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Letters

Comment

Braking the Accelerator Hypothesis?

Keywords Accelerator · Type 1 diabetes · Obesity · Insulin resistance · Body mass index

To the Editor: The accelerator hypothesis was first suggested in 2001 [1]. It postulates that Type 1 and Type 2 diabetes are not discrete but part of a spectrum of disease caused by three main processes or accelerators; insulin resistance, autoimmunity and constitution. It suggests that in Type 1 diabetes, obesity associated with insulin resistance is compounded by an autoimmune reaction that precipitates presentation. Support for the hypothesis comes from findings that excess weight gain in the first eighteen months of life could be associated with Type 1 diabetes in childhood [2]. A separate study has shown that, in children destined to develop diabetes, BMI SDS measured at birth and at preschool age, are greater than national standards. However local anthropometric data also showed this rise in BMI SDS suggesting that this could be accounted for by secular trend [3]. In Sweden, the incidence of childhood diabetes has increased whilst incidence decreased in young adults [4]. This suggests accelerated pathogenesis rather than an absolute increase in diabetes.

Data from the United Kingdom has shown a relationship between younger age at diagnosis of Type 1 diabetes and higher BMI [5]. We tested whether this association between high BMI and early age of onset of diabetes was true for our population. As insulin resistance is increased in South Asian children [6], we wanted to test whether any relationship would be more pronounced in our South Asian Type 1 diabetes patients. We compared BMI at diagnosis with age of diagnosis of Type 1 diabetes in South Asian and white children from the United Kingdom.

Inclusion criteria were Type 1 diabetes (short history of osmotic symptoms, ketonuria, and absolute insulin dependence >0.5 u·kg^{-1}·day^{-1} to achieve normoglycaemia); age <16 years; ethnic origin white from the UK or South Asian; and full anthropometric data available. Exclusion criteria were co-existing pathology such as thyroid or coeliac disease; and regular medication other than insulin. Our patients and their parents consented to their data being made anonymous and used in diabetes research and audit.

Height and weight were converted to age-standardised standard deviation scores (SDS) using the 1990 United Kingdom growth standards [7, 8]. Weight at diagnosis might reflect dehydration so we used measurements from the subjects' first visit to the clinic after diagnosis. To exclude the confounding effect of catabolism prior to diagnosis we also analysed BMI a year after diagnosis.

To investigate the relationship between age at diagnosis and BMI SDS, we used Spearman's rank correlation and assumed statistical significance at a p value of less than 0.05.

Between the years 1992 and 2002, 24 South Asian children (10 female) and 71 white children from the UK (40 female) presented to our unit and fulfilled our criteria. The mean ages at diagnosis were 8.5 years (range 1.4–14) South Asian female, 9.9 years (range 1.9–15.5) South Asian male, 7.8 years (range 1.28–13) white female from the UK, 6.7 years (range 1.29–14) white male from the UK. There was a statistically significant difference (p<0.03) between age at presentation of the two ethnic groups.

Mean height SDS for South Asian children was 0.45 (95% C.I –0.05–0.95), and mean weight SDS was 0.54 (95% C.I. – 0.05 – 1.13). Mean BMI SDS for South Asian children was 0.36 (95% C.I. –0.32 to 1.04). Mean height SDS for white UK children was 0.21 (95% CI –0.03 to 0.45), and mean weight SDS was 0.4 (95% CI 0.15 to 0.65). Mean BMI SDS for white UK children was 0.49 (95% C.I. 0.23–0.75). These differences were not statistically significant. Table 1 shows our data broken down by age at diagnosis quartile.

Spearman rank coefficient for correlation between body mass index at diagnosis and age at diagnosis in all children showed no correlation (n=95, r=0.067, p>0.5). When the children were analysed separately by ethnic origin, there was no correlation (white UK children n=71, r=–0.04, p>0.5; South Asian children n=24, r=0.19, p>0.1).

Subsequent body mass index one year after diagnosis showed a weak inverse correlation with age of diagnosis in white UK children but did not reach statistical significance (r=–0.2, p>0.1). There was no correlation in South Asian children (r=0.13, p>0.1).

The accelerator hypothesis unifies the aetiology of diabetes by proposing that Type 1 and Type 2 diabetes are part of the same spectrum of disease, differing only by tempo of the three accelerators. If this hypothesis is true, then it would relate the earlier presentation of Type 1 diabetes to the rising epidemic of child obesity.

Data for 94 children (92 white) from Middlesborough (1980–2000) showed a negative correlation (r=–0.39, p<0.001)

Table 1. Relationship of body weight to age-at-diagnosis quartile

Quartile	n	Age at diagnosis	Weight SDS at diagnosis	BMI SDS at diagnosis
1	25	2.7±1.2	0.49±1.0	0.27±1.0
2	23	6.6±1.0	0.29±1.3	0.37±1.3
3	24	9.7±0.8	0.58±1.3	0.58±1.3
4	23	12.6±1.5	0.37 ±1.0	0.33±1.2
All	95	7.8±3.9	0.44±1.2	0.39±1.2

Data are means ± SD

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between BMI-SDS at diagnosis and age of diagnosis [5]. We have not shown a negative correlation in our population, despite adequate power in our cohort of white children (80% power to detect r=0.33). The diagnostic criteria used in both studies are similar. Our population is similar in age of presentation and sex ratio to that previously presented. However our lowest quartile by age was lighter (mean weight SDS 0.49 vs 0.71) and the highest quartile by age was heavier (mean weight SDS 0.37 vs 0.04) than the Middlesborough data (Table 1). Our data was collected more recently and may show that the general rise in obesity in the childhood population is most marked in adolescents. There could be socio-economic differences between the Birmingham and Middlesborough populations that account for the anthropometric differences. Our "diagnosis" weight was made at the first visit to the clinic (median 11 days after diagnosis) whereas the Middlesborough patients were measured 6 weeks after diagnosis. However both studies also looked at BMI-SDS one year after diagnosis, but we found no inverse correlation with age at diagnosis.

The fact that a relationship between age and weight at diagnosis is not found in our Asian population where it should be strengthened by greater insulin resistance is puzzling. If insulin resistance is accelerating the presentation of diabetes, one would expect Asian children to present earlier with Type 1 diabetes than white children due to greater insulin resistance [6]; this was not the case with our patients. It could be that BMI is too crude of a surrogate measure of insulin resistance. Analysing body fat composition might be a better technique, particularly when comparing ethnic groups.

In conclusion, childhood obesity is not the main influence on the age of presentation of Type 1 diabetes in our population.

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Abbreviations: BMI-SDS, body mass index standard deviation score · SDS, standard deviation score

Observations

Neutrophil antigen exposure is altered with age in relatives of patients with Type 2 diabetes

Keywords Cytoskeleton · CD11b/CD18 · Neutrophil · Type 2 diabetes · First-degree relatives

To the Editor: Neutrophil dysfunction contributes to the pathogenesis of the vascular complications of Type 2 diabetes. Adhesion of neutrophils to the vascular endothelium is mediated by surface exposure of the β_2 integrin CD11b/CD18, which is closely associated with the actin cytoskeleton [1]. We have shown that neutrophils respond to activation with phorbol ester by rapidly increasing surface expression of CD11b, followed by loss of surface CD11b in a proportion of cells [2]. Loss of surface CD11b in response to phorbol ester is associated with actin polymerisation and leads to loss of neutrophil adherence [3]. In Type 2 diabetes both the proportion of neutrophils polymerising actin and losing CD11b and the proportion of cells exocytosing primary granules (an important step in microbial killing and identified as surface exposure of the antigen CD69) is reduced [2].

Several aspects of neutrophil dysfunction in Type 2 diabetes have been attributed to the metabolic consequences of hyperglycaemia and normalisation of glycaemia has been associated with an overall improvement in neutrophil function [4]. However, it is unclear whether impaired neutrophil-cytoskeletal remodelling and abnormal trafficking of cell surface antigens in Type 2 diabetes is due to altered metabolism. Therefore, we studied the effect of phorbol ester on neutrophil actin polymerisation and antigen exposure in samples from non-diabetic first-degree relatives of patients with Type 2 diabetes to test the hypothesis that these aspects of neutrophil function are familial and unaffected by the degree of glycaemia.

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