Previous Episodes of Hypoglycemic Coma Are Not Associated With Permanent Cognitive Brain Dysfunction in IDDM Patients on Intensive Insulin Treatment

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Intensive insulin treatment of IDDM is associated with increased frequency of hypoglycemic coma. The extent of possible cerebral sequelae after recovery is still unknown. We studied the impact of previous hypoglycemic coma on neurophysiological measures of cognitive brain function in 108 patients with adult-onset IDDM receiving intensive insulin treatment. In the study, 55 IDDM patients (age 38 ± 14 years, mean ± SD) who had a history of ≥1 (median 3, range 1–35) comatose hypoglycemic event were compared with 53 IDDM patients (age 34 ± 12 years) with no history of hypoglycemic events using P300 event-related potentials and psychometric tests (the Mini-Mental State Exam and trail-making test, part A). Findings on these patients were compared with those from 108 matched healthy control subjects. No difference was observed in P300 latencies and psychometric tests between patients with and without a history of hypoglycemic coma (P300 latency, 346 vs. 342 ms; trailmaking test, 31 vs. 30 s; Mini-Mental State Exam, 29.5 vs. 29.6; NS). In diabetic patients, however, P300 latencies were delayed compared with those of healthy control subjects (344 vs. 332 ms; $P < 0.001$) and were correlated to diabetes duration but not to total hypoglycemic episodes. Scores on the Mini-Mental State Exam (29.5 vs. 29.6; $P = 0.59$) and trail-making test (31 vs. 28 s; $P = 0.10$) were not different between patients and control subjects. In conclusion, previous episodes of hypoglycemic coma are not associated with permanent impairment of cognitive brain function in patients with adult-onset IDDM receiving intensive insulin treatment compared with patients without such episodes. Cognitive brain function, however, is subclinically impaired in relation to duration of diabetes. ***Diabetes*** **47:1909–1914, 1998**

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EEG, electroencephalogram; Cz, vertex; Fz, frontal; MRI, magnetic resonance imaging.

Intensive insulin treatment is considered the most effective strategy for preventing complications of diabetes (1,2). However, intensive treatment is associated with increased frequency of comatose hypoglycemia (3,4). Although acute moderate hypoglycemia causes reversible cognitive deficits in diabetic and healthy subjects, it is difficult to assess potential long-term brain damage after comatose hypoglycemia. Reports of impaired neuropsychological performance after recurrent comatose hypoglycemia have been challenged by large prospective trials in which no such impairment has been observed (4,5).

Event-related (P300) potentials have been used as an objective measure of cognitive brain function (6–8). P300 latency increases with age and is a neurophysiological correlate of information processing, such as stimulus evaluation, alertness, and memory updating; the P300 amplitude reflects the amount of conscious attention paid to a task (6). The P300 method is more sensitive than psychometric tests and electroencephalogram (EEG) in detecting subclinical effects of acute hypoglycemia (9), and results in abnormal findings in patients with dementia, focal brain lesions, cerebrovascular disease, and diffuse brain damage after irradiation (6,8,10). Cerebral sequelae of sarin poisoning were detected by prolonged P300 latencies but not by neuropsychological tests 6 months after the Tokyo subway attack (11). Because the hippocampus, which is a key generator of P300, is a particular target of hypoglycemic damage, this method seems to be an appropriate tool for objective assessment of hypoglycemic sequelae (6,12). This cross-sectional study compared intensively treated diabetic patients who had experienced comatose hypoglycemic events with matched patients with no history of comatose hypoglycemic events and healthy subjects.

RESEARCH DESIGN AND METHODS

Patient selection. We studied 108 IDDM diabetic outpatients (age 36 ± 13 years; 49 males). Clinical diagnosis of IDDM was established by sudden ketoacidotic onset of the disease at an age <50 years, usually with a BMI <20 kg/m^2. Patients were eligible for the study if diabetes manifestation had occurred at age 16 years or older, serum C-peptide was <0.5 ng/ml, the duration of the disease was >1 year, and intensive treatment had been applied for >6 months. Informed consent was obtained from all patients, and the study protocol was approved by institutional review. Adherence to treatment was ensured at outpatient visits at least every 3 months.

Patients' clinical characteristics are given in Table 1. Out of 109 consecutive IDDM patients with a history of comatose hypoglycemia who were screened at

the outpatient service of two tertiary diabetes centers, 55 were recruited for the study. Reasons for exclusion were onset of IDDM before age 16 years (n = 20), a comatose hypoglycemic event <4 weeks before examination (n = 8), insufficient recall of hypoglycemic events (n = 6), declined participation (n = 5), intensive treatment duration <6 months (n = 4), spontaneous recovery from coma (n = 3), use of sedatives or alcohol (n = 2), presence of mental disorders (n = 2), presence of cerebrovascular disease (n = 2), opiate withdrawal (n = 1), and renal failure (n = 1). These 55 patients were compared with 55 age-matched IDDM patients who had no history of comatose hypoglycemic events and none of the above contraindications. Two of the latter patients were excluded from analysis for concealed use of sedatives.

The 108 healthy control subjects (age 36 ± 14 years) were sex- and age-matched out of a group of 221 nonpaid apparently healthy volunteers recruited over a period of 5 years to generate a P300 reference database (7,8). They were tested with the Mini-Mental State Exam (13) (score ≥27 in all) and the trailmaking test, part A (14), before the P300 recording. Subjects with a history of neurological or psychiatric illness or attention and learning deficits as well as those taking central nervous system–active drugs were excluded.

Diabetes management. All patients studied were self-recruited and not randomized to intensive treatment. They had initially undergone a 10-day in-hospital training in the use of a multiple insulin injection regimen using the basis-bolus concept of functional insulin therapy (15); they were instructed to perform reflectometer blood glucose tests at least four times per day and were meticulously trained for recognition and avoidance of hypoglycemia. Patients administered three or more daily injections of regular human insulin and substituted long-acting insulin for basal insulin twice daily (15). Oral therapies consisted of angiotensin-converting enzyme inhibitors (n = 6), calcium-channel antagonists (n = 5), low-dosage aspirin (n = 4), beta-blockers (n = 3), lipid-lowering drugs (n = 3), levothyroxine (n = 3), bronchodilatory agents (n = 3), long-acting nitrates (n = 1), diclofenac (n = 1), prednisolone (n = 1), and calcium dobesilate (investigational use, n = 9). A structured interview and thorough check of medical records were performed to assess demographic data, total number of comatose hypoglycemic events, current incidence of slight hypoglycemia, duration of treatment, and dietary and insulin requirements. We also interviewed relatives or partners and general practitioners of patients to confirm hypoglycemic events. If necessary, hospital or emergency department records were checked.

In the course of intensive insulin treatment, HbA_{1c} was determined every 3 months by high-performance liquid chromatography (C-R4A Chromatopac; Shimazdu, Kyoto, Japan) and renal albumin excretion was measured in 24-h urine collections twice a year. Retinopathy was assessed annually by color fundus photography and was arbitrarily staged by a score (0, absent; 1, background retinopathy; 2, proliferative retinopathy). Peripheral neuropathy was assessed by clinical examination of deep tendon reflexes, paresthesia, and sensory and vibration discrimination in all 108 IDDM patients and by additional peroneal motor nerve conduction velocity measurements in 22 patients. Patients were judged to have neuropathy if at least two clinical parameters were consistently abnormal or nerve conduction velocity was <40 m/s. Venous plasma glucose was measured immediately before neurophysiological examination by a Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA). P300 and neuropsychological tests were performed at venous glucose levels of 5.6–11.1 mmol/l (100–200 mg/dl).

Hypoglycemia. Hypoglycemic coma was defined by loss of consciousness with or without seizures and the inability to ingest carbohydrates, thereby necessitating intravenous glucose or subcutaneous glucagon administration, usually by a first-aid physician. Patients who recovered spontaneously or after oral carbohydrates were excluded. Slight hypoglycemia was defined as a hypoglycemic state without loss of consciousness, detected by either hypoglycemic symptoms or glucose levels <2.8 mmol/l (50 mg/dl) in reflectometer controls. Patients were asked for their current pattern of neuroglycopenic and adrenergic hypoglycemic symptoms.

Evoked potentials. Evoked potentials were recorded on a Nicolet CA 2000 (Nicolet, Madison, WI) with Ag/AgCl electrodes (Picker, Munich, Germany) and adhesive electrolyte gel (Grass, Quincy, MA). Active electrodes placed at the Cz (vertex) and Fz (frontal) positions according to the International 10/20 System were referenced to linked earlobes. The common electrode was C3. Impedance was maintained at <3 kΩ; the filter bandpass was 0.01–30 Hz (6). Random background (80%, 1,000 Hz) and target (20%, 2,000 Hz) tones were delivered by headphones at 55 dB normal hearing level. Patients and control subjects were seated comfortably and asked to keep a running mental count of target tones. At least 25 EEG epochs following the target tones were averaged; the task was repeated to confirm reproducibility. Artifacts were automatically rejected. Attention was verified by comparing actual number of target tones with the number counted by the subjects. In cases in which there was >10% discrepancy, the task was repeated. A large positive deflection later than 280 ms was defined as P300 (6). Peak latencies were obtained by extrapolation of adjacent slopes and reviewed by a second physician; amplitudes were calculated between P300 and N400 peaks (6).

Psychometric tests. The trailmaking test, part A (14), and the Mini-Mental State Exam, a 10-min bedside test of neurocognitive function (13), were performed for global assessment of cognitive and psychomotor function.

Statistics. Data are expressed as means ± SD unless indicated otherwise. Statistical analysis was performed with SAS software (SAS Institute, Cary, NC). P < 0.05 was considered statistically significant; all tests were two-tailed. Normality was checked using the Wilks-Shapiro test. Group comparison was performed with analysis of variance, Wilcoxon two-sample procedures, or χ^2 test if appropriate. The influence of clinical parameters (as described below) on P300 and psychometric findings was investigated with Pearson and Spearman correlation coefficients and linear regression analysis. Potential confounding of age and diabetes duration with effects of hypoglycemic episodes on psychometric and P300 findings was corrected for using partial correlation.

RESULTS

Clinical data. Clinical data of IDDM patients are given in Table 1. Patients with a history of hypoglycemic coma reported experiencing a median of 3 comatose events (range 1–35). They had a longer duration of diabetes, were more likely to be female, had more advanced retinopathy, displayed a trend for higher urinary albumin excretion, and had lower BMI than patients with no history of hypoglycemic coma. They also reported a higher ratio of neuroglycopenic to adrenergic hypoglycemic symptoms (1.44 vs. 0.96; P = 0.02). No difference was seen between patient groups as to incidence of slight hypoglycemia, insulin and dietary requirements, and current blood glucose and HbA_{1c} levels.

Evoked potentials and psychometric tests. No difference was observed for P300 latency, P300 amplitude, and scores on the trailmaking test and Mini-Mental State Exam between patients with a history of hypoglycemic coma and those without (Table 2). However, when comparing the total cohort of diabetic to healthy subjects, P300 peaks were significantly delayed in IDDM patients (P < 0.001), indicating subclinical cognitive brain dysfunction (Table 3). IDDM patients also showed a trend (P = 0.10) for slower performance in the trailmaking test. P300 amplitudes and Mini-Mental State Exam scores were similar in patients and healthy subjects (Table 3).

Subgroup analysis. There was no difference in neurophysiological measurements and psychometric test results when patients with excellent glycemic control (HbA_{1c} ≤6.5%) (5.8 ± 0.5%; n = 49) were compared with those with HbA_{1c} levels >6.5% (7.8 ± 1.3%; n = 59) (Table 4). Patients with low HbA_{1c} were of the same age (36 ± 12 vs. 36 ± 13 years; P = 0.85) but had a later onset (25 ± 8 vs. 20 ± 7 years; P = 0.02) and a shorter duration of diabetes (11.8 ± 11.6 vs. 16.1 ± 10.8 years; P = 0.02) as well as lower insulin requirements (37 ± 11 vs. 42 ± 13 U/day; P = 0.04) than patients with higher HbA_{1c} levels. Current blood glucose levels were lower in patients with low than in patients with higher HbA_{1c} (7.8 ± 3.1 mmol/l [140 ± 56 mg/dl] vs. 8.8 ± 2.8 mmol/l [159 ± 50 mg/dl]; P = 0.02). No difference was seen between high and low HbA_{1c} groups for the number of comatose hypoglycemic episodes (3.0 ± 6.7 vs. 3.4 ± 6.3; P = 0.41) or the degree of retinopathy (P = 0.19), neuropathy (P = 0.26), or microalbuminuria (P = 0.71).

Correlation analysis. P300 peak latency was significantly correlated to age of both IDDM patients and healthy subjects (Fig. 1) and to the duration of diabetes after correction for age (r = 0.26, P = 0.007 for Cz; similar data from Fz not shown). Inverse correlations were observed for age and P300 amplitude in patients (r = –0.34, P < 0.001) and control subjects (r = –0.34, P < 0.001) and for age and Mini-Mental State Exam

TABLE 1
Patient characteristics

	Patients with no history of hypoglycemic coma	Patients with a history of hypoglycemic coma	*P* value
n	53	55	—
Age (years)	34 ± 12	38 ± 14	0.08
Sex (M/F)	30/23	19/36	0.02
Diabetes duration (years)	10.8 ± 10.6	17.6 ± 11.6	< 0.001
Age at diagnosis (years)	23 ± 6	21 ± 7	0.41
Intensified insulin therapy duration (years)	2.5 ± 3.9	3.2 ± 2.9	0.045
Conventional insulin therapy duration (years)	8.6 ± 9.7	13.5 ± 12.0	0.02
Daily insulin requirement (U/kg)	0.58 ± 0.21	0.59 ± 0.18	0.73
Incidence of slight hypoglycemia per week	1.9 ± 2.0	2.2 ± 3.1	0.61
Blood glucose levels at time of study (mg/dl)*	151 ± 49	153 ± 61	0.75
HbA_{1c} (%)	6.9 ± 1.3	7.0 ± 1.6	0.71
Microalbuminuria ($mg \cdot m^{-2} \cdot min^{-1)}$	24 ± 70	88 ± 341	0.06
Retinopathy score (arbitrary units)†	0.3 ± 0.6	0.7 ± 0.8	0.002
Distal sensomotoric neuropathy (*n*)	4	6	0.79
BMI (kg/m^2)	24.7 ± 3.5	23.4 ± 3.5	0.065

Data are means ± SD. *To convert glucose values from milligrams per deciliter into millimoles per liter, multiply by 0.05551. †0, normal; 1, background retinopathy; 2, proliferative retinopathy.

score ($r = –0.20$, $P = 0.04$ [patients] and $r = –0.38$, $P = 0.01$ [control subjects]), whereas the trailmaking test score was directly related to age ($r = 0.34$, $P = 0.01$ [patients] and $r = 0.30$, $P = 0.004$ [control subjects]).

There was no correlation between total number of comatose hypoglycemic episodes and P300 after correction for age and diabetes duration (partial correlation, P300 latency: $r = 0.09$, $P = 0.36$; amplitude: $r = –0.14$, $P = 0.30$). HbA_{1c}, urinary albumin excretion, neuropathy, and retinopathy as well as time since the last hypoglycemic coma were not correlated with P300 and psychometric results.

DISCUSSION

This study indicated that previous episodes of comatose hypoglycemia in intensively treated patients who developed IDDM in adult life were not necessarily associated with permanent cognitive impairment. Brain function, however, was subclinically impaired in IDDM patients. This impairment correlated to the duration of disease but not to the number of previous hypoglycemic comas and current glycemic control.

Our neurophysiological data confirmed psychometric findings from both the Diabetes Control and Complications Trial (5) and Stockholm trial (4), in which cognitive brain function was stable during a long period of intensive insulin treatment despite a threefold increased frequency of comatose hypoglycemia. If anything, a slight improvement in motor speed was observed (5). In accordance with those results, brain morphology as studied by magnetic resonance imaging (MRI) and metabolism of glucose and oxygen as studied by positron emission tomography were not different between IDDM patients with a history of up to 100 comatose hypoglycemic events and those with no history of these events (16). The usually short duration of hypoglycemia and the capability of the brain to use alternative substrates during hypoglycemia might explain those findings (17). By such adaptation, the brain is largely protected from hypoglycemic damage in the short term. This does not apply to prolonged coma with concomitant hypoxia (12).

Our findings are at variance with those of previous cross-sectional studies that hypothesized that hypoglycemic coma was the main cause of cognitive impairment (18–21). Langan et al. (18) reported a reduction in performance IQ but not verbal IQ in 24 patients after more than five episodes of severe hypoglycemia as compared with 23 patients with no history

TABLE 2
Comparison of brain function in IDDM patients with and without a history of hypoglycemic coma

	Patients with no history of hypoglycemic coma	Patients with a history of hypoglycemic coma	*P* value
n	53	55	—
P300 latency			
Cz (ms)	342 ± 21	346 ± 23	0.40
Fz (ms)	337 ± 20	342 ± 21	0.24
P300 amplitude			
Cz (μV)	20.9 ± 6.9	19.6 ± 7.0	0.34
Fz (μV)	22.5 ± 8.7	21.2 ± 8.7	0.45
Trailmaking test, part A (s)	31.0 ± 9.6	30.1 ± 10.5	0.50
Mini-Mental State Exam score	29.5 ± 0.9	29.6 ± 0.7	0.35

TABLE 3
Comparison of brain function in IDDM patients and healthy subjects

	Diabetic patients	Healthy subjects	*P* value
n	108	108	—
Age (years)	36 ± 13	36 ± 13	0.87
P300 latency			
Cz (ms)	344 ± 22	332 ± 21	<0.001
Fz (ms)	340 ± 21	330 ± 21	<0.001
P300 amplitude			
Cz (μV)	19.6 ± 7.0	18.1 ± 5.6	0.11
Fz (μV)	21.2 ± 8.7	18.7 ± 7.1	0.06
Trailmaking test, part A (s)	30.6 ± 10.5	28.3 ± 10.1	0.10
Mini-Mental State Exam score	29.5 ± 0.7	29.6 ± 0.7	0.59

of such episodes. Further, a larger difference between estimated and actual premorbid intelligence was calculated in the hypoglycemia group. It may be argued that comparing arbitrarily defined subgroups of highly selected patients cannot prove causality and that preexisting cognitive impairment might have caused hypoglycemia by insufficient diabetes management. A comparison of the same sample to matched control subjects by Deary et al. (19) suggested that IDDM patients overall had slightly lower performance IQ and verbal IQ; the difference in performance IQ was abolished after correction for frequency of hypoglycemia. Their main finding, however, was not reproduced in a more recent study where performance IQ was found to be higher in IDDM patients (P > 0.01 for comparison with Deary's control group) (20). Wredling et al. (21) reported slight impairment in some psychometric tests in a small group of selected patients with and without repeat hypoglycemia. Again, it is difficult to decide whether such findings may apply to other IDDM patients. Interestingly, none of those studies reported significant memory problems after hypoglycemia, although such a correlate of hippocampal damage would have been expected from the pathophysiology of severe hypoglycemic brain damage (12). Consequently, it is less likely that hypoglycemia is a cause of cognitive impairment than has been previously suggested.

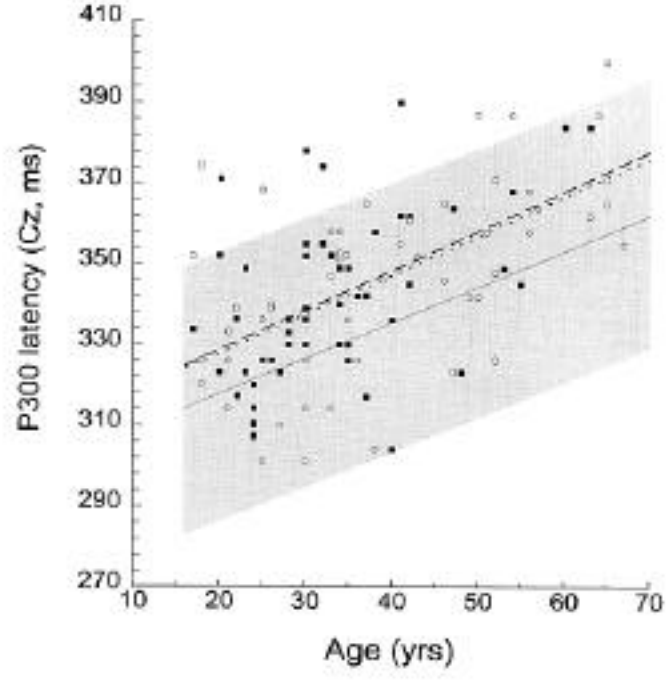

FIG. 1. Linear regression analysis of age (×) and P300 latency (milliseconds). ○, patients with a history of hypoglycemic coma (---; r = 0.56, P330 latency = 310 + 0.94×, P < 0.001); ■, patients without a history of hypoglycemic coma (· · · ; r = 0.55, P330 latency = 309 + 0.92×, P < 0.001). The shaded area depicts the 95% CI for P300 latencies obtained from 108 matched healthy control subjects (——; r = 0.59, P330 latency = 298 + 0.90×, P < 0.001).

TABLE 4
Comparison of brain function with respect to HbA_{1c} levels

	HbA_{1c} ≤6.5%	HbA_{1c} >6.5%	*P* value
n	49	59	—
P300 latency Cz (ms)	342 ± 23	344 ± 23	0.59
P300 amplitude Cz (μV)	20.0 ± 6.7	20.5 ± 7.3	0.74
Trailmaking test, part A (s)	30.6 ± 11.8	30.6 ± 8.5	0.97
Mini-Mental State Exam score	29.4 ± 0.8	29.6 ± 0.7	0.20

Despite excellent metabolic control, our cohort of IDDM patients showed a significant delay of P300 latency equivalent to ~10 years of normal aging (Fig. 1). There was, however, no difference in the comparatively insensitive neurocognitive tests. A significant correlation of P300 latency to diabetes duration but not to the number of previous hypoglycemic comas indicated that long-standing metabolic abnormalities were probably more relevant than single hypoglycemic events in the evolution of subclinical cognitive impairment (22). This view was supported by a recent study in which prolonged P300 latencies were found in NIDDM patients who had no history of hypoglycemia (23). An even more pronounced delay was reported by Pozzessere et al. (24) in a smaller sample of conventionally treated IDDM patients. Given the frequent subclinical impairment of central visual and auditory pathways in IDDM (25), it seems likely that cognitive function, depending on interaction between cortical and subcortical structures, is at least subclinically impaired in some IDDM patients (24). Cerebral abnormalities consistent with premature aging have been demonstrated on MRI in patients with and without comatose hypoglycemia (26,27). Glycosylation damage, disturbance of cellular metabolism, microvascular damage, and altered cerebral blood flow may all contribute pathophysiologically to such a central diabetic neuropathy complicating chronic hyperglycemia (28,29). We did not observe a clear association of neurocognitive impairment with peripheral neuropathy, as has been previously reported (30,31). However, measuring nerve conduction velocity in all patients might have revealed such an association.

The limitations of our study are attributable to its cross-sectional design, the absence of information on the pre-

morbid cognitive state, and the lack of exact knowledge about duration and number of hypoglycemic comas. However, hypoglycemic comas treated with intravenous glucose or subcutaneous glucagon, usually followed by hospital admission, alone qualified for selection, and such events were well memorized and verified by partners, relatives, or general practitioners. Highly accurate information was provided in a comparative setting (18). Another limitation was that we used psychometric methods not particularly sensitive to hypoglycemia. We may have missed a subtle degree of cognitive dysfunction as our study had statistical power to detect P300 latency differences >5.8 ms between diabetic and healthy subjects and >8.4 ms between patients with or without comatose hypoglycemia. No cohort of conventionally treated IDDM patients was studied, since the majority of our patients had already been allocated to intensive treatment at start of the study. The possibility cannot be excluded that individuals with a greater risk of hypoglycemia-induced brain damage were screened out initially, as patients were not randomized to intensive treatment. Because a patient's acceptance of such treatment strongly depends on individual motivation, which is an inherent bias to any intervention study (32), results from our motivated, well-educated group are not necessarily representative for unselected patients. Further, because only patients who developed IDDM in adulthood were studied, a potential adverse effect of hypoglycemia when it occurs in children or adolescents cannot be excluded.

Although not observed in this study, it should be emphasized that prolonged hypoglycemia can cause permanent cognitive damage, particularly in children with IDDM (33), and that hypoglycemia is considered a cause of the "dead-in-bed syndrome" (34). All patients should therefore receive structured training focusing on early recognition and prevention of hypoglycemia. Given such training, intensive treatment can be associated with a decrease in the risk of severe hypoglycemia (35,36).

In conclusion, episodes of hypoglycemic coma are not necessarily associated with permanent impairment of cognitive brain function in patients with adult-onset IDDM on intensive insulin treatment. Secondly, it appears that cognitive brain function of IDDM patients is subclinically impaired, probably as a consequence of long-standing metabolic abnormalities. Prolonged near-normoglycemia as provided by intensive insulin therapy might prevent such impairment.

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Author Queries (please see Q in margin and underlined text)

Q1: Addition of the word “Patients” OK in title?
Q1a: Please spell out LKH.
Q2: Edits to sentence beginning “The P300 method is more sensitive” okay?
Q3: Edits to phrase referring to substituting long-acting insulin okay?
Q4: Change from calcium dobexilate to dobesilate okay?
Q5: Change to every 3 months as meant?
Q6: Correct that 55 dB is the normal hearing level?
Q7: Change from epoque to epoch as meant?
Q8: Reference numbers for the two exams have been changed to reflect reference list; are they correct now?
Q9: In sentence beginning “No difference was seen” have the groups you meant been correctly specified?
Q10: Have reference numbers been correctly matched with the DCCT and Stockholm trials?
Q11: Edits to sentence beginning “Consequently” okay?
Q12: Please cite ref. 23 in text.
Q12: Is 5.8 ms instead of 5,8 ms and 8.4 instead of 8,4 ms correct?

In references 7, 8, 9, 11, 16, 29, and 36, please list all authors.

Ref. 28: Page numbers correct now?
Ref. 20: Please provide initials for the first author, Lincoln.

FIG. 1. Multiple linear regression analysis of age (×) and P300 latency (years). ○, patients with a history of hypoglycemic coma (----; r = 0.56, years = 310 + 0.94×, P < 0.001); ■, patients without a history of hypoglycemic coma (· · · · ; r = 0.55, years = 309 + 0.92×, P < 0.001). The shaded area depicts the 95% CI for P300 latencies obtained from 108 matched healthy control subjects (——; r = 0.59, years = 298 + 0.90×, P < 0.001).