

Insulin dependent diabetes in thalassaemia

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SUMMARY Diabetes mellitus was observed in 29 of 448 patients with thalassaemia major attending seven Italian centres. Twelve patients, at onset of clinical diabetes, presented with an asymptomatic glycosuria, 13 with ketosis, and four with ketoacidosis. All were diagnosed after 1979, at a mean age of 17 years. Mean age at diagnosis of diabetes was lower in patients born in the last two decades. In these patients transfusions were started at a younger age and pre-transfusion haemoglobin concentration, serum ferritin concentration, incidence of liver disease, and the presence of a family history of diabetes were higher than in patients born previously. Although 27 (93%) cases had iron chelating treatment the mean serum ferritin concentration was 5600 µg/l; 25 (92%) of these patients had signs of liver impairment. The determination of C peptide in 10 patients showed a wide variation in pancreatic β cell function, and insulin requirements ranged between 0.15 and 1.72 U/kg body weight. Metabolic control was generally poor. The onset of diabetes mellitus was followed in most patients by the appearance of other endocrine or cardiac complications, or both. Fourteen patients died within three years of presenting with overt diabetes. Haemosiderosis, liver infections, and genetic factors seemed to be crucial in diabetes development. Thalassaemic patients developing clinical diabetes mellitus are at high risk for other complications and should be strictly monitored, especially for thyroid impairment.

In recent years there have been many reports of impairment of glucose tolerance in thalassaemic patients who had received frequent transfusions.^{1–5} No detailed descriptions of diabetes in thalassaemia and its complications, however, have been reported. The present study was undertaken to investigate the incidence and clinical and epidemiological characteristics of diabetes developing in thalassaemic patients who had had many blood transfusions.

Patients and methods

The study was carried out of all cases of insulin dependent diabetes mellitus observed in a series of 448 patients with β thalassaemia major who were diagnosed between 1970 and 1983 and followed up at the departments of paediatrics in clinics in Bari, Catania, Ferrara, Genoa, Milan, and Turin in Italy. Standard flow sheets specifically designed to record the history of thalassaemia, any family history of diabetes in first and second grade relatives, the clinical onset of diabetes mellitus and the successive history, and the coexistence of other endocrin-

opathies were used for data collection. Treatment by blood transfusion was the same at all centres.

The concentration of haemoglobin at which transfusions were given was gradually increased from 50–60 g/l in the 1960s to 115–120 g/l in the 1980s according to national protocols.⁶ Desferrioxamine mesylate (Desferal, Ciba Geigy) was given intramuscularly from the early 1970s and by subcutaneous infusion in all patients older than 3 years from 1978–9. Not all patients complied consistently with this treatment.

A diagnosis of diabetes was made on either the classical symptoms or the concentration of fasting plasma glucose being above 7.8 mmol/l on several occasions, or both; this is according to the National Diabetes Data Group criteria.⁷ In each case metabolic control of diabetes was assessed on the personal knowledge of the patient, the concentration of fasting blood glucose, the concentration of glucose in a 24 hour urine sample, and the results of glycosuria monitoring at home. Poor control was arbitrarily defined as the presence of persistent glycosuria or acetonuria or a fasting blood glucose

concentration above 11.1 mmol/l, or both. Urine analysis, liver function tests, thyroid function tests (triiodothyronine(T₃), thyroxine(T₄), thyroid stimulating hormone (TSH) by standard radioimmunoassay techniques), funduscopy, and electrocardiography were carried out by all the centres at regular intervals. The test for thyrotrophin releasing hormone (TRH) was performed only when there were clinical or laboratory indications. Thyroid function was defined as uncompensated when there were increased TSH and decreased T₄ concentrations or when the concentration of TSH was too low in comparison with that of T₄ or when there was a blunted TSH response to the administration of TRH.

Concentrations of serum ferritin were determined by radioimmunoassay⁸ at a serum dilution of 1:1000 (normal concentrations (SD): men, 108 (68) µg/l; women, 32 (25) µg/l). Residual β cell function was assessed in only 10 patients by C peptide concentrations after stimulation with intravenous arginine: 24 hours after insulin injection arginine hydrochloride (0.5 g/kg body weight, maximum 25g) was injected over 30 minutes, and blood samples were collected at 0, 30, 60, 90, and 120 minutes after the start of the infusion. Percutaneous liver biopsy was performed in 12 patients who had biochemical signs of parenchymal liver damage; informed consent was obtained from parents or patients, or both.

Results

A total of 29 cases (6.5%) of diabetes mellitus (13 male, 16 females) in 448 patients with thalassaemia major, all diagnosed after the tenth year of life, were observed in the seven centres. Altogether 19 cases were observed in Ferrara, five in Milan, two each in Bari and Genoa, and one in Catania; no cases were reported in Turin.

MEDICAL HISTORY UP TO TIME OF DIAGNOSIS OF DIABETES

Mean age at the start of blood transfusion treatment was 13 months for males (range 4–24 months) and 20 months for females (range 3–54 months). In 27 patients (93%) iron chelation treatment was given: they received chelation treatment intra-muscularly for a mean period of six years (range 1–10 years). The details of treatment were available in only six patients: they had a mean dose of desferrioxamine 170 mg/kg/week (range 11–500) and a mean number of doses per year of 154 (range 76–250). Twenty five of the 27 (92%) (of whom 24 were previously treated intramuscularly) received subcutaneous chelation treatment for a mean of 4.9 years (range 1–8 years). Details of treatment were available in

only 17 patients: they had a mean dose of desferrioxamine of 155 mg/kg/week (range 50–280) and a mean number of doses per year of 233 (range 60–340). The serum ferritin concentration at the time of onset of diabetes mellitus was available in 26 patients and ranged from 2300 to 10 600 µg/l (mean 5600). Twenty five of these patients had undergone splenectomy between one and 11 years of age.

Liver impairment was present in 25 of the 27 patients for whom data on liver function were available, and the age when diagnosed ranged from 1 to 21 years, with a mean of 12.6 years in males and 8 years in females. Liver function data in the year preceding onset of diabetes were available in 24 cases and nine had persistently increased serum aspartate transaminase activities. Seven experienced an episode of acute hepatitis during this period. Histological examination of liver parenchyma performed in 13 patients (12 at biopsy and one at postmortem examination) showed siderosis of hepatocytes (grade 1 to 4) in all cases, in addition five had chronic persistent hepatitis, one chronic active hepatitis, and four cirrhosis. No patient had signs or symptoms of heart disease before diagnosis of diabetes.

Oral glucose tolerance was tested in 24 patients before the onset of diabetes mellitus. Impaired glucose tolerance was present in two patients five years before the onset of clinical diabetes, in two patients two years before onset, and in two one year before onset, and in the others a few months before onset. One patient was found to have a condition similar to maturity onset diabetes and remained well controlled for over a year, the only treatment being a restricted carbohydrate diet. A family history in first or second degree relatives with insulin dependent diabetes was present in six patients, seven patients had a relative with type II maturity onset diabetes. Two pairs of siblings with diabetic thalassaemia were reported.

DIABETES MELLITUS

There was a wide range of symptoms at clinical onset of diabetes from asymptomatic glycosuria (12 cases) to ketosis (13 cases), or ketoacidosis (four cases). The mean age at diagnosis was 17 years (range 11–24). There was a progressive decrease of age at onset of diabetes mellitus with the calendar year of birth (figure). While none of the 80 patients born before 1964 developed diabetes before the 15th year (group B, table), nine of the 146 patients born in the following period presented clinical signs between 11 and 14 years (group A). In the younger group (group A) transfusions were started earlier, there were higher concentrations of serum ferritin, a higher incidence of liver disease and acute hepatitis

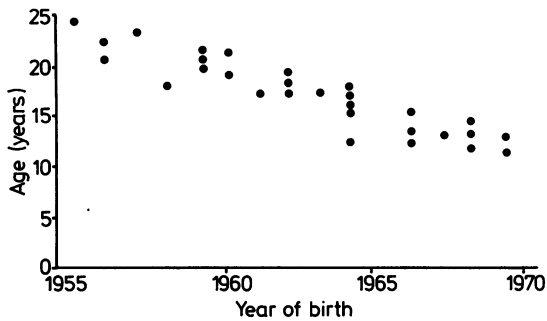


Figure Age at diagnosis of diabetes related to year of birth.

Table Comparison of characteristics at time of diagnosis in patients developing diabetes before the age of 15 years (group A) and after 15 years (group B)

| | Group A (n=9) | Group B (n=20) |
|--|------------------|-------------------|
| Males | 4 | 9 |
| Females | 5 | 11 |
| Median age at diagnosis of diabetes (years) | 12 | 18 |
| Range | 11-14 | 15-24 |
| Median age at first blood transfusion (months) | 8 | 21 |
| Range | 3-24 | 6-54 |
| No of patients with pre-transfusional haemoglobin concentrations of over 100 g/l (%) | 6 (63) | 9 (45) |
| Theoretical subcutaneous iron chelation* (%) | 8 (89) | 19 (95) |
| Median duration (years) | 7 | 5 |
| Range | 0-8 | 0-8 |
| Concentration of ferritin ($\mu\text{g/l}$): | | |
| Median | 5900 | 4250 |
| Range | 4550-9400 | 2300-10600 |
| No of patients who underwent splenectomy (%) | 7 (78) | 18 (90) |
| No of patients with chronic liver disease (%) | 9 (100) | 16 (80) |
| No of patients with acute hepatitis within one year before diagnosis of diabetes (%) | 3 (33) | 4 (20) |
| No of patients with a positive family history | | |
| Type I diabetes (%) | 3/6 (50) | 3/17 (18) |
| Type II diabetes (%) | 3/7 (43) | 4/18 (22) |

*Compliance with treatment was unknown.

in the 12 months before diagnosis of diabetes and a higher incidence of a positive family history.

The mean daily insulin requirement in this series was 0.98 U/kg body weight (range 0.15-1.72). In general terms the metabolic control was good in four patients, poor in eight, and very poor in 17. There was a negative correlation between insulin dose and metabolic control. The determination of C peptide

concentrations in 10 patients from Ferrara showed a variation in pancreatic β cell function: it was increased in one, normal in three, and reduced in six cases. Eleven patients (38%) developed heart disease six to 36 months after the onset of diabetes. In 23 patients the coexistence of other endocrine disease was reported: five had hypoparathyroidism, 19 had hypogonadism, and 14 had hypothyroidism (12 primary and two secondary). No cases of adrenal failure were seen. None of the patients developed clinical complications of diabetes possibly because of the short follow up after diagnosis of diabetes (mean 32 months, range 0-81).

Fourteen patients died within three years of developing overt diabetes. Causes of death were ketoacidosis with cardiac failure in one patient, refractory heart failure associated in several cases with severe arrhythmias or cirrhosis, or both in 10 patients, and cerebral thromboembolism in two patients. One patient died at home from unknown causes.

Discussion

Glucose intolerance and diabetes mellitus are possible complications in patients with thalassaemia major treated with transfusions.¹⁻⁵ Possible pathogenetic conditions are pancreatic cell destruction with consequent insulin deficiency,^{1 2 5} liver derangement with consequent insulin resistance,⁹⁻¹¹ and genetic factors.^{4 5} All these, either singly or together, have been found in our patients with diabetes mellitus. In addition 28% of these patients developed diabetes mellitus shortly after an acute viral hepatitis infection. This suggests that some hepatitis viruses might precipitate diabetes mellitus in thalassaemic patients. No data regarding the clinical picture of diabetes mellitus that complicates thalassaemia major have been reported. We found abnormal glucose tolerance at various stages before the appearance of diabetes mellitus: from five years to only a few months before. A wide range in insulin requirements and a high incidence of poor metabolic control were observed.

During the short period of follow up, disease of the retina, glomerular microvasculopathy, or clinical signs of neuropathy were not observed. Two patients, however, who had undergone splenectomy died one year after the onset of diabetes from cerebral thromboembolism. Rheological factors, due to diabetes, such as enhanced platelet aggregation,¹² increased blood viscosity, red cell rigidity,¹³ and distorted prostaglandin homeostasis^{14 15} might have contributed to the vascular accident in these patients. A high incidence of heart disease of varying clinical severity and a high incidence of

endocrine complications were present in our population. The majority of the 29 diabetic patients with thalassaemia had hypogonadism (19/29) and hypothyroidism (14/29). The precise relation between diabetes mellitus and thyroid disorders is not clear. A possible immunological disturbance was suggested by some authors.¹⁶ In our patients, however, the antithyroglobulin and thyroid microsomal antibodies were not present. Heavy iron deposits have been found in the thyroid gland in patients with thalassaemia, therefore iron toxicity is probably the common factor that causes diabetes mellitus and other endocrinopathies in some patients.

Before the introduction of subcutaneous chelation treatment diabetes mellitus was reported to have occurred at mean age of 17.9 (5.2) years (range 11–25 years).^{1–5} The overall prevalence of overt diabetes in 47 thalassaemic patients older than 11 years was 23.4%.^{1–5} Most of our patients had iron chelation treatment subcutaneously with desferrioxamine on average for 4.9 years. We expected that iron chelation would have been followed by a reduced incidence of diabetes mellitus and an increased age of presentation. In our series we found diabetes mellitus in 29 out of 182 thalassaemic patients (15.9%) who were older than 10 years. Our data show that prevalence is lower in chelated than in unchelated patients, which is what we expected.

Age of presentation, however, has decreased progressively over the years (figure) and instead of being higher was lower in chelated patients. These data seem to suggest that administration of desferrioxamine has precipitated the earlier appearance of diabetes mellitus. This is unlikely, however, as a diabetogenic property of desferrioxamine should also have caused an increased incidence of diabetes mellitus. There must be other causes to explain the earlier appearance of diabetes mellitus in thalassaemic patients who had undergone chelation treatment. The reasons might be: (i) underdiagnosis or undernotification of diabetes mellitus, or both, in the years preceding the subcutaneous administration of desferrioxamine. This seems very unlikely, if not impossible, as it is difficult to believe that diabetes mellitus could remain undiagnosed; (ii) a relative excess of milder cases of thalassaemia in the past years, due to the early death of the patients more severely affected. This hypothesis is very likely and may explain the later presentation of diabetes mellitus in the past; (iii) increased iron load in the younger patients (group A) due to the increased amount of transfused blood not balanced by increased chelating treatment. Before 1980 our patients were transfused when their haemoglobin concentrations were about 95 g/l. Starting from 1980

the transfusion regimen was modified, according to the suggestion of Propper *et al* who proposed transfusion at haemoglobin concentrations of about 115–120 g/l.¹⁷ This regimen was supposed to prevent skeletal abnormalities and hypersplenism without requiring an increased amount of blood, which would worsen the iron overload.

Although our previous evaluations seemed to confirm the Propper data, a recent analysis showed that there is, on the contrary, a direct correlation between pre-transfusional haemoglobin concentrations and blood consumption (unpublished data). This suggests that most of our patients on the regimen maintaining a higher haemoglobin concentration received amounts of blood greater than those transfused in the past and therefore received greater amounts of iron. In addition, the greater number of transfusions increased the risk of viral infections. This might be the cause of the earlier occurrence of diabetes mellitus. On the basis of these observations we do not transfuse until the haemoglobin concentration is lower (about 105 g/l). If we are correct in this policy the incidence of diabetes mellitus in the next few years should be reduced even further and the age of presentation increased.

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