

Does recurrent exposure to severe hypoglycaemia affect cognitive function?

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Severe hypoglycaemia is such a common side-effect of insulin therapy affecting people with diabetes, that sometimes the potentially serious outcomes in terms of morbidity are overlooked by physicians. However, fear of hypoglycaemia is prominent among people with diabetes and their relatives. Although permanent neurological deficit following hypoglycaemic coma or seizure is rare, the possibility that recurrent exposure to severe neuroglycopenia may have a cumulative adverse effect on cognitive function and intellectual ability has long been a concern of people with insulin-treated diabetes. Anecdotal accounts have described people affected in this way after experiencing multiple episodes of hypoglycaemia over many years [1], which can jeopardise employment in intellectually-demanding occupations, and ultimately interfere with everyday activities. Although such extreme cases are uncommon, cross-sectional studies of adults with type 1 diabetes, that have relied upon retrospective assessment of the frequency of hypoglycaemia, suggested that a modest but significant decrement in intellectual capacity may be associated with exposure to multiple episodes of severe hypoglycaemia [2-5]. These subtle but detrimental changes in cognition may have practical importance depending on how much an individual requires their intellect for their job, but overall the adult brain appears to be relatively resistant to recurrent neuroglycopenia. Severe hypoglycaemia may have a much greater impact on the more vulnerable brain of the young child, particularly when type 1 diabetes commences early in life [6,7].

Much larger prospective studies, such as the Stockholm Diabetes Intervention Study (SDIS) [8], and specifically, the Diabetes Control and Complications Trial (DCCT) [9,10], failed to show any adverse relationship between severe hypoglycaemia and cognitive ability. While this apparently refuted the findings of the cross-sectional studies, the duration of these large prospective trials was thought to have been insufficient to have allowed any significant cognitive deficit to emerge. Patients were followed in the DCCT for an average of 6.5 years, and the patients with type 1 diabetes who were

recruited for this study, were young and had been selected for inclusion in the trial on the basis of their relatively low risk of severe hypoglycaemia. This cohort was therefore not typical of the wider population of adults with type 1 diabetes, many of whom have risk factors for severe hypoglycaemia such as impaired symptomatic awareness and long duration of the disorder. It has been pointed out that caution must be exercised in extrapolating these findings to everybody with type 1 diabetes [11]. The criticism that the duration of the period of treatment in the DCCT was inadequate to assess the potential effects of recurrent severe hypoglycaemia on the brain has now been addressed by the long-term follow-up of many of the patients in the original study, and reported by the Epidemiology of Diabetes Interventions and Complications Study (EDIC) [12]. This has allowed follow-up of these patients for an average of 18 years.

Approximately 75% of the original DCCT cohort was recruited into the EDIC study; 537 had been in the intensively-treated group and 522 in the conventionally-treated group of the DCCT. The average age of the participants was 47 years, and a stricter (and more robust) definition of severe hypoglycaemia (coma or seizure) was used in EDIC to identify events prospectively. During the period of follow-up a total of 348 patients experienced between one and five episodes of severe hypoglycaemia, while 59 people reported more than five events. No change was found in any of the cognitive domains that had been measured at baseline and were repeated after 18 years of follow-up, in relation to the frequency of severe hypoglycaemia after adjusting for several potential confounding factors, and irrespective of the previously assigned treatment group [12]. The only cognitive abnormalities observed were a moderate decline in motor speed and psychomotor efficiency, which were associated with higher glycated haemoglobin values, suggesting that chronic hyperglycaemia is more detrimental to cognitive ability than severe hypoglycaemia. This unexpected observation is consistent with evidence emerging from studies combining neuroimaging techniques with cognitive assessment that the brain in type 1 diabetes is more vulnerable to the effect of chronic hyperglycaemia, which appears to promote cerebral microangiopathy [13-15].

These EDIC study findings and other emerging evidence of the effects of the metabolic derangements of diabetes on the brain, particularly with respect to severe hypoglycaemia, are reassuring for people with type 1 diabetes, and may help

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to allay anxiety about potential long-term cognitive sequelae associated with recurrent neuroglycopenia. Patients with type 1 diabetes can be reassured that any effort to maintain strict glycaemic control, although it may potentially increase the risk of severe hypoglycaemia, is unlikely to lead to significant intellectual decline as a consequence. However, one major limitation of the EDIC study must not be overlooked, in that the age-group studied (young adults progressing into middle-age), does not provide definitive information about the possible effects of multiple episodes of severe hypoglycaemia on cognitive function in young children with type 1 diabetes, nor does it provide insight into the risk to the insulin-treated elderly patient who may have other co-morbidities that may promote the development of cognitive impairment.

So does recurrent severe hypoglycaemia pose no long-term risk to the brain in people with diabetes? It would be premature to dismiss this dangerous acute metabolic emergency as having little long-term consequence. Aside from the major role of recurrent hypoglycaemia in inducing the acquired clinical syndromes of impaired awareness of hypoglycaemia and hypoglycaemia-associated autonomic failure, it may compound the detrimental effect of chronic hyperglycaemia on cognitive function. A cross-sectional study of 142 adults with type 1 diabetes, all of whom had developed diabetes in childhood or adolescence, found that the best predictor of cognitive decline was the presence of peripheral neuropathy (as a surrogate marker of poor glycaemic control), while a history of severe hypoglycaemia was not significant [16]. However, a significant interaction was observed between neuropathy and severe hypoglycaemia that magnified the degree of cognitive impairment, suggesting that intermittent neuroglycopenia could aggravate the adverse effects of chronic hyperglycaemia on the brain. It would be prudent to avoid repeated exposure to severe hypoglycaemia to avoid any potential long-term risk to the brain in all age-groups with type 1 diabetes.

REFERENCES

1. Gold AE, Deary IJ, Jones RW, et al. Severe deterioration in cognitive function and personality in five patients with long-standing diabetes: a complication of diabetes or a consequence of treatment? *Diabet Med.* 1994; 11: 499-505.
2. Wredling R, Levander S, Adamson U, Lins PE. Permanent neuropsychological impairment after recurrent episodes of severe hypoglycaemia in man. *Diabetologia.* 1990; 33: 152-157.
3. Langan SJ, Deary IJ, Hepburn DA, Frier BM. Cumulative cognitive impairment following recurrent severe hypoglycaemia in adult patients with insulin-treated diabetes mellitus. *Diabetologia.* 1991; 34: 337-344.
4. Deary IJ, Crawford JR, Hepburn DA, et al. Severe hypoglycemia and intelligence in adult patients with insulin-treated diabetes. *Diabetes.* 1993; 42: 341-344.
5. Lincoln NB, Faleiro RM, Kelly C, et al. Effect of long-term glycemic control on cognitive function. *Diabetes Care.* 1996; 19: 656-658.
6. Northam EA, Anderson PJ, Jacobs R, et al. Neuropsychological profiles of children with type 1 diabetes 6 years after disease onset. *Diabetes Care.* 2001; 24: 1541-1546.
7. Northam EA, Rankins D, Cameron FJ. Therapy insight: the impact of type 1 diabetes on brain development and function. *Nature Clin Pract Neurol.* 2006; 2: 78-86.
8. Reichard P, Pihl M, Rosenqvist U, Sule J. Complications in IDDM are caused by elevated blood glucose level: the Stockholm Diabetes Intervention Study (SDIS) at 10-year follow up. *Diabetologia.* 1996; 39: 1483-1488.
9. The Diabetes Control and Complications Trial Research Group: Effects of intensive diabetes therapy on neuropsychological function in adults in the Diabetes Control and Complications Trial. *Ann Int Med.* 1996; 124: 379-388.
10. Austin EJ, Deary IJ. Effects of repeated hypoglycemia on cognitive function: a psychometrically validated reanalysis of the Diabetes Control and Complications Trial data. *Diabetes Care.* 1999; 22: 1273-1277.
11. Frier BM. Intensive glycaemic management in type 1 diabetes: a commentary. In: Williams R, Herman W, Kinmonth A-L, Wareham NJ, eds. *The evidence base for diabetes care.* Chichester, John Wiley & Sons, 2002: 317-332.
12. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research Group: Long-term effect of diabetes and its treatment on cognitive function. *N Engl J Med.* 2007; 356: 1842-1852.
13. Ferguson SC, Blane A, Perros P, et al. Cognitive ability and brain structure in type 1 diabetes: relation to microangiopathy and preceding severe hypoglycemia. *Diabetes.* 2003; 52: 149-156.
14. Wessels AM, Rombouts SA, Simsek S, et al. Microvascular disease in type 1 diabetes alters brain activation: a functional magnetic resonance imaging study. *Diabetes.* 2006; 55: 334-340.
15. Ryan CM. Diabetes and brain damage: more (or less) than meets the eye? *Diabetologia.* 2006; 49: 2229-2233.
16. Ryan CM, Williams TM, Finegold DN, Orchard TJ. Cognitive dysfunction in adults with type 1 (insulin-dependent) diabetes mellitus of long duration: effects of recurrent hypoglycaemia and other chronic complications. *Diabetologia.* 1993; 36: 329-334.

From the Editor

Synopsis: Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research Group. Long-term effect of diabetes and its treatment on cognitive function. *N Eng J Med.* 2007; 356: 1842-1852.

In this observational follow-up study of 1375 diabetic patients who participated in a randomized controlled trial and were followed up for 18 years it was shown that intensive insulin therapy compared to conventional insulin treatment did not cause the deterioration of any cognitive domain despite higher frequency of severe hypoglycemia. The worse glycemic control expressed as increased glycated hemoglobin values was associated with the decline in psychomotor efficiency and motor speed.

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