Cognitive Function in Type 1 Diabetic Adults With Early Exposure to Severe Hypoglycemia

A 16-year follow-up study

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OBJECTIVE — We assessed adulthood cognition in relation to early exposure to severe hypoglycemia (SH).

RESEARCH DESIGN AND METHODS — Sixteen years subsequent to a study of cognitive function in 28 diabetic children and 28 matched control subjects, we reexamined the same subjects with a 96% participation rate. Diabetic subjects were classified as with (n = 9) or without (n = 18) early (≤10 years of age) SH, which was defined as convulsions or loss of consciousness.

RESULTS — Overall, cognitive scores were 0.9 SDs lower in subjects with early SH compared with subjects without early SH (P = 0.003). The two diabetic groups particularly differed with respect to problem solving, verbal function, and psychomotor efficiency. Earlier age at first incident of SH was associated with poorer cognition (P for trend = 0.001).

CONCLUSIONS — The findings suggest that early exposure to SH may have lasting and clinically relevant effects on cognition.

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Early-onset diabetes is associated with reduced cognition (1), possibly due to the effects of severe hypoglycemia (SH) on the developing brain (2–5). Although moderate (1), this cognitive deficit seems to be enduring (5–7). We hypothesized that earlier age at SH occurrence would entail more pronounced effects on cognition. In this 16-year follow-up study of diabetic subjects, we investigated cognitive function in relation to early exposure to SH.

RESEARCH DESIGN AND METHODS

In 1992–1993, we studied cognitive function (8) and quantitative electroencephalograms (9) in diabetic children attending Trondheim University Hospital, the only referral center for childhood diabetes in the region. We included all 15 children who had experienced SH and 13 diabetic children of the same age without previous SH. For each subject, we included a sex- and age-matched control subject, 20 of whom were schoolmates of the diabetic subjects.

In 2008, the participants were invited to participate in a follow-up at mean age 28 years: 27 of 28 diabetic subjects (96%) and all the control subjects participated. The study was approved by the regional ethics committee.

Information on SHs (i.e., episodes with convulsions or loss of consciousness), A1C levels, and comorbidity was obtained from hospital records and personal interviews. Diabetic subjects were classified as with (n = 9) or without (n = 18) early SH (≤10 years of age) (supplementary Table 1, found in the online appendix available at http://care.diabetesjournals.org/cgi/content/full/dc10-0621/DC1).

As in the baseline study (8), neuropsychological tests were grouped into seven cognitive domains (supplementary Table 2). For each domain, we computed a relative score, expressing the difference between diabetic subject and matched control subject, with the SD among control subjects as the unit of measure (e.g., a relative score of −1 implied that the diabetic subjects scored on average 1 SD poorer than the control subjects within that domain). By averaging these relative scores, we obtained an overall relative score as a measure of overall cognition. We estimated mean relative scores for diabetic subjects with and without early SH and examined whether relative scores differed between the diabetic groups.

Using data from the baseline study, we estimated childhood cognitive function and change in cognition from childhood to adulthood. For this analysis, we excluded neuropsychological tests that had no equivalent at baseline.

We studied whether age at first SH (≤5 years of age, n = 4; 6–10 years of age, n = 5; or no early SH, n = 18) was associated with overall adulthood cognition (expressed by P value for trend across categories), and we assessed overall cognition in relation to the total number of SHs and lifetime mean A1C (the average A1C since diabetes onset, weighted for the frequency of recordings).

For all analyses, we used the general linear model. As a consequence of the

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Table 1—*Mean cognitive relative scores* in adulthood and childhood, and change in relative scores from childhood to adulthood† in diabetic subjects with and without early‡ SH*

	Diabetes with early SH			Diabetes without early SH						
Cognitive domain	Relative score	95% CI		Relative score	95% CI		Difference§	95% CI		*P*‖
Adulthood										
Memory	−0.7	−1.4	0.0	0.1	−0.3	0.6	−0.8	−1.7	0.0	0.06
Motor speed	0.1	−0.6	0.8	−0.3	−0.8	0.2	0.4	−0.5	1.3	0.35
Psychomotor efficiency	−1.1	−2.0	−0.3	0.1	−0.4	0.7	−1.3	−2.3	−0.2	0.02
Attention	−0.3	−1.0	0.3	−0.1	−0.6	0.3	−0.2	−1.0	0.6	0.61
Problem solving	−2.2	−3.0	−1.5	0.0	−0.6	0.5	−2.2	−3.2	−1.2	<0.001
Spatial function	−1.0	−2.0	0.1	−0.1	−0.8	0.6	−0.9	−2.2	0.4	0.18
Verbal function	−1.7	−2.6	−0.8	−0.2	−0.8	0.4	−1.5	−2.6	−0.4	0.01
Overall	−1.0	−1.5	−0.5	−0.1	−0.4	0.2	−0.9	−1.5	−0.3	0.003
Childhood										
Memory	−0.5	−1.3	0.3	0.2	−0.4	0.7	−0.7	−1.7	0.3	0.18
Motor speed	0.1	−0.7	0.9	−0.3	−0.9	0.2	0.4	−0.5	1.4	0.36
Psychomotor efficiency	−0.8	−1.5	0.0	0.2	−0.3	0.7	−1.0	−1.9	−0.1	0.04
Attention	−1.9¶	−3.7	−0.1	0.5	−0.6	1.7	−2.4	−4.7	−0.2	0.04
Problem solving	−0.3	−0.8	0.2	0.0	−0.4	0.3	−0.3	−0.9	0.4	0.41
Spatial function	−0.2	−1.1	0.7	−0.1	−0.7	0.5	−0.1	−1.2	1.0	0.80
Verbal function	−1.0	−1.7	−0.3	0.0	−0.5	0.4	−1.0	−1.8	−0.1	0.03
Overall	−0.7	−1.2	−0.1	0.1	−0.3	0.5	−0.7	−1.5	0.0	0.048
Change from childhood to adulthood										
Memory	−0.1	−0.8	0.6	−0.1	−0.5	0.4	0.0	−0.9	0.8	0.94
Motor speed	0.0	−0.8	0.8	0.0	−0.5	0.6	0.0	−1.0	0.9	0.96
Psychomotor efficiency	−0.4	−1.0	0.3	−0.1	−0.5	0.4	−0.3	−1.1	0.5	0.45
Attention	1.5¶	−0.4	3.4	−0.5	−1.7	0.7	2.0	−0.3	4.3	0.09
Problem solving	−1.9	−2.7	−1.2	0.0	−0.6	0.5	−1.9	−2.9	−0.9	<0.001
Spatial function	−0.8	−1.6	0.0	0.0	−0.6	0.5	−0.8	−1.8	0.3	0.14
Verbal function	−0.7	−1.5	0.1	−0.2	−0.7	0.3	−0.5	−1.5	0.5	0.28
Overall	−0.3	−0.7	0.0	−0.1	−0.4	0.1	−0.2	−0.7	0.2	0.34

*Difference in test scores between diabetic subjects and control subjects with the SD among control subjects as the unit of measure. †Computed as (relative score at follow-up–relative score at baseline). ‡Defined as first SH ≤10 years of age. §Difference in relative score between diabetic subjects with and without early SH. ‖*P* value for the difference between diabetic subjects with and without early SH. ¶$n = 8$ (diabetic–matched control subject) pairs.

matched design, the results were controlled for the effects of sex and age. The results were adjusted for parental education and work (8). The data were analyzed using SPSS statistical software, version 14.0, for Windows (SPSS, Chicago, IL).

RESULTS — The characteristics of the participants are given in supplementary Table 1 and the mean neuropsychological test scores in supplementary Table 2. Diabetic adults without early SH had similar cognitive function as control subjects (overall relative score −0.1 SD), whereas subjects with early SH scored on average 1.0 SD lower than control subjects (Table 1). Overall relative score was 0.9 SD lower in subjects with early SH compared with subjects without early SH ($P = 0.003$). The diabetic groups particularly differed in problem solving, verbal function, and psychomotor efficiency. They also tended to differ in memory. All results were adjusted for parental education and work at baseline, but even before this adjustment, the overall relative score was 0.9 SD lower in subjects with early SH compared with subjects without early SH.

Subjects with early SH already had reduced cognitive function in childhood (overall relative score −0.7 SD) (Table 1). They also tended to have a less favorable development in cognitive function during follow-up compared with control subjects (overall relative score −0.3 SD). This adverse tendency was driven by a reduced problem–solving ability.

Earlier age at first SH was associated with poorer cognitive function in adulthood (*P* for trend = 0.001). Overall, diabetic subjects with first SH before 6 years of age scored 1.3 (95% CI [0.7–2.0]) SD lower than control subjects, whereas subjects with first SH 6–10 years of age scored 0.7 (0.1–1.3) SD lower than control subjects. Overall cognition in adulthood was not related to the total number of SHs or to mean lifetime A1C (data not shown).

CONCLUSIONS — In this 16-year follow-up study, diabetes with early SH was associated with ~1 SD poorer cognitive function in adulthood, which is considered a large effect size (3). The deficit was found across several cognitive domains and was most pronounced in subjects exposed to SH before 6 years of age.

Most (1,5,6,8,10,11), but not all (12–14) studies indicate cognitive effects from SH occurring in childhood. Possibly the developing brain is particularly vulnerable to the effects of SH (2,3,5,6,11). Unlike previous long-term studies, we specifically included diabetic subjects

with exposure to SH in early childhood. This could explain why our data suggest larger persistent cognitive decline than previously reported in the studies of early-onset diabetes or SH in childhood (5–7).

Our subjects with early SH were younger at diabetes onset than subjects without early SH (average 5 vs. 10 years of age). Even though we did not find an association between lifetime A1C and cognition, we cannot exclude the possibility that hyperglycemia in early childhood, or a synergism between hyperglycemia and the occurrence of SH (15), may underlie the cognitive deficits demonstrated.

We present a nearly complete follow-up of diabetic subjects and matched control subjects from childhood to adulthood. Participants were enrolled in childhood, and any effects from diabetes on cognitive abilities appearing later did not bias the selection. Influence from recall bias is not likely since all early SHs were contemporarily documented in hospital records. Potential confounding by parental cognition is possible; however, adjustment for parental education and work did not change the results. In conclusion, our findings suggest that early exposure to SH may have lasting and clinically relevant effects on cognition.

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