Cognition and Type 1 Diabetes in Children and Adolescents

Allison Cato[1] and Tamara Hershey[2]

IN BRIEF In children and adolescents with type 1 diabetes, exposure to glycemic extremes (severe hypoglycemia, chronic hyperglycemia, and diabetic ketoacidosis) overlaps with the time period of most active brain and cognitive development, leading to concerns that these children are at risk for cognitive side effects. This article summarizes the existing literature examining the impact of glycemic extremes on cognitive function and brain structure in youth with type 1 diabetes and points out areas for future research.

Type 1 diabetes typically is diagnosed in childhood and currently affects >170,000 youth in the United States (1,2). Alarmingly, diagnosis rates are increasing by 3–5% per year (3–5). Treatment, via injections of insulin throughout the day or continuous infusion from an insulin pump, provides an imperfect solution for the fundamental deficit in endogenously produced insulin. Because of the nonphysiological nature of this treatment, patients are vulnerable to blood glucose excursions, both low (hypoglycemia) and high (hyperglycemia), throughout their lifetime.

Before clinical diagnosis and insulin treatment, children with type 1 diabetes may experience prolonged exposure to particularly severe hyperglycemia. In 30% of patients around the time of diagnosis, this leads to life-threatening metabolic derangement referred to as diabetic ketoacidosis (DKA). DKA can, but does not always, lead to brain swelling and reduced cerebral blood flow, with a potential long-term impact on brain development (6). Overall, risk for these events can be higher in childhood and adolescence than at any other time of life. These excursions (particularly chronic hyperglycemia) can lead to complications affecting the retina, heart, kidneys, peripheral nerves, and, more recently appreciated, the brain in youth and adults.

The brain is a complex target organ of diabetes complications, particularly in childhood and adolescence, when it undergoes significant white matter (myelination) and gray matter (synaptic pruning) development (7,8). Simultaneously, the young brain has a heightened and rapidly changing metabolic demand. Brain glucose uptake reaches adult rates by the age of 2 years and increases to nearly twice the adult rate by the age of 5 years (Figure 1), followed by gradual reduction toward adult levels in the next decade (9–11). These unique properties have led to the suggestion that the developing brain may be especially vulnerable to glycemic extremes (12,13). Thus, it is possible that exposure to glycemic extremes during childhood could alter normal brain developmental trajectories depending on the age and severity at which these extremes are experienced. In this article, we review the current literature reporting cognitive and brain differences in youth with type 1 diabetes and identify several

[1]*Nemours Children's Health System, Jacksonville, FL*

[2]*Washington University School of Medicine, St. Louis, MO*

Corresponding author: Allison Cato, acato@nemours.org

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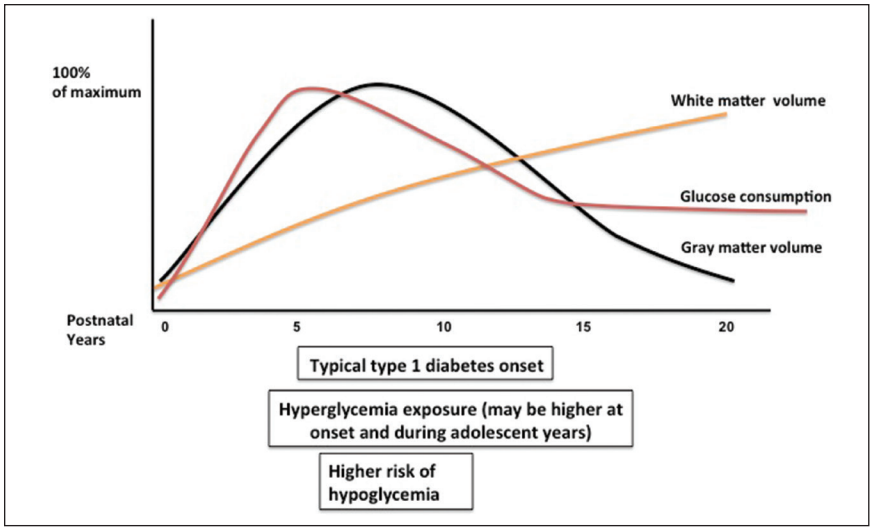

FIGURE 1. Time course of changes in brain glucose consumption, white matter volume, and gray matter volume during child development.

issues that require more research and greater clarity.

Cognitive Function and Risk Factors

Recent meta-analyses of this literature have found that youth with type 1 diabetes tend to have slightly lower overall intellectual function than comparison groups without type 1 diabetes and that the domains of executive functions, learning and memory, and processing speed are also particularly affected (14,15). However, effect sizes tend to be quite small, suggestive of a 3- to 7-point difference in IQ, for example. Thus, it is clear that type 1 diabetes is not typically associated with clinically significant cognitive dysfunction in youth. However, larger differences in cognitive function can emerge among a subset of youth with certain risk factors such as earlier age of onset and greater exposure to glycemic extremes (i.e., severe hypoglycemia, chronic hyperglycemia, and DKA).

Age of Onset

Patients with early-onset diabetes (commonly defined as <5 years of age at time of diagnosis) are more likely than those with later onset to have lower cognitive scores on tests of IQ (16–18), executive functions (19,20), learning and memory (14,20), and processing speed (20–22). These findings persist into adulthood (23). Most of these studies either noted that patients with early-onset diabetes tended to have more frequent or more severe hypoglycemic episodes than later-onset patients or did not report these variables at all (22,24–27). Thus, age of onset may be a mediating variable for early exposure to hypoglycemia or hyperglycemia because early exposure can only occur in those with early onset of diabetes. This confounding variable is particularly crucial because severe hypoglycemic episodes themselves have been associated with decreased cognitive function.

Severe Hypoglycemia

Studies using retrospective and, less commonly, prospective methods in children with type 1 diabetes have found that a greater frequency of severe hypoglycemic episodes is associated with worse performance than control subjects or type 1 diabetes comparison groups on certain types of attention tasks, overall cognitive functioning, and verbal and visual memory, even when controlling for the effects of age of onset (20,21,28–33). For example, Hershey et al. (30) found that the frequency and timing of past severe hypoglycemic episodes was related to worse cognitive function such that children with early and repeated severe hypoglycemia had lower delayed recall of explicitly learned information and spatial analysis skills. In addition, Northam et al. (17) reported that past severe hypoglycemia was associated with poorer performance on verbal and spatial memory tasks only 2 years after diagnosis in children. Furthermore, hypoglycemic events accompanied by seizures were associated with a wider range of performance deficits, including overall cognitive functioning, attention tasks, and verbal and visual memory (33,34). These findings contributed to and were supported by a recent meta-analysis (28), which concluded that past severe and recurrent hypoglycemia was most associated with reduced learning and memory in youth with type 1 diabetes.

Notably, nighttime is the most vulnerable period for hypoglycemia in youth with type 1 diabetes because sleep blunts counterregulatory responses to hypoglycemia (35). However, no studies have accurately ascertained rates of nocturnal severe hypoglycemia. With the advent of more accurate and feasible continuous glucose monitoring (CGM), this issue may be better characterized in future studies.

Hyperglycemia

More recently, chronic exposure to hyperglycemia has become recognized as a risk factor for differences in brain structure and function in type 1 diabetes. Previous studies suggesting a link between hyperglycemia and lower cognitive outcomes yielded findings of lower processing speed (36) and lower verbal intelligence (32,37,38). Recently, a large study of very young children (ages 4–10 years) with short duration of type 1 diabetes (mean 2.5 years) found cognitive differences compared to control subjects (39). Differences were observed in global IQ and executive functioning even after controlling for parent IQ and internalizing mood symptom levels. Importantly, the degree

of exposure to hyperglycemia, but not severe hypoglycemia, was modestly associated with performance in these domains. As measured by CGM data, Tansey et al. (40) reported for the Diabetes Research in Children Network (DirecNet) that 50% of participating children with type 1 diabetes (n = 144) experienced glucose levels >180 mg/dL for >12 hours per day and >250 mg/dL for >6 hours per day.

It appears that young children with type 1 diabetes are experiencing hyperglycemia for long portions of the day. The long-term impact of chronic exposure to prolonged hyperglycemia deserves additional study. Other factors, including DKA and extreme hyperglycemia at diagnosis, may play an additional detrimental role in cognitive outcomes.

DKA

Studies that have examined the impact of DKA, a potentially life-threatening condition associated with the build-up of acidic ketone bodies and, in some cases, brain edema, have consistently identified cognitive differences. For example, Ghetti et al. (41) found that children who experienced DKA at any age had lower memory performance than those who never had such an event. These differences in memory function were present even when there was no clinically apparent cerebral edema. We previously found that, after adjusting for age, sex, and socioeconomic status, youth with type 1 diabetes and a DKA event at diagnosis performed worse on a long-delay memory task 4 months after diagnosis compared to sibling control subjects (42). Another study found that youth presenting with DKA at diagnosis had poorer performance on a verbal delayed memory task and a mental state task within 48 hours of diagnosis compared to those presenting without such an event at diagnosis (43). Furthermore, Cato et al. (44) reported for DirecNet that a history of DKA (which occurred primarily at diagnosis) was correlated with lower verbal IQ scores in a cohort of young children with type 1 diabetes followed for 18 months. These findings have clinical implications, suggesting that early detection of type 1 diabetes may limit potential cognitive impairments by decreasing the degree of hyperglycemia exposure before diagnosis and avoiding a ketoacidotic state.

Other Outcomes

Academic Function

There have been few studies exploring the impact of type 1 diabetes and exposure to glycemic extremes on everyday cognitive and academic function. One recent study used teacher reports to estimate students' skills and difficulties and their most recent A1C level to estimate hyperglycemia exposure (45). The researchers found that children with type 1 diabetes with higher recent A1C levels had more teacher-rated inattention and lower academic performance. A reanalysis of older data from two small studies (46) indicated that participants with a longer duration of type 1 diabetes and higher A1C levels may be at a higher risk for learning disabilities. We and others have also found that youth with type 1 diabetes had lower performance in spelling compared to control subjects and that lower spelling skill was related to greater hyperglycemia exposure (38). In addition, one large study on academic performance in youth with type 1 diabetes found that severe hypoglycemia was associated with lower academic achievement overall, whereas greater chronic hyperglycemia was associated only with lower reading abilities (47). School absences or early age of onset did not explain these effects. However, there is a clear need for further investigation into the functional effects of cognitive differences found in a laboratory setting.

Underlying Brain Structure

With the knowledge that cognitive differences are found in children with type 1 diabetes, researchers have asked whether there are associated underlying brain structural effects and whether glycemic extremes have regionally specific effects on the brain in youth with type 1 diabetes. Cross-sectional studies of youth with preexisting type 1 diabetes (not newly diagnosed) suggest that exposure to chronic hyperglycemia and severe hypoglycemia may lead to subtle differences in brain structure. In youth with type 1 diabetes, Perantie et al. (48) reported an association between a history of severe hypoglycemia and reduced gray matter volume in the left superior temporal gyrus. In a prospective analysis, severe hypoglycemia was associated with greater decreases in occipital and parietal white matter volume over 2 years. In contrast, prolonged exposure to hyperglycemia appears to have significant effects on white matter integrity over time (49,50). Perantie et al. (48) also reported that greater hyperglycemia exposure was associated with reduced gray matter volume in the right posterior cortex (cuneus and precuneus) and smaller white matter volume in the right posterior parietal cortex. In a prospective study, Perantie et al. (51) reported decreased whole-brain gray matter volume in youth with type 1 diabetes and greater exposure to hyperglycemia.

Despite some disparity in how hypoglycemia and hyperglycemia relate to brain structure, our group and others (48–51) have found that posterior cortical regions of the brain, most commonly the precuneus/cuneus cortex, appear to be the most commonly affected by glycemic extremes. These posterior cortical regions were unexpected findings initially, but on reflection, they have many interesting properties that could provide the basis for a vulnerability to extreme glycemic states. The precuneus/cuneus are part of the default mode network (DMN), which also includes the posterior cingulate, medial prefrontal, medial temporal, and lateral temporal/parietal cortex. These regions share unique properties

in that they are highly active at rest but dramatically decrease activity during goal-oriented tasks. It is possible that the high baseline demand for glucose metabolism in the DMN may create a heightened vulnerability to alterations in blood glucose delivery (52). There is significant spatial overlap between the posterior regions of the DMN and regions affected in type 1 diabetes that appear to deserve more experimental attention.

Limitations

Cross-Sectional Versus Longitudinal Design

A major limitation in most previous studies (with exceptions, e.g., Northam et al. [17,21] and Rovet and Ehrlich [33]) is that the direction of the relationship between glycemic extremes and brain effects is undetermined. Cross-sectional studies cannot support causal inferences.

Large, longitudinal, prospective study designs are necessary to understand the impact of multiple risk factors on the individual child with type 1 diabetes. In Australia, Northam et al. (17,20,21,31) have followed a cohort of newly diagnosed youth with type 1 diabetes and community controls for >18 years, assessing them at different time points with an evolving battery of cognitive tests and, on at least one occasion, neuroimaging (53). We in DirecNet are performing a longitudinal study measuring cognitive and structural brain changes in very young children with type 1 diabetes (ages 4–10 years at study entry). By using repeated assessments of cognition and brain structure with stable methods over time and determining exposure to glycemic extremes prospectively through A1C results, medical records, and CGM, we will be able to perform analyses to answer complex questions about the interplay between cognitive and brain development and combinations of risk factors for abnormal developmental trajectories. Interestingly, differences between the diabetes and control groups that were seen at the first time point were no longer significant at 18 months, but greater hyperglycemia exposure was inversely related to executive functioning at 18 months (44). In contrast, neuroimaging in these children suggested that greater exposure to hyperglycemia was associated with slower rates of growth across gray and white matter regions over 18 months (49). These data suggest that cognitive and brain trajectories do not parallel each other across this early childhood age range.

This study is now following the same group of children into and through adolescence, which will help to determine how these trajectories continue to evolve and whether hormonal changes introduce additional risk of cognitive dysfunction. Pubertal changes could interact with these risk factors and lead to more significant impact during this time frame (54). Studies have suggested that, by middle age, many adults with a history of childhood-onset type 1 diabetes exhibit clinically significant cognitive deficits, particularly in the case of individuals with a history of chronic exposure to hyperglycemia (55). Again, a longitudinal approach is necessary to illuminate when in development and how these clinically significant differences emerge.

Other Limitations

Other factors that may influence the variability of findings across studies include differences in the age-groups examined, measures used, extent of exposure to glycemic extremes, and quality of the control group. Group studies in childhood that have yielded the most prominent group differences have used a wide range of ages and thus greater exposure to risk factors associated with diabetes. In addition, the field now demands large and diverse samples to understand how risk factors such as early onset and exposure to glycemic extremes at diagnosis might interact to predispose children to poorer responses to subsequent hyperglycemia or hypoglycemia.

Conclusion

In summary, research findings to date are generally consistent with the hypothesis that exposure to repeated severe hypoglycemia, chronic hyperglycemia, and DKA have detrimental effects on cognitive and brain outcomes in youth with type 1 diabetes. However, these factors may occur in combination within the same individual and so can be difficult to disentangle, particularly within retrospective, cross-sectional study designs.

Longitudinal studies are needed to further understand the impacts that type 1 diabetes per se and that glycemic extremes may have on brain structure and function and their consequences on everyday life. Such studies would allow us to better understand the risk factors, mechanisms involved, and real-world consequences of identified cognitive differences. Importantly, not all youth with type 1 diabetes display cognitive deficits or differences compared to control subjects. Thus, resilience and neuroprotective factors may be a fruitful area of investigation.

Our findings and others suggesting a relationship, albeit in some cases subtle, between ongoing glycemic control and cognitive, academic, and brain developmental outcomes lead to several clinical recommendations. First, these findings may suggest that achieving tighter glycemic control early in childhood could help to minimize the risk for suboptimal development. However, this hypothesis needs to be tested directly. In addition, it may be useful to include academic or cognitive screening in youth with type 1 diabetes—a practice that is not currently part of routine clinical care for these patients—to be able to detect alterations from normal development and provide supportive measures within the school or home.

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Duality of Interest

No potential conflicts of interest relevant to this article were reported.

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