Ibbotson and Crompton, 1964). The second patient’s marrow showed megaloblastic change which was probably due to folate deficiency, despite previous treatment with folic acid. It also showed sideroblasts with some ring forms. Sideroblastic anaemia had been described following partial gastrectomy (MacGibbon and Mollin, 1965).

Thus, the iron overload in this patient might be ascribed to increased ingested iron, low serum folate (due to the thalassaemia minor and partial gastrec-
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tomy), increased erythropoiesis and sideroblastic anaemia. On the present evidence it is not possible to rule out the coincidence of idiopathic haemochromatosis.

The third case is believed to be unique because of the association between thalassaemia minor, iron overload, without exogenous iron therapy, and hepatoma. It is surprising that this patient with hypochromic microcytic anaemia never received iron therapy following his gastrectomy. Nonetheless the gastrectomy failed to protect this patient from the complications of iron overload. As with the previous case, increased but ineffective erythropoiesis and the low serum folate may have contributed to increased iron absorption. Bowdler and Huehns (1963) have described 2 cases of haemosiderosis in siblings with thalassaemia minor. They suggested that the abnormality might be ascribed to the presence of 2 abnormal genes, one causing thalassaemia minor and the other haemochromatosis. A study of the iron metabolism of the descendants of Case 2 and Case 3 should help in defining the relationship between excess iron absorption and thalassaemia minor.

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References

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