Absence of Adverse Effects of Severe Hypoglycemia on Cognitive Function in School-Aged Children With Diabetes Over 18 Months

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OBJECTIVE — Some children with type 1 diabetes may be at risk of cognitive impairments, but mechanisms of this effect have not been confirmed. The objective of this study was to determine whether severe hypoglycemia (SH) in children with type 1 diabetes is associated with cognitive decline over 18 months.

RESEARCH DESIGN AND METHODS — A sample of 142 6- to 15-year-old children with type 1 diabetes (mean age 11.6 ± 2.7 years) enrolled in a trial of intensive therapy (IT) or usual care (UC) were tested with the Das-Naglieri Cognitive Assessment System at baseline and after 9 and 18 months. Episodes of SH were recorded by parents and reported promptly for verification by study nurses. HbA_{1c} was measured quarterly.

RESULTS — Over 18 months, 58 of 142 patients (41%) experienced 111 SH episodes, with a RR of SH of 1.12 for IT over UC. Neither occurrence nor frequency of SH was associated with decline in full-scale intelligence quotient (IQ), standard scores for planning, attention, simultaneous processing, or successive processing, or scaled scores on any of eight subtests. The same findings emerged when only patients who had experienced hypoglycemic seizures or coma were included in the SH group for analyses. These effects persisted when the child's age, sex, type 1 diabetes duration, and age at diagnosis were controlled statistically. HbA_{1c} during the trial was not associated with cognitive changes.

CONCLUSIONS — SH did not induce adverse changes in the measures of cognitive function administered to 6- to 15-year-old children with type 1 diabetes in this study. Although SH should be avoided in all children with diabetes, these episodes did not have adverse effects on cognition in this age-group over 18 months.

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Some children with type 1 diabetes may be at risk of cognitive deficits, especially those diagnosed at earlier ages, those with lower socioeconomic status, and boys (1–6). These findings are well established but not well explained (1,4,5) because putative mechanisms such as duration of type 1 diabetes, average long-term glycemia, frequency of diabetic ketoacidosis, total duration of hypoglycemia, and frequency of severe hypoglycemia (SH) are confounded. Differentiating the effects of these variables requires prospective studies that isolate their cognitive effects (1,5). Acute hypoglycemia impairs cognition transiently (7–9). It has been more difficult to prove that the adverse cognitive effects of hypoglycemia persist or accumulate. Some studies implicate SH as a factor in cognitive decline (10–16), whereas others do not (17–20). Different studies often report different SH-related cognitive impairments (10–16). The literature is beset by methodological issues such as small samples, retrospective evaluation of SH, failure to control for other mechanisms, and collection of numerous cognitive measures relative to sample size. These concerns must be addressed in subsequent studies to resolve these contradictory findings.

This article analyzes associations between SH and cognition prospectively. The data reported here were collected during a randomized trial of usual care (UC) versus intensive therapy (IT) for 6- to 15-year-old children with type 1 diabetes. That study followed 142 children in their randomly assigned treatments for 18 months, with various measures collected at baseline, 9 months, and 18 months, including the Das-Naglieri Cognitive Assessment System (CAS) (21–23), a new test of cognitive processing. Parents completed prospective diaries of SH, defined as in the Diabetes Control and Complications Trial (DCCT) (24).

Our hypotheses were that *1*) SH will be associated with a decline in CAS primary domain and subtest scores over 18 months and *2*) decline in CAS scores associated with SH will be independent of the child's age, sex, duration of diabetes, age at diagnosis, or mean HbA_{1c} over this period.

RESEARCH DESIGN AND METHODS

Participants

Participants were 142 youth who completed an 18-month prospective study of

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Abbreviations: CAS, cognitive assessment system; DCCT, Diabetes Control and Complications Trial; IQ, intelligence quotient; IT, intensive therapy; SH, severe hypoglycemia; UC, usual care.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

predictors of outcomes of IT ($n = 72$) or UC ($n = 70$) at either of two centers. Participants were 6–15 years old and were diagnosed with type 1 diabetes for at least 2 years or for 1 year with a negligible stimulated C-peptide level. Randomization was stratified according to the patient's age and HbA_{1c} and was performed by the trial coordinator at the other center. The primary purpose of the trial was to identify variables that predicted benefit from the two regimens. Because comparison of these treatments is not the focus of this report, the regimens are described briefly. IT comprised at least three daily insulin injections, including premeal injections or use of an insulin pump; at least four blood glucose tests daily; and utilization of expertise in medicine, nursing, nutrition, and psychology needed to assist families to maintain, to the degree attainable, an HbA_{1c} ≤6.5%. IT patients received approximately four times more contacts with nurses, dietitians, and psychologists than those in the UC group. UC patients received the routine professional assistance available at the two clinics, administered two or three daily insulin injections, performed three to four blood glucose tests daily, and strove for an HbA_{1c} ≤8.0%. For purposes of ethical treatment, glycemic targets were relaxed for children who experienced ≥2 episodes of SH within 6 months. Parents and children gave informed consent or assent before enrollment. An external panel of three pediatric endocrinologists reviewed the data and adverse events semiannually.

Measures

Comprehensive evaluations of psychological factors that could affect IT outcomes were completed before randomization and 9 and 18 months later. Measures analyzed for this report were the Das-Naglieri CAS (21–23), parental reports of SH episodes, and HbA_{1c}.

Cognitive processing. The Das-Naglieri CAS was used to measure the components of intelligence (21–23). The CAS yields a full-scale intelligence quotient (IQ) and standard scores (100 ± 15; means ± SD) for four domains of cognitive function: planning, attention, simultaneous processing, and successive processing, each with α reliabilities ≥0.84. Each cognitive domain was measured using two subtests with a normative mean scaled score of 10 ± 3 and with α reliabilities ≥0.75. Construction of the CAS was based a priori on modern empirical research on the structure of intelligence and on a well-validated theoretical model. A total of 9 years of psychometric validation of the subtests preceded its standardization with a large, carefully stratified national sample of 3,072 youth (21–23). Previous studies have shown that the CAS is sensitive to parental retrospective reports of their children's histories of SH (25), to closed-head injuries in children (26), and to subtle processing deficits found in learning disabilities (23). The CAS domains of cognitive function and their associated subtests are described below.

Planning encompasses evaluating a novel problem, generating solutions to that problem, projecting the outcomes of those strategies, selecting a strategy for implementation, and monitoring its effectiveness. These processes are assessed with the Matching Numbers subtest, in which the child must select a multidigit number identical to one of several similar numbers, and the Planned Codes subtest, in which the child must detect repeating sequences of letters.

Attention involves recognizing and responding to specific stimuli while inhibiting reaction to distractors. Within this domain, the Number Detection subtest requires the selection of "target" numerals hidden within an array of distractors, and the Expressive Attention subtest requires the child to state whether a pictured animal is big or small in reality, regardless of the relative size of the animal's picture on the page.

Simultaneous processing includes mental operations that require consideration of all elements of a complex stimulus concurrently. Within this domain, the Nonverbal Matrices subtest requires the child to select the geometric design that completes a progression of designs, and the Verbal-Spatial Relations subtest requires the child to select one of four pictures that illustrate the examiner's description of the objects' relationships in space. Successive processing consists of mental operations in which stimuli are considered sequentially, and these operations must be completed in a certain order. Within this domain, the Word Series subtest requires the child to restate, in order, sequences of words spoken by the examiner, and the Sentence Repetition subtest requires the repetition of nonsense sentences spoken by the examiner.

We selected the CAS because it measures the same cognitive functions over the 5- to 18-year age range; it is based on Luria's model of cognitive processing and on modern research on the structure of intelligence; it consists of tasks that are influenced minimally by the child's academic, social, or linguistic experiences; and it was expected to be sensitive to subtle changes in cognitive function (21–23).

SH. Parents recorded their children's apparent SH episodes. As in the DCCT, SH was defined as the occurrence of coma or seizure, or an episode requiring administration of intravenous glucagon or dextrose or assistance from another person (24). Diary forms recorded the child's symptoms, possible causes, blood glucose test results, and treatment(s) administered. Parents documented this information immediately after any apparent SH episode. Parents telephoned the study nurse during the next business day to review each such episode to verify that it met the DCCT criteria (24). The measurement of SH in young children is problematic because they typically require assistance from others in correcting any hypoglycemia. Project nursing staff differentiated mild and moderate hypoglycemia from more severe episodes based on the nature and severity of the child's symptoms as reported by the parents. Appropriate education and/or changes in medical regimen were instituted after each SH episode to minimize recurrences.

Average glycemia. HbA_{1c} was measured by the DCA-2000+ (Bayer, Indianapolis, IN) every 3 months for all participants. Analysis of split blood samples at the two laboratories before this study confirmed the near-identity of results at these centers.

Statistical analyses

Repeated-measures multivariate ANOVA was the primary analytic strategy. Separate analyses were conducted with the presence or absence of SH and the frequency of SH as between-subject factors, and with CAS primary domain and subtest scores at baseline, 9 months, and 18 months as the dependent variables. These analyses were repeated with the child's age, sex, duration of type 1 diabetes, and age at onset of type 1 diabetes as covariates.

Table 1—*Demographic characteristics of the IT and UC* groups and for the total sample*

	Intensive therapy	Usual care	Total sample
n	72	70	142
Child's age in years	11.7 ± 2.6	11.5 ± 2.8	11.6 ± 2.7
Duration of diabetes	4.8 ± 2.8	5.2 ± 3.0	5.0 ± 2.9
Baseline HbA_{1c} (%)	8.2 ± 1.1	8.1 ± 0.9	8.1 ± 1.0
Sex			
Male	45.5	65.2	55.6
Female	54.5	34.8	44.4
Race/ethnicity			
Caucasian	79.5	91.3	85.6
African American	15.9	6.5	11.1
Hispanic	2.3	0.0	1.1
Other	2.3	2.2	2.2
Family composition			
Intact	70.5	76.1	73.3
Blended	6.8	15.2	11.1
Single parent	13.6	8.6	11.1
Other	9.1	0.0	4.4

Data are means ± 1 SD or %. *IT and UC groups had significantly different proportions of male ($P < 0.003$) and female subjects ($P < 0.005$).

RESULTS

Sample characteristics

Table 1 shows that the study enrolled a diverse sample of children with type 1 diabetes in terms of age, duration of type 1 diabetes, baseline HbA_{1c}, race/ethnicity, and family composition. Distribution of Hollingshead (27) socioeconomic classes was: lower, 4.4%; lower-middle, 8.9%; middle, 30.0%; upper-middle, 32.2%; and upper, 24.4%. The IT group had significantly more male subjects [χ^2 (1) = 8.80; $P < 0.003$] and fewer female subjects [χ^2 (1) = 7.64; $P < 0.005$] than did the UC group. The two groups did not differ significantly on other demographic dimensions.

Glycemic effects of IT versus UC

The IT and UC groups did not differ in baseline HbA_{1c} (8.2 vs. 8.1%, respectively), but mean HbA_{1c} during 18 months of treatment with their respective regimens was 7.7% for IT and 8.6% for UC, yielding a statistically significant group-by-time interaction [$F(6,122) = 2.99$; $P < 0.03$]. Significant differences favoring IT were obtained at every quarterly follow-up during the study. Of 72 IT patients, 32 (44%) had 59 SH episodes (56.2 episodes/100 patient-years), whereas among 70 UC patients, 26 (37%) had 52 SH episodes (50.2 episodes/100 patient-years). Of 58 patients who experienced SH, 33 (57%) had one episode, 11 (19%) had two, 8 (13%) had three, and 6 (10%) had more than three. The RR of SH for patients in the IT group was 1.12 (56.1/50.2), and SH frequency did not differ significantly between the IT and UC groups.

Of the 111 SH episodes, 52 episodes in 39 patients included seizures or coma. These episodes, and another 27 without seizures or coma, required administration of glucagon or intravenous dextrose. The remaining episodes were treated with the assistance of another person using oral administration of fast-acting carbohydrates.

Glycemic effects on cognitive function

Table 2 reports mean CAS standard scores and subtest scores at 0, 9, and 18 months for the 58 patients who experienced SH (SH) versus the 84 patients who did not (No-SH). The CAS standard scores for the primary cognitive domains (full-scale IQ, planning, attention, simultaneous processing, and successive processing) increased over time for both groups of

Table 2—*Mean standard scores for the CAS full-scale IQ and four primary domains of cognitive processing (normative mean standard score 100 ± 15) and the mean scaled scores for each of the eight CAS subtests for 58 patients who did (SH) and 84 patients who did not (No-SH) experience one or more episodes of SH during the study (normative mean scaled score 10 ± 3)*

	Baseline		9 months		18 months	
	SH	No-SH	SH	No-SH	SH	No-SH
Full-scale IQ	108.0 ± 12.3	108.1 ± 12.1	110.1 ± 13.3	109.9 ± 12.6	114.4 ± 12.9	112.9 ± 12.8
Planning	100.8 ± 11.9	103.5 ± 13.6	101.6 ± 13.1	103.0 ± 12.8	105.2 ± 12.6	105.1 ± 12.2
Matching Numbers	9.9 ± 2.6	10.8 ± 2.9	10.0 ± 2.6	10.5 ± 2.8	10.9 ± 2.8	10.8 ± 2.7
Planned Codes	10.4 ± 2.3	10.4 ± 2.4	10.6 ± 2.3	10.6 ± 2.3	10.9 ± 2.1	11.0 ± 2.4
Attention	104.2 ± 11.4	105.3 ± 14.3	109.0 ± 14.9	108.5 ± 13.9	112.8 ± 14.1	111.3 ± 14.3
Expressive Attention	10.6 ± 2.7	10.4 ± 2.5	11.1 ± 2.9	11.0 ± 2.9	11.9 ± 2.8	11.5 ± 2.8
Number Detection	11.1 ± 2.4	11.0 ± 2.7	12.0 ± 2.9	11.7 ± 2.5	12.5 ± 3.0	12.3 ± 2.6
Simultaneous Processing	108.7 ± 13.8	107.3 ± 13.2	110.7 ± 13.2	108.0 ± 12.1	112.7 ± 14.2	111.7 ± 13.7
Nonverbal Matrices	11.3 ± 2.8	11.4 ± 2.3	11.3 ± 2.5	11.1 ± 2.6	11.8 ± 2.6	11.7 ± 2.5
Verbal-Spatial Relations	11.5 ± 2.7	11.2 ± 2.8	12.4 ± 2.9	11.6 ± 3.4	12.6 ± 3.2	12.5 ± 3.0
Successive processing	109.8 ± 13.2	107.6 ± 11.7	108.8 ± 12.8	109.7 ± 14.6	112.1 ± 11.9	109.9 ± 13.3
Word Series	11.0 ± 2.4	11.2 ± 2.7	12.0 ± 2.8	11.7 ± 2.5	12.5 ± 3.0	12.4 ± 2.7
Sentence Repetition	11.6 ± 3.0	11.3 ± 2.7	11.4 ± 2.6	11.6 ± 2.4	12.3 ± 2.7	11.5 ± 2.3

Data are means ± SD.

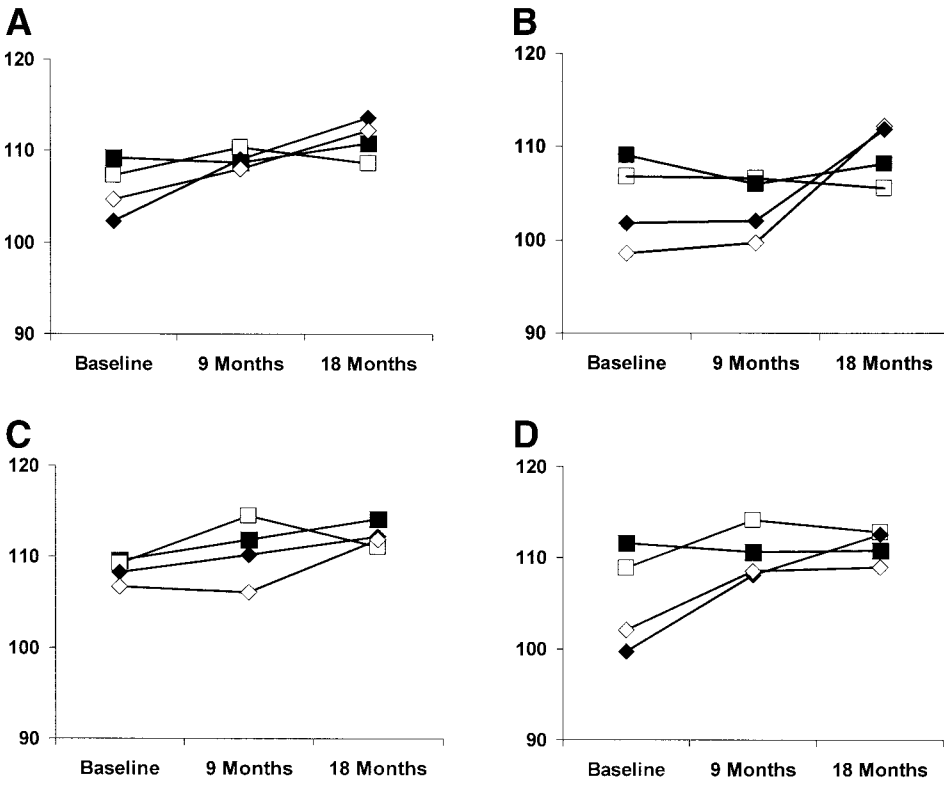

Figure 1—*Mean CAS standard scores on the four primary cognitive domains for younger (<9 years old) and older (≥9 years old) children with presence (SH) or absence (No-SH) of SH at each measurement point.* A: *Planning.* B: *Attention.* C: *Simultaneous processing.* D: *Successive processing.* ■, *SH younger;* ◆, *SH older;* □, *No-SH younger;* ◇, *No-SH older.*

patients. Repeated-measures multivariate ANOVA confirmed that there was no statistically significant main effect of group or time nor a group-by-time interaction effect on either the multivariate or univariate levels of analysis for these five measures. Occurrence of SH did not result in a decline in scores on any primary cognitive domain. Because SH episodes with coma or seizures could have more potent effects on cognitive function, we repeated the analyses comparing the 39 patients who had experienced such an event with the 84 No-SH patients. Again, none of these analyses showed statistically significant between-group or group-by-time interaction effects, indicating decline in cognitive function among patients who had experienced this most severe type of SH episode.

The above analyses of SH vs. No-SH effects on the CAS primary domains were repeated with age as a covariate. These analyses also failed to reveal significant main or interaction effects. Figure 1 illustrates that the youngest quartile of children (age 6–9 years) was no more likely to experience adverse effects of SH on the five primary CAS standard scores than were older children. Repetition of these analyses with age at diagnosis of diabetes, duration of diabetes, and child's sex as covariates did not change the results.

Additional analyses examined possible effects on the most fine-grained measures of cognition obtained in this study. Table 2 also summarizes the results of the eight CAS subtests that were administered. Repeated-measures multiple ANOVA revealed no statistically significant main effects for group (SH vs. No-SH) or group-by-time interaction effects on either the multivariate or univariate levels. When age, duration of diabetes, and age at diagnosis were entered as covariates in these analyses, the absence of significant differences remained for all eight subtests.

Table 3 examines the effects of SH frequency on cognitive changes. More frequent SH was not predictive of decline in

Table 3—*Change in CAS scores from baseline to 18 months as a function of frequency of SH*

	Number of SH episodes/18 months				
CAS Measures	0	1	2	3	>3
n	84	33	11	8	6
Full-scale IQ	+2.4 ± 5.4	+3.2 ± 4.8	+1.4 ± 6.7	+4.2 ± 6.2	+4.6 ± 7.4
Planning	+1.2 ± 6.6	+3.0 ± 5.7	+4.9 ± 7.0	+8.0 ± 8.4	+5.0 ± 7.7
Attention	+2.3 ± 6.5	+0.7 ± 4.9	+3.2 ± 6.1	+11.3 ± 7.9	+10.1 ± 7.3
Simultaneous processing	+4.7 ± 7.2	+5.8 ± 5.3	−0.8 ± 5.7	+1.0 ± 7.8	+6.8 ± 6.3
Successive processing	+2.7 ± 4.7	+1.6 ± 5.1	+0.0 ± 6.3	+4.6 ± 5.9	+6.3 ± 5.8

Data are means ± 1 SD.

any measure of cognitive function. None of the five SH frequency groups experienced significant declines in any CAS measure over 18 months; scores increased slightly over time in all subgroups. Controlling statistically for the child's age, age at diagnosis, and duration of type 1 diabetes did not alter the results of these analyses.

Mean HbA_{1c} over the 18 months was also evaluated as a correlate of cognitive decline. Patients were divided into tertiles based on mean HbA_{1c} over the study (<7.7, 7.7–8.5, and >8.5%). There were no significant main or interactive effects among these HbA_{1c} groups on any CAS score.

CONCLUSIONS — Neither the presence/absence nor the frequency of SH was associated with a decline in children's performance on a modern intelligence test. Scores on these measures increased, rather than decreased, independently of the occurrence of SH. The magnitude of the increases in scores did not differ as a function of either the presence/absence or frequency of SH. These findings held when age, duration of diabetes, sex, and age at diagnosis were controlled statistically, indicating that boys, younger children, and those with earlier diagnosis were at no increased risk of cognitive decline due to SH during the study. A comparison of CAS scores among No-SH patients with those who had experienced either a hypoglycemic coma or seizure also failed to reveal adverse effects on cognitive function. The results also indicated that mean HbA_{1c} during the study was not associated with changes in any measure of cognitive function. At the finest level of analysis that is possible with the CAS, there were no statistically significant changes in scaled scores on any of the eight subtests related to SH.

These findings demonstrate that SH did not result in a measurable decline in the domains of cognitive function examined in this study. These observations are important because the present study evaluated children's cognitive functioning and occurrence of SH prospectively, rather than retrospectively, in a sample that was comparatively large relative to similar investigations (6–18). The findings contrast with those of other studies that have reported deleterious cognitive effects of SH (10–16,25) but are consistent with those studies reporting no such association (17–20). Among the former reports, the most ambitious and sound study, contributed by Northam et al. (16), found that Wechsler full-scale IQ and verbal IQ scores were affected mildly by SH, with regression analyses indicating that SH accounted for 3 and 6%, respectively, of the variance in these two types of scores. Using different tests, the present study found no such effect on any of the five CAS primary cognitive domains, including the full-scale IQ. The CAS was intentionally designed to incorporate cognitive tasks that are relatively unaffected by linguistic stimulation and cultural opportunities. Thus, it includes no measure that can be compared directly to the verbal IQ measured by Northam et al. (16). Other methodological differences are that the Northam study had a longer follow-up period (6 years vs. 18 months) and that the comparison group in the Northam study consisted of healthy children from the community, whereas the comparisons in the present study were of children with type 1 diabetes who did and did not experience SH during an 18-month period. Northam et al. (16) concluded that SH was a plausible cause of cognitive decline over time in children with type 1 diabetes, but they could not rule out that chronic hyperglycemia may have yielded these changes.

There are limitations to this study. Sensitivity to adverse cognitive effects of SH may be greatest among children who are younger than those enrolled in this study. The present results cannot be generalized to children <6 years of age. Furthermore, adverse cognitive effects of SH that were not evident during this 18-month study could emerge with a longer follow-up interval. Also, children in this study were retested over a rather short interval. The 9-month interval between evaluations was relatively brief, such that scores from the second and third administrations may have been inflated by practice effects. Conceivably, these practice effects may have masked real deterioration in cognitive function by diminishing the sensitivity of the CAS to subtle differences in cognitive function. However, the magnitude of the practice effects did not differ with respect to either the presence or absence or the frequency of SH. The tests used in this study differed from those of previous investigations, and the findings could have differed if other tests had been selected. The present study did not compare performance directly on the CAS with tests previously shown to be sensitive to SH. Other studies have shown adverse effects of SH on subtler measures of cognitive function than were administered here (5,11–13). It is reasonable to suspect that the CAS may have been insensitive to such effects. However, in previous studies, CAS scores were sensitive to retrospective parental reports of their children's frequency of SH (25) and to cognitive sequelae of closed-head injury (26). Administration of a battery including measures previously found to be sensitive to SH, along with the CAS, could clarify whether the present findings are specific to this battery or are more general.

Avoidance of SH must always remain a cornerstone of the management of type 1 diabetes. However, the present findings suggest that SH did not impair cognitive function in children ≥6 years old who were followed for 18 months on either standard or intensive therapies for type 1 diabetes.

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