SHORT REPORT

Pancreatic dysfunction in severe obesity

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Abstract

Aims—**To investigate pancreatic function in children attending an obesity clinic.**

Methods—**Thirty six children (of which 34 were white) with severe obesity of prepubertal onset (body mass index more than +2 SDS) were reviewed clinically and dysmorphologically, with assessment of pancreatic function.**

Results—**Eight had dysmorphic features and 13 had learning difficulties. Four of 17 prepubertal children had hyperinsulinaemia and seven had hyperproinsulinaemia. All 19 pubertal children had hyperinsulinaemia, 14 had hyperproinsulinaemia, and one had type II diabetes.**

Conclusions—**Metabolic abnormalities predictive of type II diabetes occur in severely obese white children.**

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Keywords: obesity; non-insulin dependent diabetes mellitus; syndromic obesity

The prevalence of obesity is increasing in childhood.[1] Children with significant obesity after the age of 2 years are more likely to be obese adults, particularly if they are obese as teenagers.[2] The incidence of type II diabetes in US youth has risen in parallel with increasing obesity over the past 20 years, predominantly in minority populations.[3] Obesity in adolescence increases the risk of insulin resistance, glucose intolerance, hypertension, and abnormal lipid profiles.[4] We present data showing serious metabolic abnormalities associated with a high risk of type II diabetes in severely obese, mainly white UK children.

Methods

Children with severe obesity (body mass index (BMI) more than +2 SDS), were referred to a regional childhood obesity clinic. Body mass index (weight/height^2) standard deviation score was calculated using the revised (1996) British growth reference data provided by the Child Growth Foundation. Each child was seen by a consultant paediatrician and a clinical geneticist. Clinical assessment included a history of birth weight, developmental progress/presence of learning difficulties, previous illnesses, and age of onset of obesity; dysmorphic features and pubertal stage were recorded. A pedigree was constructed and included the occurrence of obesity and type II diabetes in other family members. Karyotype and microdeletion studies excluded Prader–Willi syndrome. Fasting blood samples were immediately frozen and sent to the University of Cambridge Department of Medicine and Biochemistry for leptin, fasting insulin, proinsulin, and split 32/33 proinsulin concentrations.

Results

Thirty six children (17 boys) with prepubertal onset of obesity were assessed. Median age at assessment was 10.38 years (range 3.6–17.9); 17 children (seven boys) were prepubertal. Thirty four were white, one Asian, and one was of white/West Indian parentage. BMI SDS median was +3.46 (range +2.04 to 6.36).

CLINICAL FINDINGS

We noted dysmorphic features in eight individuals. In three of the children, these were suggestive of Cornelia de Lange syndrome (one girl), Alström syndrome (one girl), and Rud syndrome (one boy). One boy has ocular albinism, nystagmus, and hypogonadism; another has a karyotype of 46Xi(Y)(p10)/46XY. We noted learning difficulties in 13 (36%), including seven of those with dysmorphic features.

BIOCHEMICAL RESULTS

Leptin concentrations were normal for percentage body fat and age in all children. Of the 17 prepubertal children, four had raised fasting insulin (range 61–168 pmol/l; normal <60 pmol/l; fig 1), and seven had raised proinsulin (range 5.9–12 pmol/l; normal <5 pmol/l; fig 2). All children in the pubertal group (n = 19) had fasting hyperinsulinaemia; seven had fasting insulin values more than twice the upper limit of normal for adults. Fourteen of 19 had raised fasting proinsulin (range 5.2–101, mean 23 pmol/l), and 10 of 19 raised split proinsulin (range 15–54 pmol/l, mean 33 pmol/l; normal <13 pmol/l). One white pubertal female (13 years, BMI SDS +3.07) had type II diabetes (fasting insulin 68 pmol/l, standard oral glucose tolerance test: fasting glucose 4.8 mmol/l; two hour glucose 15.6 mmol/l).

Biochemical results were also abnormal in those with dysmorphic features. The pubertal dysmorphic children had raised fasting insulin (95–167 pmol/l) and proinsulin (12–39 pmol/l), while the one prepubertal dysmorphic child

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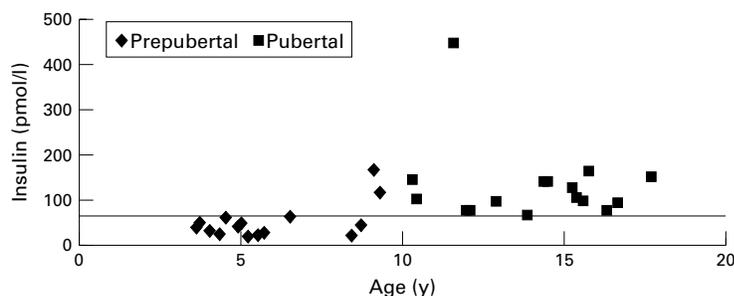j.p.h.shield@bristol.ac.uk

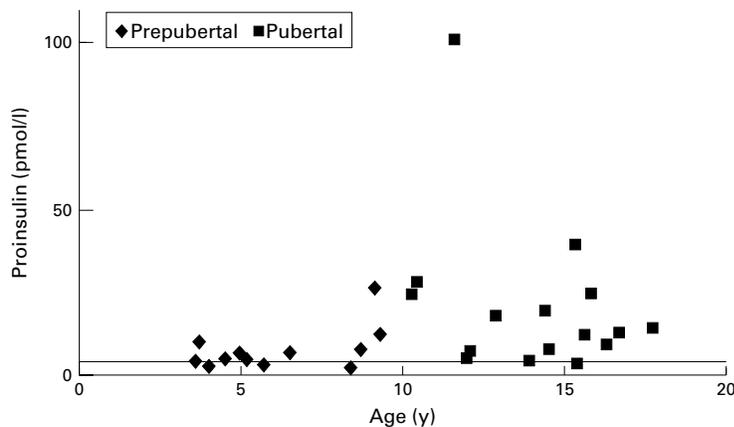Figure 1 *Fasting insulin concentrations.*

Figure 2 *Fasting proinsulin concentrations.*

had a normal fasting insulin of 44 pmol/l but a raised proinsulin of 6.9 pmol/l.

We noted acanthosis nigricans in five children, two with dysmorphic features, and two prepubertal. All had raised fasting insulin (80–168 pmol/l) and proinsulin (5.2–26 pmol/l).

Discussion

There is little information available on the metabolic abnormalities seen in obese children from low risk populations in the UK. These morbidly obese, mainly white patients referred to a specialist clinic, show a high incidence of fasting hyperinsulinaemia and pancreatic dysfunction.

Extrapolating from adult data, this suggests a significant risk of developing type II diabetes (a consequence of both insulin resistance and β cell failure). β Cell dysfunction is characterised by high concentrations of the insulin precursors, intact proinsulin and 32/33 split proinsulin[5]; studies have shown that raised fasting proinsulin concentrations are highly predictive of the development of type II diabetes.[5]

The pubertal group is more difficult to assess, as hyperinsulinaemia is a normal accompaniment of puberty.[6] However, these patients also had raised proinsulin and split proinsulin concentrations, both normally associated with pancreatic dysfunction. There are no normal ranges published for insulin precur-

sors in puberty, but we anticipate that in severely obese individuals, puberty puts an additional burden on pancreatic function, and may unmask incipient β cell failure.

Although there is evidence that both fasting hyperinsulinaemia and obesity predict the development of type II diabetes in high risk childhood populations, for example, Pima Indians,[7] there are no data on the prevalence and predictive value of these abnormalities in children from low risk populations. Our findings, admittedly in a selected population, imply that severely obese children from non-minority populations may also be at high risk of developing type II diabetes in adolescence or early adult life. The identification of one child with obesity and established glucose intolerance, underlines the need to evaluate metabolic status in these patients, as unrecognised hyperglycaemia would undoubtedly contribute to both microvascular and macrovascular risk in later life.

There are well recognised syndromes associated with the development of obesity and type II diabetes in childhood, such as Prader–Willi and Bardet–Biedl syndromes, but also less well known associations. A number of single gene defects associated with the development of obesity have been identified, some carrying specific phenotypic features.[8] We therefore recommend clinical genetic review of these children.

As a minimum, we consider severely obese children require assessment of pancreatic function and clinical dysmorphology. Longitudinal studies are also required to provide further data in order to assess risk factors in these children, and the role of therapeutic intervention.

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