β cell function in siblings of diabetic children and HLA type

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SUMMARY β cell function was tested in HLA-DR typed siblings of insulin dependent diabetic children. HLA identical siblings showed an increased insulin response compared with controls and HLA non-identical siblings. This β cell hyperactivity may be an early carbohydrate intolerance or a genetically determined increase in β cell metabolism.

Studies of HLA typing in families with more than one diabetic child show that siblings with HLA typing identical to the diabetic child have a high risk of developing insulin dependent diabetes (IDD). In recent investigations of IDD1 2 3 a long, clinically asymptomatic stage before any clinical manifestation of the disease has been shown. It is of interest, therefore, whether siblings with the highest genetic risk of IDD have an abnormal β cell function.

Patients and methods

Forty four families with one child with IDD and at least one sibling without IDD were included in the study. The age of the diabetic children (24 boys and 20 girls) was mean (SD) 11·8 (2·8) years, and that of their 66 non-diabetic siblings (37 boys and 29 girls) was mean (SD) 13·1 (3·4) years. An oral glucose tolerance test (OGTT) (glucose 1·75 g/kg) was performed between 8 and 10 am in all siblings, after overnight fasting. Blood samples, drawn using an indwelling needle at 0, 60, and 120 minutes, were centrifuged and frozen at −20°C until assay.

Control data were obtained from 33 healthy school-children with no family history of diabetes (age mean (SD) 13·9 (1·1) years).

Serum glucose values were measured by the glucose oxidase method and insulin determination was performed by radioimmunoassay. HLA-ABC typing was performed by means of a standard NIH lymphocytotoxicity technique and DR locus typing by the 2 colour fluorescence technique.

Informed written consent was obtained from the parents. For statistical analysis a non parametric test (U test) was applied.

Results

Nineteen children were HLA identical, 25 were haplidentical, and 22 were not HLA identical to their diabetic siblings. One boy, who did not have clinically apparent diabetes, had an abnormal OGTT, (blood glucose 13·3 mmol/l at 60 min and 18·1 mmol/l at 120 min). After fasting his blood glucose value (5·5 mmol/l) and immunoreactive insulin value (6·4 μU/ml) were normal, but the increase in the latter after the oral glucose load was low (24·7 and 28·4 μU/ml at 60 and 120 minutes, respectively). The results of this child’s tests were excluded from the analysis. He had both risk antigens for IDD—HLA-DR3 and HLA-DR4—and was haplidentical to his diabetic brother. All other siblings showed normal blood glucose values during the test.

The insulin response to the oral glucose load was
increased in HLA identical siblings of diabetic children compared with controls and HLA non-identical siblings at 120 min (Table 1), but the difference did not reach statistical significance. Insulin secretion (calculated as the area between the insulin curve and the baseline) was appreciably higher in HLA identical siblings compared with controls and HLA non-identical siblings (Table 2). There was a wide range of insulin response in the HLA identical group (1188-46 626 \( \mu U/ml/min \)). Three HLA identical siblings showed rather low insulin responses (1188-1458 \( \mu U/ml/min \)), while 11 had an immunoreactive insulin value above 4500 \( \mu U/ml/min \). No relation between certain HLA-DR antigens and insulin secretion was observed.

### Discussion

Hyperinsulinaemic responses with a delayed peak to oral glucose load have been reported in some siblings of children with IDD. In agreement with other investigators, we found an increased insulin response in HLA identical siblings compared with controls.

Recent studies indicate that the clinical manifestation of IDD is preceded by a long prediabetic period, and that typically such patients were islet cell antibody positive. Ilonen reported an increased insulin response to OGTT one year before clinical manifestation of IDD in a patient, while Rosenbloom et al. in their long term follow up, observed relative insulinopenia (values > mean -1 SD of controls) in three of four HLA identical siblings, who subsequently developed diabetes. The fourth sibling, however, showed a high insulin response.

It is interesting that Ginsberg et al. reported contrary observations to Barbosa's, and our findings; with low insulin values in HLA identical siblings (exceptions, 2 of 25). Three of our HLA identical siblings had rather low insulin responses as well.

One possible explanation for the observed hyperinsulinaemic \( \beta \) cell response may be that \( \beta \) cells with
Ineffectiveness of ipratropium bromide in acute bronchiolitis

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SUMMARY In a double blind randomised trial, we found no evidence that nebulised ipratropium bromide was of clinical benefit in acute bronchiolitis.

No pharmacological agent has been shown to alter the natural history of acute viral bronchiolitis. Further lung function studies have failed to show any objective benefit from salbutamol, orciprenaline, phenylephrine, adrenaline, and isoprenaline. We recently confirmed the ineffectiveness of salbutamol but found that the anticholinergic agent ipratropium bromide led to a reduction in work of breathing in 6 of 15 infants with severe bronchiolitis. This present study was designed to assess the clinical benefit of ipratropium bromide in the treatment of acute viral bronchiolitis.

Patients and methods

Sixty six children who had been admitted to hospital with acute bronchiolitis were included in the study. The diagnosis of bronchiolitis was based on the typical clinical features of a tight, irritating cough, breathlessness, respiratory distress, hyperinflation, fine crepitations, and expiratory rhonchi. Respiratory syncytial virus (RSV) was isolated from 45 (68%) of the children. Their average age was 130 days (range 49–368 days), 40 were boys and 26 girls.

In a randomised, double blind fashion, the children received 6 hourly nebulised solutions containing 250 µg of ipratropium bromide in 2 ml of saline (34 patients) or normal saline alone (32 patients). Treatment was stopped when the respiratory signs had resolved sufficiently for discharge home. One of us made daily measurements of pulse and respiratory rate together with assessments of cough, rhinitis, nasal flaring, cyanosis, hyperinflation, tracheal tug, intercostal recession, subcostal recession, respiratory distress, crepitations, and rhonchi, using a four point scale scoring system for each parameter. Another of us obtained detailed information from parents and nursing staff about