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Brain MRI in Children With Type 1 Diabetes: Snapshot or Road Map of Developmental Changes?

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COMMENTARY

The impact of diabetes on the developing brain is a complex subject. From the perspective of children and parents, potential harm to the brain can be a frightening but elusive topic. Many factors can affect a child's well-being and mental development. The challenge is to disentangle potential consequences of diabetes from all these other factors. For health care workers the topic may be no less elusive. There is quite an abundance of literature on the potential adverse effects of type 1 diabetes on the brain in children, but it is difficult to translate the available data into clinically meaningful information that can be applied to the day-to-day care for an individual child. In this issue, Marzelli et al. (1), on behalf of the Diabetes Research in Children Network, present an important study that answers several questions on the impact of diabetes on the developing brain, but also generates new ones.

It is well established that development of diabetes early in life can have consequences for cognitive functioning (2,3). Several studies have shown that—on average—children with diabetes perform worse on several cognitive domains than children without diabetes (4). Among children with diabetes, cognitive decrements are most marked for children with an early diabetes onset—usually defined as an onset within the first 4–7 years of life (2,4). These decrements tend to evolve slowly over time, mounting up to a reduction in IQ scores, relative to control subjects, of around 3 points at adolescence (5). These observations have led to further studies to identify structural and functional alterations to which these cognitive decrements may be attributed. Perantie et al. (6) conducted a brain magnetic resonance imaging (MRI) study in children between ages 7 and 17 with diabetes and reported no significant differences in cerebral gray or white matter volumes compared with control subjects. However, looking within the diabetic group, a history of severe hypoglycemia was associated with smaller gray matter volume in the left superior temporal region, whereas greater exposure to hyperglycemia was associated with smaller gray matter volume in the right cuneus and precuneus, smaller white matter volume in a right posterior parietal region, and larger gray matter volume in a right prefrontal region. The same group of researchers also estimated hippocampal volumes with a stereologic method (7). Contrary to expectations, results showed that greater exposure to severe hypoglycemia was associated with larger hippocampal volumes.

Marzelli et al. (1) further expand these observations by examining children at an even younger age, just a few years after diabetes diagnosis. In a multicenter study, brain MRI scans were obtained in 142 children with type 1 diabetes and 68 age-matched control subjects (mean age 7 years). Whole brain voxel-based morphometry showed that the group of children with type 1 diabetes displayed decreased gray matter volume in bilateral occipital and cerebellar regions and increased gray matter volume in the left inferior prefrontal, insula, and temporal pole regions compared with control subjects. Within the diabetes group, hyperglycemic exposure was associated with decreased gray matter volume in medial frontal and temporal-occipital regions and increased gray matter volume in lateral prefrontal regions. Correlations between IQ and gray matter volumes were present in the control subjects, but not in the children with diabetes. The authors rightfully emphasize that this the first study to investigate the neuroanatomical effects of glycemic dysregulation in a large cohort of such young children with type 1 diabetes and conclude that they may have identified the brain regions that are involved in the effect

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of early-onset diabetes on cognitive function. It is clearly a major achievement to perform this complex, state-of-the-art imaging study in such young children. It is somewhat puzzling, however, why, in many aspects, the findings are different from the earlier studies. Could this be due to the younger age of the participants, differences in MRI analysis techniques, or the relative subtle nature of the MRI changes that makes the signal-to-noise ratio unfavorable?

Let us return to the worried parent and the health care worker who are trying to provide the best care for the child with diabetes. What can they learn from these findings? Is the reduction in gray matter volume in one part of the brain and increase in volume in another good or bad? Reduced neuronal growth, altered osmolarity, and gliosis have been suggested as possible underlying mechanisms. Alternatively, the increase in brain volume may reflect an adequate compensatory response of the plastic brain to the diabetic condition and associated disturbances in glycemic regulation. In our view, Marzelli et al. clearly highlight the fact that young-onset diabetes does affect the brain and that functional decrements in children with type 1 diabetes have a neuroanatomical correlate. The findings also highlight the complexity of studying the impact of a multifaceted condition such as diabetes in the context of brain development (Fig. 1). If we want to give clear answers about the true clinical relevance of these findings, we will need additional data. In particular, we need more insight in how these findings relate to clinically meaningful functional outcomes. School performance is an outcome that could be considered. Recent studies report a small but significant negative effect of type 1 diabetes on schooling (8), but whether this effect is attributable to neuroanatomical changes in the brain acquired in early childhood will need to be determined. Another question is whether early neuroanatomical changes in children with diabetes have consequences for cognitive functioning in late-life.

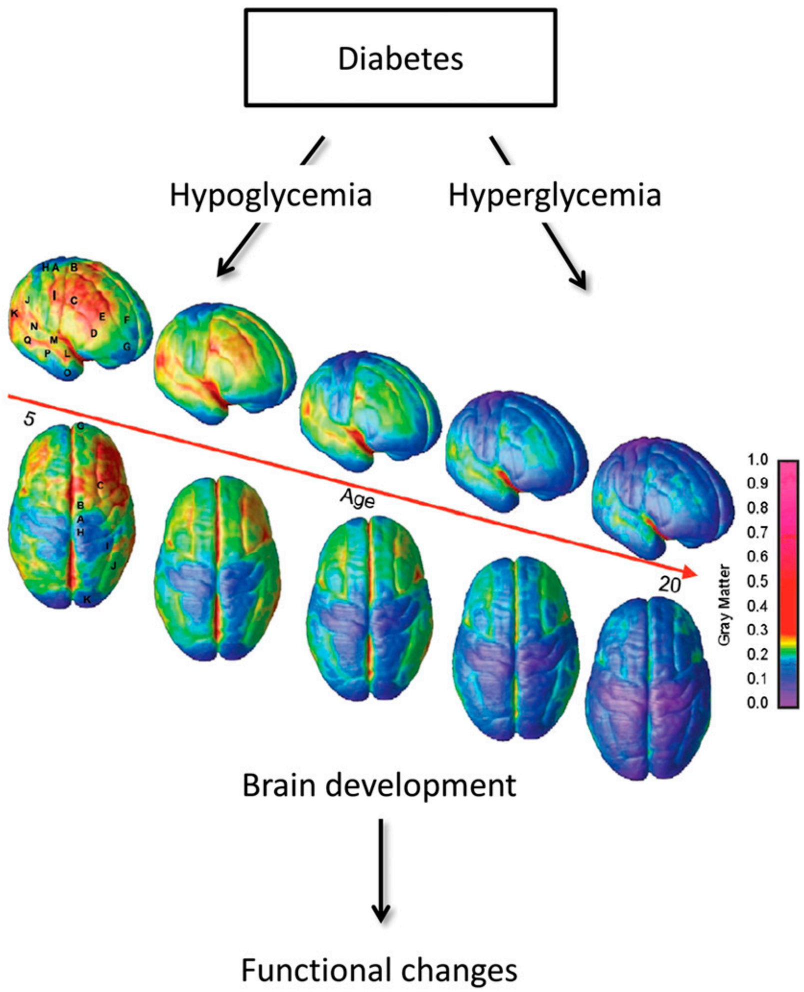

Figure 1—The complexity and dynamics of human cortical development from childhood to adolescence are shown. Diabetes and diabetes-related factors, such as hypoglycemia and hyperglycemia, may affect the developmental processes, leading to adverse cognitive outcomes in childhood or even later in life. Adapted with permission from Gogtay et al. (10), copyright (2004) National Academy of Sciences, U.S.A.

Diabetes-related structural alterations may draw on the reserve capacity of the brain, making the brain more vulnerable to the effects of aging-related insults, such as stroke or neurodegenerative conditions (3,9).

Marzelli et al. (1) presents an important step on the long ladder toward a better understanding of the impact of diabetes on the brain in children. We hope they will be able to collect long-term follow-up data on the participating children, allowing the current cross-sectional MRI study to evolve from a "snapshot of the brain" to a road map on brain development in diabetes.

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