Serum immunoreactive trypsin in β -thalassaemia major

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SUMMARY To assess the exocrine pancreatic function in β -thalassaemia major with iron overload, serum immunoreactive trypsin (IRT) was measured in 38 patients with this condition. In 23 (60%) patients' IRT was abnormal: it was subnormal in 16 patients and supranormal in seven. Whereas subnormal IRT concentrations were more frequent in patients of more than 12 years old, supranormal IRT concentrations were more frequent in younger patients. These data provide the first antemortem evidence of exocrine pancreatic damage in this condition. They also suggest that this acinar cell damage is initially associated with a rise in IRT which is followed by a fall in the serum concentration of this enzyme.

Exocrine pancreatic abnormalities based on post-mortem examination have been described in patients with iron overload.¹ Since serum immunoreactive trypsin (IRT) has recently been shown to be valuable in assessing pancreatic exocrine function in conditions such as cystic fibrosis and chronic pancreatitis,²⁻⁴ we measured serum IRT concentrations in patients with thalassaemia major and transfusional iron overload in order to detect exocrine pancreatic damage. The results show a high incidence of pancreatic damage among these patients.

Patients and methods

Thirty-eight patients (22 male and 16 female) with β -thalassaemia major regularly maintained on blood transfusions were included in this study. Their ages ranged from 4 to 25 yr (mean: 15) and they had received from 64 to 429 (mean: 99) units of blood each of 400 to 450 ml. Their serum ferritin concentrations ranged from 1740 to 22 400 (mean: 10 060) μ g/l at the time of the study (normal range up to 340 μ g/l). None of the patients had clinical evidence of chronic pancreatitis, chronic diarrhoea, malabsorption or renal failure. Two of the patients included had concomitant insulin-dependent diabetes. Serum IRT was measured by a radioimmunoassay by a double antibody technique using a kit (Hoechst). Samples of blood were taken two hours after a normal breakfast, allowed to clot, centrifuged,

frozen and stored at -20°C . On this assay, normal reference values for adults are 140 to 400 μ g/l. Those for children are lower (100 to 240 μ g/l) as is shown in the Figure.

Results

The results as shown in the Figure have been divided according to age since serum IRT concentrations in the young tend to be lower than those in adults. A separate reference range was hence established for children aged less than 12 yr (mean $\pm$ SD 170 $\pm$ 35 μ g/l). IRT in patients aged 13 to 34 yr had been compared with the established adult reference range (140-404 μ g/l).

Twenty-three out of 38 (60%) patients studied had abnormal IRT concentrations in their serum. Two types of abnormality were observed: some patients had subnormal IRT concentrations whilst in others IRT was markedly raised. Eleven out of 22 (50%) patients under 12 yr had abnormal IRT concentrations: five of these 11 had markedly raised IRT whereas six had subnormal concentrations. Twelve out of 16 (75%) patients above 12 yr of age had abnormal IRT: in two out of these 12 IRT was higher than normal whilst in 10 it was subnormal. Thus there was a tendency for the prevalence of abnormality to be greater in older patients. The frequency of subnormal rather than raised IRT concentrations was also greater in older patients (67% v 27%) although this difference did not reach statistical significance.

Immunoreactive trypsin (IRT) concentration in patients with iron overload. Note that the reference values for children under 12 years of age are lower than those in adults. The frequency of normal IRT concentrations was lower in adults than children with iron overload and the proportion of subnormal IRTs was greater. Control IRT volume shown as mean $\pm$ 1 SD.

Discussion

The present study shows that over 60% of patients with β -thalassaemia major and transfusional iron overload have abnormal serum concentrations of IRT. The majority with abnormal IRT (22 of 26, 86%) had low concentrations while four (14%) had raised IRT concentrations. Whereas low IRT concentrations reflect a significantly diminished exocrine pancreatic reserve,^{2,3} the significance of raised IRT in serum is not clear. It has, however, been shown that in at least one other condition with chronic damage of exocrine pancreatic acinar tissue—cystic fibrosis—serum IRT can be raised without clinical evidence of acute pancreatitis.⁴ It is possible that

raised IRT concentrations reflect a breakdown of the acinar-blood barrier with leakage of exocrine secretion into blood.

The mechanism underlying exocrine pancreatic damage in these patients is probably the infiltration of the acinar tissue with iron. Damage to endocrine components of the pancreas—the islets of Langerhans, and β cells in particular—due to iron overload is well recognised but there has been no previous evidence of antemortem exocrine pancreatic damage. It is important, however, to mention that serum ferritin (or age or units transfused) and IRT concentrations in these patients did not correlate. Thus individual tissue susceptibility to iron may determine the eventual damage to pancreas as well as the degree of iron overload.

The fact that the two patients with insulin-dependent diabetes had the lowest IRT concentrations of all may either reflect the degree of iron infiltration in their pancreatic acini or an additional effect of diabetes on exocrine pancreatic reserve.³

The availability of IRT as a marker of exocrine pancreatic damage in thalassaemic patients provides us with an index which could be used to monitor possible beneficial effects of iron chelation treatment in these patients. It has recently been shown that continuous subcutaneous infusion of desferrioxamine is an effective way to reverse iron from the tissues in conditions with transfusional iron overload. Such treatment has been shown to improve specific organ function.⁵ It would now be of interest to measure sequentially IRT concentrations in patients with transfusional iron overload on chelation treatment.

References

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