

Childhood diabetes and cognitive function

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ABSTRACT

Although diabetes might not be typically associated with reduced intelligence in children, mild cognitive function impairment may occur if onset is before 5 years of age, or the child has recurrent hypoglycemic seizures for longer periods. Therefore, children receiving intensive insulin therapy should be closely monitored to prevent hypoglycemic seizures. Some studies have showed that the hypoglycemic effect is minimal on cognition, and may be due to hyperglycemic microvascular disease associated with diabetes. Others suggested a protective effect for hypoglycemia on developing cognitive function decrement in diabetic children. Both electronic as well as published databases were searched, and studies assessed regarding their methodology. The conclusion showed that this issue is still controversial with better evidence toward negative effects of hypoglycemia on younger age group memories, especially those exposed to cumulative hypoglycemic attacks for a longer time and intensity.

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Glucose is the main fuel for the brain, acute or chronic recurrent hypoglycemic attacks may alter local glucose metabolism leading to increased use of lactate as fuel, thus, causing brain injury in the form of hippocampal cell loss.¹ Others,² suggested that lactates and pyruvates circumvent a sustained impairment in neural glucose utilization resulting from Poly (ADP-Ribose) polymerase-1 activation leading to improvement in the recovery phase after severe hypoglycemia. Two other mechanisms causing neuronal pathology in hypoglycemia are suppression of circulating epinephrine, which leads to memory deficit via modulation of vagal input,³ and, by glucocorticoid deficiency, which leads to delays in hippocampal cognitive function processing.⁴

Recently, a deficit in the synaptic plasticity was suggested behind the learning and memory impairment in young diabetic children.⁴ During acute hypoglycemia, significant deterioration occurs in attentional abilities, while fluid intelligence is preserved.⁵ However, executive skills are distorted.⁶ Processing speed is also affected considerably.⁷ The deficits in attention and processing speed may be

linked to the longer evoked potential latencies in children with type 1 diabetes.⁸ On the other hand, long-term visual memory impairment in children has been reported with children exposed to hypoglycemic attacks.⁹ Most of these deficits are generalized in nature with involvement of the higher level of organization and strategy as well as executive functions.⁶ If this were true, one would expect deficits to be more apparent on long term recall tasks.

It was reported that young females with diabetes are more prone to poorer frontal lobe and executive functions due to the presence of a special gene called Apolipoprotein E,¹⁰ however, it seems that other factors play a role, such as early onset of the disease that acts as a surrogate for the impact of hypoglycemia on the immature brain,¹¹ and unawareness of hypoglycemic attacks in very young children, as well as unpredictability of their activity and food intake. Chronic hypoglycemia may disrupt myelin formation and neurotransmitter regulation in the developing brain, and the younger the age of the child the worse the effects will be.¹¹ Granston suggested this was not exactly what happens, and

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any previous hypoglycemia will enhance the glucose uptake by the brain if exposed to new hypoglycemic attacks,¹² supporting basic brain cognitive functions at the expense of more complex cognitive faculties.

Evidence that cognitive functions are affected by hypoglycemia in adults. A meta-analysis was conducted to investigate the exact nature and magnitude of cognitive impairment in patients with type 1 diabetes, and the possible association with other disease variables such as recurrent episodes of hypoglycemia and metabolic control in diabetic patients.¹³ Thirty-three studies were included in the analysis (comparisons were carried out with non-diabetic control subjects). The diabetic group demonstrated a significantly lowered performance on the following cognitive domains: intelligence, speed of information processing, psychomotor deficiency, visual perception, sustained attention, and cognitive flexibility. Lowered cognitive performance in diabetic patients appeared to be associated with the presence of microvascular complications, but not with the occurrence of severe hypoglycemic attacks or with poor metabolic control. They observed that the pattern and the severity of cognitive changes in a study population of adult diabetic patients with an average age of diabetic onset below 15 years were comparable to those with an average age of onset above this age, which means that there is no increased risk in children below 15 years of age in suffering from cognitive impairments than other age groups.

Wysocki et al,¹⁴ conducted an 18-month prospective study on 142 children aged 6-15 years, to evaluate the effects of severe hypoglycemia on their cognitive functions. The patients were enrolled in a trial of intensive therapy (IT) or usual care (UC) and were all tested with the Das-Naglieri cognitive assessment system at the baseline and after 9 and 18 months. They concluded that neither occurrence nor severity of hypoglycemic attacks was associated with decline in the full-scale intelligence quotient (IQ), standard score in planning, attention, simultaneous processing or successive processing. An interesting finding in the previous study, was that the glycosylated hemoglobin rise is not associated with a decline in cognitive functions. Other studies^{15,16} have demonstrated decline in verbal, but not visuospatial skills, over the first 7 years of diabetes, changes in mood and decrease in the well being of the children, however, these studies have weaknesses in their methodology.

The reliability of cognitive tests that are used in children was questioned by Ryan¹⁷ and Amiel¹⁸ and declared inappropriate for this task, especially those used for attention tasks, digit vigilance and single reaction time. The reasons are that some tools are not

designed for this purpose, and these tests improve with familiarity and may deteriorate with boredom and imitation. The cause of this controversy in this issue arose due to difficulty in controlling previous hypoglycemic history and confounding effects of tests used in assessment of cognitive functions. An important study was carried out in 2001 by Northam et al,¹⁹ in this respect with a longer follow-up period of 6 years, and comparison with healthy children from the community, they found that severe hypoglycemia was an important cause of cognitive decline over time in children with insulin dependent diabetes mellitus, and the skills mostly affected in this cohort were information processing speed and conceptual reasoning abilities, but they could not outline the effect of hyperglycemia on cognitive function.

In conclusion, the effects of recurrent hypoglycemia (RH) on cognitive functions in human subjects remain controversial; perhaps in part due to difficulty in controlling previous hypoglycemic history and the confounding effects of tests used to assess the deficits in cognitive functions. Young children below 5 years of age are much more susceptible to the effects of severe hypoglycemia on cerebral functions, resulting in intellectual impairments, however, this needs time and a cumulative pattern. Memory seems to be affected mostly in children. More research in this area is expected and invited until this controversy is clarified, so that clinicians can decide the best regimens to prevent both the complications of hypoglycemia and hyperglycemia.

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