was always the same. In three of the cases, cerebral Doppler blood flow studies, performed between 2 and 6 months after the episodes, were normal. Computed tomography (CT) scan and magnetic resonance imaging (MRI) of the brain were normal in the two cases in which these investigations were performed. Glucose and counterregulatory hormone profile (adrenaline, cortisol, glucagon, growth hormone) were studied in three cases, and no abnormalities were seen. However, two of the cases did not become hypoglycemic during the period of overnight monitoring. In the third case, the blood glucose fell to 2.7 mmol/l, but this was probably not low enough to trigger an autonomic response. The threshold for this response is determined by the level of prevailing glycemic control. In fact, those with tight control need to reach a lower blood glucose before activating their autonomic response.

An electroencephalogram (EEG) in one child, 7 days after an episode of transient hemiparesis, showed a significant abnormality, with persistent multifocal spikes and predominantly slow activity in the right posterior quadrant. Two months later, when the EEG was repeated, there was considerable improvement of the right posterior focus, but there were still foci of sharp and slow waves more marked on the left. EEG abnormalities in diabetic children seem to be related to young age, early onset of diabetes, and a history of severe hypoglycemic episodes (5).

The Diabetes Control and Complications Trial (DCCT) demonstrated that intensive insulin treatment increases the incidence of severe hypoglycemia in adult patients with IDDM. This has implications in the choice of the range of glycemic control that is appropriate for young children. Children receiving more than one injection of insulin per day may experience more severe hypoglycemia and may have a greater susceptibility to hypoglycemia because of strict glycemic control (6).

The mechanism underlying hypoglycemia-induced hemiparesis is unclear. Current hypotheses include cerebral vasospasm, impaired cerebral autoregulation, selective neuronal vulnerability (2), and underlying cerebrovascular disease. In adults with long-standing diabetes, there is an increased frequency and severity of cerebrovascular atherosclerosis, which may contribute to transient hemiparesis. However, such cerebrovascular complications are unlikely in children.

Different regions of the nervous system demonstrate variable responses to systemic insult such as anoxia, intoxicant, and metabolic disorders. The selectivity of damage caused by hypoglycemia in the nervous system is of considerable interest. The neurones of the middle layer of the cerebral cortex are most affected, the basal ganglia and anterior thalamus are the next most sensitive, while the brainstem and the spinal cord are the most resistant. Vascular spasm and impairment of cerebral autoregulation may also be implicated (2). Previous studies have shown that hypoglycemia causes a symmetrical increase in cerebral blood flow (7); however, a recent study has shown that mild hypoglycemia is associated with an increase in cerebral blood flow, which is greater in the gray matter and in the right hemisphere (8). This may explain the laterality of neurological deficits observed during severe hypoglycemic episodes.

In conclusion, we think that children who are diagnosed to be affected by IDDM before the age of 5 years are particularly at risk of transient hemiparesis associated with episodes of hypoglycemia. These signs are more likely to recur in the same children. The consequences of recurrent episodes of transient hemiparesis on cognitive function and neurological development have yet to be studied, and the long-term risk for these children remains unknown. Tight glycemic control to prevent long-term complications is likely to increase the frequency and severity of hypoglycemic episodes and may carry risks in young children.

Severe hypoglycemia is associated with EEG abnormalities whose clinical relevance is not known. Diabetic children with documented EEG abnormalities may be at increased risk of brain injury during recurrent hypoglycemic states. Future neurological follow-up of these patients is important as the significance of these episodes is unclear.

LUISA SPALLINO, MD
HEATHER F. STIRLING, MD
MARY O'REGAN, MD
LESLEY ROSS, MD
MARIA ZAMPOLLI, MD
CHRIS J.H. KELNAR, MD

From the Department of Pediatrics (L.S., M.Z.), Sant'Anna Hospital, Como, Italy; and the Department of Child Life and Health (H.F.S., M.O, L.R., C.J.H.K.), University of Edinburgh, Edinburgh, Scotland, U.K.

Address correspondence to Luisa Spallino, MD, Department of Pediatrics, Sant'Anna Hospital, Via Napoleona 60, 22100 Como, Italy.

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No Differences in Attentional Functioning Between Type 1 Diabetic Patients With and Without a History of Severe Hypoglycemia

In past years, increasing concern has arisen about the long-term detrimental effects of recurrent severe hypoglycemia on neurocognitive abilities in type 1 diabetic patients (1,2). There is convergent evidence that in children, recurrent episodes of severe hypoglycemia contribute to a slowed mental development and may reduce eventual IQ level (3). There is less agreement about the effects of hypoglycemia on cognitive functioning in adults with type 1 diabetes. Evidence gathered from different studies suggests that

decreased attentional functioning is the central cognitive problem, observed as a slower functioning on tests of simple and choice reaction time and the digit symbol task and decreased performance on the forward digit span (4–6). To test the hypothesis that recurrent severe hypoglycemia results in decreased attentional functioning, we examined cognitive functioning in nine adult male type 1 diabetic patients with a history of recurrent (>5 episodes) severe hypoglycemia (HH), nine adult male type 1 diabetic patients with no history of severe hypoglycemia (NH), and nine matched healthy control subjects. Patients were recruited from the diabetes outpatient clinic of our hospital (mean age 36.9 ± 6.7 years). To rule out potential effects of age-related intellectual decline, patients older than 50 years were not included. Likewise, to avoid confounding effects of hypoglycemia on the developing brain, patients who were included had diabetes onset after the age of 17 years. In addition, we ensured that none of the patients included suffered from secondary complications, nor from previous head injury, epilepsy, cerebrovascular disease, alcohol abuse, or psychiatric illness. History of severe hypoglycemia was obtained by self-report, asking patients how often they had suffered severe hypoglycemia, which was defined as "not having been able to recover from the hypoglycemia without the assistance of others." The three groups were comparable for mean age, educational level, intelligence (7), and depression scores (Well-Being Questionnaire) (8). The NH and HH groups were comparable for mean diabetes duration (14 and 13.4 years, respectively), age at onset, and glycemic control (HbA_{1c} 7.8 and 7.4%, respectively). Between-group comparison revealed no significant differences in mean blood glucose levels at testing (all in the nonhypoglycemic range). Patients and control subjects were tested neuropsychologically using two measures of attention. First, they were tested with the Bourdon Inhibition Test (BIT), a two-choice reaction-time vigilance test (9) that allows a subject's reaction time performance to be described in terms of speed (slowness) of processing, concentration, and errors. Second, a modified version of the Wechsler Adult Intelligence Scale (WAIS) digit span subtest was administered, where three (instead of two) series of the same length were read aloud to the subjects, thereby minimizing floor effects and allowing for separate interpretation of the forward and backward condition (10). Between-group analyses were performed using *t* tests for independent samples and one-way analysis of variance.

No significant differences ($P < 0.05$) were found between the two patient groups on any of the outcome measures, nor did we find any significant differences in cognitive performance between diabetic patients as a group and the healthy control subjects. Although the data were derived from a relatively small sample, they strongly suggest that a history of severe hypoglycemia is not inevitably associated with attentional dysfunction, at least not in otherwise healthy male patients with late-onset type 1 diabetes. We should, of course, bear in mind that attention is a highly complex process, incorporating elements of focused, sustained, selective, and divided attention across visual and auditory/verbal modalities. We cannot exclude the possibility that other cognitive tests may have shown different results. However, we did examine different aspects of attention (i.e., vigilance, speed, concentration) and related functions (short-term and working memory), and mean scores for the groups were strikingly comparable. To substantiate our findings, replication in a larger prospective study is warranted, with careful documentation of both frequency and intensity of severe hypoglycemic episodes.

FRANK J. SNOEK, PHD
NIENKE VAN DER VEER, MSC
ROBERT J. HEINE, MD, PHD
EDWARD H.F. DE HAAN, PHD

From the Departments of Medical Psychology (F.J.S., N.v.d.V.) and Endocrinology (R.J.H.), Institute for Endocrinology, Reproduction and Metabolism, the University Hospital of Vrije Universiteit, Amsterdam; and the Department of Psychonomics (E.H.F.d.H.), the University of Utrecht, Utrecht, The Netherlands.

Address correspondence to Frank J. Snoek, PhD, PO Box 7057, 1007 MB Amsterdam, The Netherlands. E-mail: fj.snoek@azvu.nl.

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A Novel Missense Mutation in the Homeodomain of the Hepatocyte Nuclear Factor-1α/ Maturity-Onset Diabetes of the Young 3 in a Japanese Early-Onset Type 2 Diabetic Patient and Time-Course of Glucose-Stimulated Insulin Secretion

Recently, mutations in the gene encoding the hepatocyte nuclear factor (HNF)-1α, a homeodomain-containing transcription factor, were shown to be a cause of maturity-onset diabetes of the