Cognitive function and mood after profound nocturnal hypoglycaemia in prepubertal children with conventional insulin treatment for diabetes

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Abstract

***Objectives*—To examine the frequency of nocturnal hypoglycaemia, and the effects on cognitive function and mood, in children with insulin dependent diabetes mellitus (IDDM).**

***Design*—Two overnight glucose profiles, in the home environment, and assessments of cognitive function and mood the following day. Twenty nine prepubertal patients with IDDM (median age, 9.4 years; range, 5.3–12.9) and 15 healthy controls (single overnight profile), median age 9.5 (range, 5.6–12.1) years were studied.**

***Results*—Asymptomatic hypoglycaemia (glucose < 3.5 mmol/l) was observed in 13 of 29 patients studied on night 1: four of these and seven others were hypoglycaemic on night 2. The median glucose nadir was 1.9 (range, 1.1–3.3) mmol/l and the median duration of hypoglycaemia was 270 (range, 30–630) minutes. Hypoglycaemia was related to insulin dose, but not glycosylated haemoglobin (HbA1c) values, and was partially predicted by a midnight glucose of < 7.2 mmol/l. Cognitive performance was not altered after hypoglycaemia but a lowering of mood was observed.**

***Conclusions*—Young children on conventional insulin regimens are at high risk for profound, asymptomatic nocturnal hypoglycaemia, which is difficult to predict. There was no short term effect on cognitive function but mood change was detected.**

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Keywords: nocturnal hypoglycaemia; mood; cognitive function; insulin dependent diabetes mellitus

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Asymptomatic nocturnal hypoglycaemia is common in both adults[1–3] and adolescents[4 5] with insulin dependent diabetes mellitus (IDDM), especially in those aiming for tight glycaemic control.[6] Recent studies from Europe[5 7] and Australia[8] have confirmed this high prevalence even in young children (< 12 years of age), but there have been no studies of children in the UK, whose dietary management differs from those of children in France[5] and Spain.[7] Furthermore, there have been no studies to examine the potential consequences of nocturnal hypoglycaemia on school performance and mood the next day in this vulnerable age group.

Studies in adults have shown no effect of experimentally induced nocturnal hypoglycaemia on cognitive performance the next morning[9 10]; however, one of these studies did show a deleterious effect on mood.[10] The possible consequences to the young, developing brain may be greater, because children diagnosed at < 5 years of age have been found consistently to have significant defects in cognitive performance, although the association with hypoglycaemia remains unclear.[11–14] The possible contribution of prolonged or repeated nocturnal hypoglycaemia has not been evaluated.

There has been an approximately twofold increase in the incidence of IDDM, almost exclusively in those under 5 years old.[15] This, combined with the move towards intensified insulin treatment, even in young children, makes it essential that we know the prevalence and sequelae of nocturnal hypoglycaemia in this age group.

To answer these questions, we studied the frequency of nocturnal hypoglycaemia, as determined in the child's home, concentrating on prepubertal children on conventional insulin regimens, and examined the short term effect on cognitive function and mood.

Methods

SUBJECTS

We recruited children from the paediatric diabetic clinic of the John Radcliffe Hospital, Oxford, on the basis of their willingness to participate. Those eligible were prepubertal children over the age of 5 years, with a diabetes duration of greater than 12 months, and with no other important medical condition.

Twenty nine of 52 eligible children were studied (table 1). They were all on twice daily mixtures of soluble and isophane insulin given 15–30 minutes before their meal (median, 0.7 U/kg/day; range, 0.4–1.1). Breakfast was given between 07:00 and 08:00, lunch between 12:00 and 13:00, and the evening meal between 17:00 and 19:00, depending on age. Children were also given three snacks a day: one mid-morning, one mid-afternoon, and one before bed (between 20:00 and 22:00). The median glycosylated haemoglobin (HbA1c) was 8.8% (range, 6.9–11%). Two girls had treated hypothyroidism.

We also studied 15 healthy children, siblings or friends of children attending the diabetic clinic, to provide normal control data (table 1). None had significant physical or psychological problems or sleep disorders.

The study was approved by the central Oxford research ethics committee and consent

Table 1 Demographic details of participants with and without insulin dependent diabetes mellitus (IDDM)

	IDDM (n = 29)	*Controls (n = 15)*
Age (years)	9.4 (5.3 to 12.9)	9.5 (5.6 to 12.1)
HbA1c (%)	8.8 (6.9 to 11)	5.3 (5.1 to 5.7)
Duration of diabetes (years)	3.4 (1 to 10.2)	—
Insulin dose (U/kg/day)	0.7 (0.4 to 1.1)	—
BMI standard deviation score	0.34 (−1.14 to 1.89)	−0.48 (−1.48 to 2.00)

Values are median (range).
BMI, body mass index; HbAlc, glycosylated haemoglobin.

was obtained from the parents once assent had been obtained from the children.

PROCEDURES

Studies on the children with IDDM took place in their home after a normal day's routine as regards diet, activity, and dose of insulin.

Two overnight metabolic profiles were performed, one to two weeks apart. At 19:30, an intravenous cannula was sited on the dorsum of the hand and patency maintained with heparinised normal saline. Blood samples for HbA1c and C-peptide measurements were taken at 20:00 and 07:30, respectively. Venous samples were taken for glucose every 15 minutes. Children were observed constantly (by KAM) throughout the night for symptoms of hypoglycaemia (restlessness, sweating). No glucose measurements were performed in the home and intervention was only proposed if symptomatic hypoglycaemia occurred.

When blood glucose was measured the next day, we defined hypoglycaemia as a blood glucose < 3.5 mmol/l on two successive 15 minute measurements. Those children found to be hypoglycaemic on the first study night were given 25% extra carbohydrate in the form of uncooked cornstarch with their usual evening snack on the second night in an attempt to avoid hypoglycaemia.

We calculated body mass index (BMI) from children's heights and weights (kg/m^2) and derived standard deviation scores from UK national standards.[16] We studied non-diabetic children, using an identical protocol, on one occasion, either at home (seven subjects), or in hospital.

In all children with IDDM, a battery of cognitive tasks, lasting approximately one hour, were administered in the morning, after breakfast and correction of low blood glucose levels.

ASSAYS

We measured whole blood glucose using a glucose oxidase method (YSI analyser; Clandon Scientific Ltd, Farnborough, Hampshire, UK). HbA1c was measured by means of high performance liquid chromatography (HPLC) (Diamat; BioRad Laboratories Ltd, Hemel Hempstead, UK)—normal range 4.3–6.1%. The intra-assay coefficients of variation were 1.9% and 2.2% at HbA1c values of 6.9% and 11.5%, respectively. The interassay coefficients of variation were 2.7% and 2.3% at HbA1c values of 7.0% and 11.6%, respectively. C-peptide concentrations were determined by a double antibody radioimmunoassay (Diagnostic Products, Euro/DPC Ltd, Llanberis, Caernarfon, UK). Intra-assay coefficients of variation were 3.4% and 3.0% at C-peptide concentrations of 294 and 2614 pmol/l, respectively, whereas interassay coefficients of variation were 10.0% and 1.9% at C-peptide values of 297 and 2929 pmol/l, respectively.

Table 2 Frequency of glucose nadir occurring during 24 nights of hypoglycaemia

Glucose nadir (mmol/l)	*Number of episodes*
1–1.5	6
1.6–2.0	7
2.1–2.5	3
2.6–3.0	5
3.1–3.5	3

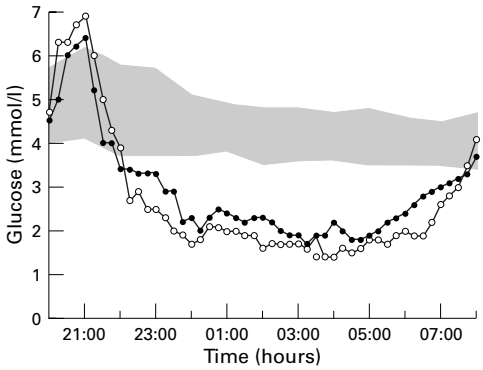

Figure 1 Overnight glucose profiles of one patient who was hypoglycaemic on both study nights. The shaded area represents the range of glucose values from the overnight profiles of the children without diabetes.

COGNITIVE FUNCTION

The tests were chosen for their psychometric properties, acceptability to children, and relevance to their daily lives. The battery of cognitive tests had been used successfully in previous studies of children with other physical disorders.[17 18] At the first testing session, children underwent a practice schedule in an attempt to eliminate practice effects.

Visuomotor coordination was assessed by the time to complete a spiral maze,[19] and the timed insertion of pegs into a grooved pegboard,[20] using both dominant and non-dominant hands, separately for the series, then alternately. The factual content of immediate and delayed recall of stories were scored as an assessment of memory.[21] Tasks to examine the functions of memory combined with attention included forward and backward digit span[22] and a letter matching task that required the child to read through a page of unpronounceable letter strings, matching ones that were identical.[23] Focal attention was assessed by sorting cards on the basis of the presence or absence of particular characteristics,[24] and sustained attention was assessed by a 16 minute continuous performance test using an audio tape of numbers, interspersed at random with 32 letters that were to be noted.[25] Ability to establish and modify an attentional set was measured by means of a letter cancellation task where subjects were required initially to cancel all the letters in columns of digits and then switch to cancelling the digits in a column of letters.[26] Divergent thinking was assessed using the Torrance test of creative thinking[27] to give

Table 3 Comparison of clinical characteristics in patients who became hypoglycaemic and those who did not

	Hypoglycaemia (n = 20)	*No hypoglycaemia (n = 9)*	*p Value*	*Mann-Whitney U value*
Age at study (years)	8.7 (5.3 to 12.9)	9.8 (8.5 to 12.2)	0.17	61.0
Age at diagnosis (years)	4.5 (0.4 to 10.7)	7.5 (1.4 to 8.8)	0.13	57.5
Duration of diabetes (years)	3.9 (1.1 to 10.2)	2.4 (1.0 to 8.6)	0.37	70.0
Insulin dose (U/kg/day)	0.8 (0.5 to 1.1)	0.6 (0.4 to 0.8)	0.006	33.0
HbA1c (%)	8.7 (6.9 to 10.3)	9.8 (8.3 to 11.0)	0.14	58.5
BMI standard deviation score	0.34 (−1.14 to 1.89)	0.34 (−0.88 to 1.8)	0.76	83.5
C-peptide status (number positive)*	4	4	0.09	–

Values are median (range).
*C-peptide positive if value > 46.3 pmol/l.
BMI, body mass index; HbAlc, glycosylated haemoglobin.

scores of fluency, originality, and flexibility of thought.

MOOD

Mood was evaluated using the well established children's depression inventory,[28] consisting of items that cover a range of depressive symptoms.

STATISTICAL ANALYSIS

All data are presented as means (SEM) or medians and range (interquartile range in the case of psychometric data), unless otherwise stated. Group comparisons were made using non-parametric Mann-Whitney tests. Cognitive function and mood were analysed only in individuals (n = 17) where a night of hypoglycaemia could be compared with a night without, using paired data (Wilcoxon). One younger child could not perform two of the cognitive tasks so for these analyses only 16 pairs were used. Spearman's correlation test was used to find the best correlation between the glucose value at 04:00 and a glucose value earlier in the evening, and predictive value was calculated according to the method of Vecchio.[29]

The computer program SPSS 7.5 for Windows 95 was used to analyse the data.

Results

EPISODES OF HYPOGLYCAEMIA

We observed 24 episodes of hypoglycaemia. Thirteen of the 29 children were hypoglycaemic on study night 1. Four of these were also hypoglycaemic on study night 2, despite cornstarch administration; one of these children agreed to a third study night during which hypoglycaemia was avoided. Seven patients were hypoglycaemic on night 2 only.

During episodes of hypoglycaemia, the median glucose nadir was 1.9 mmol/l (range, 1.1–3.3 mmol/l) and in over half of the episodes the blood glucose fell to less than 2.0 mmol/l (table 2). The median duration of hypoglycaemia was 270 minutes (range, 30–630 minutes). The median time of glucose nadir was 04:15 but there was a wide range from 21:45 to 06:45. The time at which hypoglycaemia was first detected was also variable, with a range from 21:00 to 05:15. Ten episodes began before midnight, eight between midnight and 04:00, and six between 04:00 and 08:00. The pattern of change in blood glucose was variable but could be remarkably reproducible within an individual (fig 1).

Blood glucose concentrations in the control subjects never fell below 3.5 mmol/l overnight (fig 1).

RISK FACTORS FOR HYPOGLYCAEMIA

When comparing children who became hypoglycaemic (n = 20) with those who did not, insulin dose was higher (p = 0.006) but there were no differences in age, duration of diabetes, HbA1c, or BMI standard deviation score (table 3).

There were no reliable clinical indicators (restlessness or sweating) of the presence of hypoglycaemia, either at night or the next morning. Intervention was undertaken in one child who awoke after technical difficulties with the sampling line and developed symptoms of hypoglycaemia 30 minutes later.

Table 4 Results of cognitive function tests in the 17 children with a night of hypoglycaemia and a control night without hypoglycaemia for comparison

Task	*Hypoglycaemia*	*No hypoglycaemia*	*Wilcoxon value*	*p Value*
Spiral maze (a)	79 (66 to 94)	82 (66 to 89)	−0.50	0.62
Pegboard: right hand (b)	79 (66 to 92)	75 (68 to 88)	−0.02	0.98
Pegboard: left hand (b)	86 (75 to 108)	88 (73 to 110)	−0.93	0.35
Pegboard: alternate hands (b)	83 (72 to 92)	79 (72 to 99)	−0.47	0.64
Immediate story recall (a)	23 (20 to 31)	25 (20 to 30)	−0.99	0.32
Delayed story recall (a)	22 (8 to 28)	21 (17 to 26)	−0.90	0.37
Digit span: forwards (c)	5 (5 to 6)	5 (5 to 6)	−0.34	0.74
Digit span: backwards (c)	4 (3 to 5)	4 (3 to 5)	−0.25	0.80
Letter matching (b)	170 (154 to 221)	178 (125 to 253)	−0.05	0.96
Card sorting (b)	11 (0.5 to 19)	11 (−5 to 19)	−0.88	0.38
Continuous performance test (d)	15 (14 to 16)	14 (12 to 15)	−0.87	0.39
Letter cancelling (b)	114 (104 to 127)	118 (110 to 134)	−0.88	0.38
Torrance test: originality (e)	5 (3 to 11)	6 (3 to 12)	−0.38	0.70
flexibility (f)	6 (3 to 8)	5 (4 to 10)	−0.98	0.33
fluency (g)	11 (7 to 16)	10 (5 to 16)	−0.78	0.43

Values are median (interquartile range).
Scoring systems used: (a) number of idea units recalled; (b) time to complete task (with the penalty for errors) in seconds; (c) number of digits recalled correctly; (d) number of items identified correctly; (e) number of original ideas; (f) number of different categories of ideas; (g) total number of ideas.

The wide variation in time of glucose nadir made it difficult to predict nocturnal hypoglycaemia accurately. The median time of glucose nadir was 04:00 and blood sugar at this time correlated with midnight concentrations (r^2 = 0.6; p = 0.00001). If the blood glucose at midnight was < 7.2 mmol/l, the risk of nocturnal hypoglycaemia was 84% (confidence limits, 75–93%). Conversely, if the blood glucose was > 7.2 mmol/l there was an 80% (confidence limits, 79–85%) likelihood of the patient not having a glucose value < 3.5 mmol/l overnight.

The median fasting blood glucose at 07:00 was significantly lower after hypoglycaemia than after a night with no hypoglycaemia (3.7 (range, 1.4–10.6) *v* 8.5 (range, 3.8–19.2) mmol/l; p = 0.00001).

COGNITIVE FUNCTION

The results of cognitive function tests of the 17 children where paired comparisons between hypoglycaemic and non-hypoglycaemic nights were possible were similar on both study days (table 4).

MOOD

A significant difference was found in the children's depression inventory. This was found to be higher after the night of hypoglycaemia: median score, 5 (range, 2–8.5) *v* 3 (1.5–6.5) on the control night (p = 0.03).

Discussion

We believe this is the first study where full 12 hour glucose profiles have been obtained at home to mimic normal conditions. Because glucose concentrations were not measured until after the profile, no intervention was needed, and episodes of hypoglycaemia were undoubtedly asymptomatic. The high prevalence and severity of the nocturnal hypoglycaemia was unexpected although comparable with data from other studies.[5 7 8] The prevalence of 45% (study night 1) was comparable to that seen in French children (47%),[5] despite the fact that UK children are routinely given a bedtime snack, whereas French children are not. Nocturnal hypoglycaemia has also been found to be common in young children in Spain even when food is consumed much later in the evening.[7]

A major concern is the possible effect of nocturnal hypoglycaemia on cognitive function the next day.[30 31] Studies of experimentally induced hypoglycaemia in adults suggest that cognitive performance can return to normal within an hour of glucose recovery.[32 33] Furthermore, in studies of hypoglycaemia induced during sleep in adults, no effects have been found in any aspect of cognitive performance tested, but in these studies the duration of hypoglycaemia was brief and the glucose nadir not so profound as that seen in our patients.[9 10] The hypoglycaemia that we observed was not only severe (during more than half the episodes the glucose concentration was < 2.0 mmol/l) but also prolonged (median duration, 270 minutes; range, 30–630 minutes); thus, it was reassuring that we saw no effects on cognitive function the next day. However, studies have consistently found impaired performance in a number of cognitive domains in children diagnosed with diabetes at < 5 years of age, the reasons for which remain unclear.[11–14] Thus, we cannot discount the possibility of cumulative detrimental effects of recurrent unrecognised nocturnal hypoglycaemia on cognitive function, particularly in the light of evidence that children are more susceptible than adults to neuropsychological impairment during hypoglycaemia.[34 35] Our choice of 3.5 mmol/l as the definition of hypoglycaemia was selected based on these studies, which have indicated that children have deterioration in p300 potentials and electroencephalogram changes that occur at this glycaemic value—a higher value than that seen for adults.[34 35] Interestingly, none of the control subjects had blood glucose concentrations below this threshold.

Despite the lack of change in cognitive function, we did observe a decrease in subject well being, as assessed by the children's depression inventory. Few studies have examined the effect of blood glucose concentration on mood and behaviour and most have studied changes during acute episodes of hypoglycaemia,[36 37] rather than any persistent effects. However, one study of the effects of induced nocturnal hypoglycaemia in adults also found a persistent detrimental effect on mood the next day.[10] The inventory scores in our children after hypoglycaemia were not in the pathological range but, nevertheless, it is possible that changes in mood could have affected social or educational performance the next day in ways that were too subtle to detect with the battery of tests chosen in our study.

Further studies are required to determine the long term sequelae of asymptomatic hypoglycaemia in this age group. Until these data are available, we have to decide on appropriate advice for parents. Previous studies have indicated that if the blood glucose at 22:00 is < 6 mmol/l, extra carbohydrate could prevent most episodes of nocturnal hypoglycaemia.[38] We and others were not able to confirm these safety instructions.[5 8] In our study, a midnight value of < 7.2 mmol/l had a positive predictive value of 84% with respect to 04:00 blood glucose, but only predicted 66% of episodes of hypoglycaemia. Furthermore, early morning hyperglycaemia (Somogyi phenomenon) was not a useful marker in this age group. If anything, low glucose concentrations in the morning were the best indicator of overnight hypoglycaemia. We hoped that cornstarch might provide long acting protection from hypoglycaemia because it can maintain normoglycaemia for up to nine hours in patients with type 1 glycogen storage disease.[39] In fact, we found a minimal effect and even when hypoglycaemia was prevented there was unacceptable hyperglycaemia (mean (SEM) glucose values, 5.4 (0.6) *v* 10.8 (1.0) mmol/l, hypoglycaemia *v* non-hypoglycaemia, respectively). At present, the only advice we can give is to reiterate the need for an evening snack and advise blood testing at midnight if recurrent hypoglycaemia is suspected.

We have identified an alarming prevalence of unpredictable asymptomatic nocturnal hypoglycaemia associated with mood change in these young children. This is of concern to all parents and carers of children with diabetes, particularly with the drive towards tighter control and intensive insulin treatment. Our results raise important issues regarding the pathophysiology of nocturnal hypoglycaemia in young children, the lack of glucose recovery overnight, the possibility of secondary daytime hypoglycaemia unawareness, and potentially adverse psychological consequences.

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