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COMMENTARY

Ageing brain abnormalities in young obese patients with type 2 diabetes: a cause for concern

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Early onset type 2 diabetes is increasing in prevalence, in parallel with the worldwide obesity epidemic [1], and is typically characterised by early onset obesity and severe insulin resistance in young people with a strong family history of type 2 diabetes [1, 2]. Young patients with type 2 diabetes have been shown to have higher rates of hypertension and microalbuminuria than age-matched peers who have type 1 diabetes, despite better metabolic control and a shorter duration of diabetes [3]. We and others have shown that young obese patients with this phenotype are severely insulin resistant (even when compared with equally obese non-diabetic peers of similar age) and have a characteristic dyslipidaemia, with low HDL-cholesterol and elevated fasting triacylglycerol [2, 4]. It has recently been shown that young type 2 diabetic patients also have blunted or absent metabolic and fitness responses to aerobic exercise training, associated with abnormalities in key muscle mitochondrial regulatory responses to exercise [4, 5]. Given the early onset of diabetes in these young individuals, the marked distinctions between their phenotype and that of typical type 1 diabetes and the potentially long subsequent duration of disease, the most important clinical question, unanswered up to now, has been whether this early onset form of type 2 diabetes will lead to more serious end-organ complications.

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In the current issue of *Diabetologia*, Convit and his colleagues have studied a typically obese group (BMI ~37 kg/m^2) of teenagers with early onset type 2 diabetes, and a matched (for age and BMI) group of teenage controls [6]. These patients have a phenotype very similar to those reported above in previous studies [1–5]. All participants underwent a series of neuropsychological tests and brain magnetic resonance imaging studies. The clinical and imaging findings are remarkable given the age of the study subjects. The adolescents with type 2 diabetes performed consistently worse in tests of all the cognitive domains that were assessed, with statistically significant deficits in intellectual functioning, verbal memory and psychomotor efficiency. The imaging studies show reduced white matter volumes and enlarged cerebrospinal fluid spaces in the whole brain and frontal lobe, as well some additional structural differences, compared with the obese non-diabetic participants. This is the first study to report brain abnormalities in type 2 diabetic patients of this age, and it gives cause for immediate concern for those paediatricians and endocrinologists who care for these patients.

It has been well established that older patients with typical type 2 diabetes are at increased risk for the development of modest but definite structural brain abnormalities and for clinical progression to cognitive impairment, as well as learning and memory deficits [7, 8]. Underlying these changes, at least one major contributory factor is the high rate of evolution of vascular pathology, both micro- and macrovascular disease, in patients with longstanding type 2 diabetes. In young patients with type 1 diabetes, the evidence for structural or functional changes in the brain is much less certain, and there have been very few formal studies. What has been completely unknown up to now is the status of brain structure and function in young obese patients with type 2 diabetes. The study by Convit

and colleagues reported in this issue of *Diabetologia* is the first to investigate these questions in very young patients with type 2 diabetes. Their findings are striking, and have to be viewed as a cause for concern—albeit that this is the first such study, conducted in a relatively small number of participants: 18 participants with diabetes and 18 controls. The patients in the current study have the classical severe insulin-resistant phenotype of early onset type 2 diabetes, associated with severe obesity (BMI 37 kg/m^2), fasting hyperinsulinaemia and dyslipidaemia. While it is reported that five of the diabetes group and four of the controls were hypertensive, detail regarding actual blood pressures and urinary albumin to creatinine ratios would also be of interest. It has been shown that both microalbuminuria and hypertension are features of early onset type 2 diabetes, in contrast to type 1 diabetes, even when the diabetes is of shorter duration and even when metabolic control, as measured by HbA_{1c}, is better [3]. The findings of this first report on brain structure and function in early onset type 2 diabetes must be regarded as preliminary, and based on a small initial sample size. The authors have correctly pointed out in their discussion some limitations of the current study in terms of sample size, methods and statistical approach. Nonetheless, the methodology they have used is high quality and the best currently available.

What are the implications of this study and what further research will be required to deal with unanswered questions? Although this is a report of the complications of diabetes, perhaps the bigger message is the devastating effect of early onset severe obesity in a vulnerable subset of the adolescent population. Early onset type 2 diabetes remains a relatively recent phenomenon, but it has been increasingly described and recognised over the past 20 years [1, 2]. To some extent, this phenotype has been associated with those subpopulations that are ethnically prone to diabetes, including Native Americans and various Asian populations. However, it is increasingly evident that all populations, regardless of ethnicity or prior predisposition to diabetes, are showing an increased prevalence of type 2 diabetes in younger individuals, in parallel with the pandemic of obesity. The true natural history of early onset type 2 diabetes remains unknown, as there has been no experience from previous generations from which this can be learnt. However, the signs have not been good, and for some time it has been clear that these young patients have a very high risk profile in terms of blood pressure, lipids, albuminuria and a range of other cardiovascular inflammatory markers [3]. Diabetes-related complications are more prevalent in young patients with type 2 than in those with type 1 diabetes when appropriately matched [3].

The increased prevalence of early onset type 2 diabetes brings clinical diabetes care into new and uncharted waters. The modern obesity epidemic is without precedent. Our current understanding of diabetes progression is based mostly on patients whose diabetes developed in middle age and whose BMI (and history of obesity) was and is significantly lower than that in patients in the current report by Convit and colleagues. The current study, if confirmed in larger cohorts, will mark a watershed in our understanding of the toxic and harmful effects of childhood and adolescent obesity. Unfortunately, despite increasing public awareness of the risk of diabetes and numerous government and public initiatives promoting healthy diets and lifestyles, the obesity epidemic continues to accelerate. It remains unclear why some individuals progress to obesity-related complications whereas others (such as the controls in Convit's study) appear to be unaffected. A large component of denial and group-think has allowed modern societies to ignore the threat of obesity, perhaps on the basis that it is truly a problem only for a few. However, if carefully conducted and larger scale prospective studies are now initiated in young cohorts, in which metabolic, vascular and inflammatory variables are measured and neuropsychological tests and brain imaging are conducted, this new complication of obesity and diabetes and its consequences can begin to be understood. Such studies are urgently required given the potential implications of this report for a growing and vulnerable subpopulation of those with diabetes. These individuals are additionally vulnerable because of their age, which places them right at the difficult 'lost' phase of transition between paediatric and adult clinical care. The findings in the current report must provide an urgent stimulus to develop special new approaches to transition clinics for patients with early onset type 2 diabetes, where time may be of the essence for the prevention of a new and sinister end-organ complication of diabetes.

Duality of interest The author declares that there is no duality of interest associated with this manuscript.

References

1. Fagot-Campagna A, Pettitt DJ, Engelgau MM et al (2000) Type 2 diabetes among North American children and adolescents: an epidemiologic review and a public health perspective. J Pediatr 136:664–672
2. McQuaid S, O'Gorman DJ, Yousif O et al (2005) Early-onset insulin-resistant diabetes in obese Caucasians has features of typical type 2 diabetes, but 3 decades earlier. Diabetes Care 28:1216–1218
3. Eppens MC, Craig ME, Cusumano J et al (2006) Prevalence of diabetes complications in adolescents with type 2 compared with type 1 diabetes. Diabetes Care 29:1300–1306
4. Burns N, Finucane FM, Hatunic M et al (2007) Early-onset type 2 diabetes in obese white subjects is characterised by a marked defect in beta cell insulin secretion, severe insulin resistance and a lack of response to aerobic exercise training. Diabetologia 50:1500–1508

5. Hernández MI, Thabit H, Burns N et al (2010) Subjects with early-onset type 2 diabetes show defective activation of the skeletal muscle PGC-1α/mitofusin-2 regulatory pathway in response to physical activity. Diabetes Care 33:645–651
6. Yau PL, Javier DC, Ryan CM et al. (2010) Preliminary evidence for brain complications in obese adolescents with type 2 diabetes mellitus. Diabetologia. doi:10.1007/s00125-010-1857-y
7. Manschot SM, Brands AMA, van der Grond J et al (2006) Brain magnetic resonance imaging correlates of impaired cognition in patients with type 2 diabetes. Diabetes 55:1106–1113
8. van Harten B, de Leeuw FE, Weinstein HC, Scheltens P, Biessels GJ (2007) Brain imaging in patients with diabetes: a systematic review. Diabetes Care 29:2539–2548