Congenital sideroblastic anaemia in two girls

G Dolan, M M Reid

Abstract

Transfusion dependent congenital sideroblastic anaemia occurred in infancy in two unrelated girls. One girl developed early organ failure which was not prevented by standard chelation treatment. The combination of modest iron burden and putative intrinsic mitochondrial dysfunction could have accounted for the clinical picture. The other girl remained well, receiving regular transfusion and standard chelation treatment. She had normal liver function and no other evidence of organ damage. The syndrome is unlikely to be due to extreme lyonisation in carriers of the usual X-linked condition.

The contrasting clinical patterns seen in these two patients suggest that transfusion dependent congenital sideroblastic anaemia may comprise a heterogeneous group of disorders. It is suggested that such children be carefully monitored for evidence of increasing iron overload so that organ damage can be prevented.

Congenital sideroblastic anaemia is a rare and usually X-linked disease affecting males. Female carriers may show a dimorphic red cell picture despite a normal haemoglobin concentration. Red cell size distribution can be used to detect carriers in affected females.¹ Females with congenital sideroblastic anaemia are thought either to have inherited a different disease with autosomal inheritance or, in rare cases, to be examples of variations in X chromosome inactivation.² This report describes the disorder in two unrelated girls one of whom developed rapid progression to multiple organ failure while the other so far has had a relatively benign clinical course.

Case reports

CASE 1

A 3 year old caucasian girl presented with severe microcytic anaemia that was unresponsive to oral iron treatment. Bone marrow examination showed erythroid hyperplasia with 50% ring sideroblasts. Congenital sideroblastic anaemia was diagnosed which proved to be transfusion dependent. Mother, father, sister and two brothers had normal blood counts with no anisocytosis. An atrial septal defect was repaired uneventfully. She was unresponsive to pyridoxine and folic acid. The family moved to Newcastle when she was 5. She was pale, slightly pigmented, and had frontal bossing. The liver was enlarged to the umbilicus and the spleen to 6 cm below the

costal margin. The blood film showed anisocytosis with stippled red cells and occasional ring sideroblasts. The karyotype from peripheral blood was normal 46XX. Serum ferritin concentration was 700 µg/l. Height and weight were on the 75th centile. Over four months, during which she received transfusions of 2 units of blood every six weeks, the serum ferritin rose to 1500 µg/l. There was no response to pyridoxal-5-phosphate. Treatment with subcutaneous infusions of desferrioxamine 50 mg/kg was given over eight to 10 hours at night five to six times a week. The ferritin concentration remained stable at about 2000 µg/l. By the age of 7 transfusions had increased to 3 units of blood every five weeks to prevent the haemoglobin concentration falling below 100 g/l.

At the age of 5 years and 8 months she developed tetany and had a grand mal seizure due to hypoparathyroidism. The ionised calcium was 0.6 mmol/l. Oral calcium supplements and alfacalcidol maintained her ionised calcium at 1.0 mmol/l. At the age of 6½ insulin dependent, non-ketotic diabetes developed. By the age of 7 she had developed steatorrhoea and cramping abdominal pain which responded to treatment with pancreatic enzyme supplements. Over the next six months her transfusions became associated with breathlessness and raised jugular venous pressure. Subsequent episodes of congestive failure caused ascites and painful hepatic engorgement. She was managed with thiazides, spironolactone, and frusemide. Routine echocardiographic assessment had been carried out since her earlier heart surgery, and no deterioration in left ventricular function had been noted up to this point. Aged 7 years and 9 months, bradycardia developed during a transfusion. Electrocardiography showed episodes of a Wenckebach phenomenon with periods of total atrioventricular dissociation.

Her liver function tests showed a slow rise in aspartate transaminase activity to 150 IU/l and in alkaline phosphatase activity to 500 IU/l over three years, but her serum albumin concentration remained over 30 g/l for most of her illness. The degree of hepatomegaly decreased until episodes of cardiac failure developed. Splenomegaly did not progress. Adrenal cortical function was normal, she was clinically euthyroid, and her thyroid stimulating hormone was not increased. Her height remained at the 75th centile throughout. In the early months of her ninth year left ventricular function deteriorated. Following a transfusion her heart failure worsened, she became comatose and showed signs of hepatic

Department of
Haematology, The
Children's Hospital,
Sheffield
G Dolan

Department of
Haematology, Royal
Victoria Infirmary,
Newcastle upon Tyne
NE1 4LP
M M Reid

Correspondence to:
Dr M M Reid

Accepted for publication
6 December 1990

failure. She died a week later. Necropsy was not performed.

CASE 2

A caucasian girl presented at the age of 15 months with severe microcytic anaemia (haemoglobin concentration 70 g/l) that was unresponsive to oral and parenteral iron. Her blood film was dimorphic, and she had a reticulocytosis of $160 \times 10^9/l$ with a raised fetal haemoglobin concentration at 16%. Bone marrow examination showed pronounced erythroid hyperplasia and numerous ringed sideroblasts, though her marrow karyotype was normal. Congenital sideroblastic anaemia was diagnosed; she was transfused and given pyridoxine and folic acid. Her father had normal blood indices and her mother was mildly hypochromic. During follow up her haemoglobin concentration fell progressively but initially she tolerated anaemia very well. She was transfused only when her haemoglobin reached concentrations of around 50 g/l which was usually accompanied by symptoms of breathlessness and lethargy. On this basis she required only two to three transfusions a year. Serial serum ferritin concentration was monitored as were her height and weight. By the age of 4 her weight and height had dropped to the 3rd centile and her serum ferritin concentration had risen to 500 $\mu g/l$. She was therefore started on regular transfusions every five to six weeks to maintain her haemoglobin concentration around 100 g/l. Desferrioxamine was also started at a dose of 40 mg/kg over 12 hours, five days each week.

On this regimen she began to grow more rapidly and her serum ferritin concentration remained consistently below 100 $\mu g/l$. Her only problem during subsequent years was of a severe episode of enterocolitis and septicæmia due to *Yersinia enterocolitica* which necessitated surgical removal of the appendix and part of her terminal ileum, and prolonged treatment with antibiotics. This infection may have been a complication of her transfusion/chelation treatment as there have been reports of desferrioxamine promoting infections with this organism.³

At the time of writing she is 10 years old, well, her growth is satisfactory and there is no evidence of organ dysfunction.

Discussion

Both these girls were diagnosed in infancy with severe microcytic anaemia that was unresponsive to iron. Both received regular transfusions from the age of 3 to 4, but case 1 had already developed hepatosplenomegaly and frontal bossing by this time. Despite regular chelation treatment she developed parathyroid, pancreatic (endocrine and perhaps exocrine), and cardiac failure before the age of 8; case 2 developed no evidence of organ damage.

Case 1 was given about 20 g of iron, mostly after chelation had begun. Serious cardiac problems are unusual in patients with thalassaemia major who have received similar total iron loads,⁴ so multiple organ failure developed in the face of a relatively modest iron burden. In some patients with acquired sideroblastic

anaemia inheritance of a single haemochromatosis allele may contribute to iron loading,⁵ but even homozygotes for this gene absorb only twice as much iron as normal. So even if case 1 had also been affected by haemochromatosis, she would have accumulated insufficient iron to account for the speed of organ damage. In other words it seems unlikely that iron overload was solely responsible for her organ failure.

The reason is not entirely clear, but abnormally low concentrations of mitochondrial δ -aminolaevulinic acid synthetase and serine protease have been reported in both granulocytes and red cells from patients with pyridoxine resistant hereditary sideroblastic anaemias.⁶ It is attractive to speculate that the mitochondria of other organs of these patients, and of this child in particular, may function abnormally. The combination of a transfused iron load and intrinsically compromised mitochondria might lead to earlier organ failure than would be expected in thalassaemia major.

Case 2 may have had a different disorder as evidenced by her more benign clinical course.

The clinical pattern in both of these children suggests that their disease is different from the usual X-linked form. Extreme lyonisation in a female carrier seems most unlikely because even affected males may escape diagnosis until adult life. It might have been caused by a new autosomal mutation, or the patients might have sustained a mutation of the paternally derived X chromosome, having inherited a carrier state from their mother, but this is speculative and there is no haematological or cytogenetic evidence that either was the case.

These rare cases illustrate congenital sideroblastic anaemia occurring in young girls. They had different clinical courses and this suggests that there is considerable phenotypic heterogeneity in this disorder. The first girl might have benefited from more aggressive iron chelation treatment⁷ or even early bone marrow transplantation, but, as illustrated by the relatively benign course in case 2, such action is clearly not necessary in every case. We suggest that such children be carefully monitored for evidence of increasing iron overload so that intervention as early as possible may prevent early organ damage.

We thank Dr S I Dempsey who referred case 1, Drs S Court and H H Bain for their help and support, and the late Professor J M Parkin, who coped with so many of case 1's problems. We also thank Dr J S Lilleyman for permission to report case 2 and Dr I Beddis who referred the patient.

- 1 van Waveren Hogervorst GD, van Roermund HPC, Snijders PJ. Hereditary sideroblastic anaemia and autosomal inheritance of erythrocyte dimorphism in a Dutch family. *Eur J Haematol* 1987;38:405-9.
- 2 Weatherall DJ, Pembrey ME, Hall EG, et al. Familial sideroblastic anaemia: problem of X₁ and X chromosome inactivation. *Lancet* 1970;ii:744-8.
- 3 Robins-Browne RM, Prpic JK. Desferrioxamine and systemic yersiniosis. *Lancet* 1983;ii:1372.
- 4 Nienhuis AW, Wolfe L. The Thalassaemias. In: Nathan DG, Oski FA, eds. *Haematology of infancy and childhood*. Philadelphia: WB Saunders, 1987:699-778.
- 5 Cartwright GE, Edwards CQ, Skolnick MH, Amos DB. Association of HLA-linked hemochromatosis with idiopathic refractory sideroblastic anemia. *J Clin Invest* 1980;65:989-92.
- 6 Aoki Y. Multiple enzymatic defects in mitochondria in hematological cells of patients with primary sideroblastic anemia. *J Clin Invest* 1980;66:43-9.
- 7 Fosburg MT, Nathan DG. Treatment of Cooley's anemia. *Blood* 1990;76:435-44.