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PEDIATRIC TYPE 2 AND MONOGENIC DIABETES (O PINHAS-HAMIEL, SECTION EDITOR)

Youth-Onset Type 2 Diabetes and the Developing Brain

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Abstract

Purpose of Review This review describes the literature evaluating the potential adverse effects of youth-onset type 2 diabetes on the developing brain. A summary of recently published articles and the current state of knowledge are covered succinctly in this manuscript.

Recent Findings Current literature suggests both cognitive and brain structural differences are found in youth with type 2 diabetes. Studies have shown poorer scores in a number of neurocognitive domains, particularly in areas of executive functioning and memory. Additionally, imaging studies have found differences in brain gray matter volume, white matter volume, and microstructural integrity. These findings are largely consistent with the adult literature.

Summary Youth with type 2 diabetes demonstrate lower cognitive scores and structural brain differences. Although causality has not yet been established, these findings are important because these individuals are still undergoing neurodevelopmental maturation.

Keywords Type 2 diabetes · Youth-onset diabetes · Cognitive function · Brain · Central nervous system

Introduction

The incidence and prevalence of youth-onset type 2 diabetes (T2D) in the USA continue to increase [1, 2]. Data from The SEARCH for Diabetes in Youth study indicates more than 20,000 youth currently carry a diagnosis of T2D [1]. By 2050, the total number of cases is expected to quadruple [3]. Given the young age of onset [4], the potential vulnerability of the developing brain, the severe degree of insulin resistance [5], and poor response to current treatments [6], there is a growing concern that complications, traditionally seen in older adults, will manifest by early adulthood [7].

Analysis of a Canadian registry has found that microvascular complications including nephropathy and retinopathy are seen within 5–10 years of adolescent T2D diagnosis. Results from this registry also showed that within 20 years, nearly 75% of youth with T2D develop a major complication including dialysis, amputation, or blindness [8]. Furthermore, complication rates appear higher in adolescent-onset T2D than in type 1 diabetes despite less severe hyperglycemia,

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Table 1 Cognitive function literature summary: significantly poorer cognitive domains in type 2 diabetes

Author, year, (T2D group *n* value)	Control group	Executive function and IQ	Memory	Behavior	Attention
Yau et al., 2010, (n = 18)	Obese only (n = 18)	Full scale IQ	WRAML verbal memory	n/a	DSST
Brady et al., 2017, (n = 20)	HWC only (n = 20)	WISC/WAIS Processing Speed	WISC/WAIS working memory and WRAML verbal memory	CBCL internalizing, externalizing, and total problems	n/a

IQ intelligence quotient, *HWC* healthy weight controls

virtually no hypoglycemia, and relatively short disease duration [9–11].

While cardiovascular events are rare during adolescence, there is clear evidence that subclinical cardiovascular disease is present. Using well-established, non-invasive modalities that predict future myocardial infarction and stroke in adults [12–16], studies in youth have demonstrated greater carotid intima media thickness, arterial stiffness, and endothelial dysfunction in youth with T2D compared to their obese and lean peers [17–19]. In addition, youth with T2D also have greater left ventricular mass, diastolic dysfunction, and abnormal cardiac remodeling [20, 21].

Despite well-documented evidence of cognitive impairment and brain structural abnormalities in adults, there is a paucity of studies on the effects of youth-onset T2D on the brain. Adults with T2D experience an accelerated decline in verbal memory, executive function, attention, and processing speed [22, 23] and are at a heightened risk to develop dementia [24, 25]. As early as 4 years after T2D onset in adults [26], cognitive impairment is evident [27] and progresses over time [28] . Furthermore, there appears to be more rapid loss of brain volume with reductions in both gray and white matter [29–35] occurring up to three times faster compared to adults without diabetes [28]. Recent work suggests that T2D during childhood may also affect the developing brain. Here, we review the current state of knowledge and summarize the studies that examine differences in cognitive function and brain structure in individuals with youth-onset T2D.

Cognitive Function

Around the turn of the century, there was a surge of literature describing an association between adult-onset T2D and cognitive impairment, including a number of reviews on the topic [24, 36–38]. Around that time, cognitive dysfunction was also starting to be recognized in youth-onset type 1 diabetes [39]. However, cognitive function in youth with T2D was not evaluated until more recently. To date, two studies have been published on cognitive function in youth with T2D (Table 1).

In 2010, Yau et al. [40••] found poorer cognitive scores in adolescents with T2D compared to demographically similar (age, sex, ethnicity, and socioeconomic status) obese controls. Specifically, the T2D group demonstrated a significantly lower estimated full-scale intelligence quotient, lower verbal memory score, and lower measure of psychomotor speed. There was also a trend toward lower scores in other subtests of intellectual capacity and executive functioning.

In 2017, Brady et al. [41•] evaluated cognitive function and behavior in youth with T2D compared to healthy weight controls (HWC) and population norms for the cognitive tests. In this study, the group with T2D had lower cognitive testing scores in memory domains, processing speed, and language

abilities. Furthermore, measures of executive functioning trended toward lower scores. Poorer behavior scores were also seen in the group with T2D for internalizing problems (e.g., depressed mood, anxiety) and externalizing problems (e.g., acting-out behaviors). When comparing scores on the Woodcock-Johnson calculation test to the population mean, 53% of the participants with T2D scored more than 1 standard deviation below the mean and 16% scored more than 2 standard deviations below the mean. By comparison, only 3 participants (16%) with T2D scored above the mean in this category. Brady et al. also evaluated correlations of duration of diabetes with individual neurocognitive domains and found that longer duration of diabetes was associated with worse scores on tests of working memory and processing speed [41•]. Hemoglobin A1c (HbA1c) did not significantly correlate with any of the domains tested, although body mass index (BMI) was correlated with a poorer internalizing behavior score.

While not specific to T2D, other studies have evaluated cognitive function of adolescents and young adults who have conditions associated with insulin resistance. Yau et al. [42] compared cognitive testing in 49 adolescents with metabolic syndrome to 62 adolescents without metabolic syndrome. Metabolic syndrome was defined using measures of abdominal obesity, dyslipidemia, elevated blood pressure, and laboratory evidence of insulin resistance, but participants with a diagnosis of T2D were excluded. The group with metabolic syndrome was found to have significantly poorer scores in spelling achievement, arithmetic achievement, one measure of executive function, and two measures of attention. In 2016, Rees et al. [43] compared 18 young adult women (age 31 ± 6 years) with polycystic ovarian syndrome (PCOS) to healthy controls of similar age and found significantly poorer scores in domains evaluating executive functioning, verbal ability, and memory ability. These two studies, although not specific to T2D, suggest insulin resistance needs to be considered as a potential mediator of compromised neurocognitive function in T2D.

There are notable limitations in the available data. First, there are only two studies evaluating cognitive testing in youth-onset T2D compared to controls. Second, the cross-sectional nature of the studies does not allow for interpretation of causality. Third, obesity alone is associated with cognitive dysfunction in children [44] and is a confounder for any study in which BMI is not similar between groups. In addition, there is evidence that poorer cognitive function in childhood increases the risk of T2D onset later in life [45], making it possible that neurocognitive decline may precede T2D. Despite these limitations, these data provide an important initial look into the relationship between youth-onset T2D and cognitive function, setting the stage for future work.

In summary, the literature specific to cognitive dysfunction in youth-onset T2D is sparse. However, deficits reported in executive functioning and memory domains are consistent with data in the adult literature [24, 36, 37]. Larger, longitudinal studies that properly account for confounders such as socioeconomic status and obesity, and which evaluate neurocognitive domains comprehensively, are needed.

Brain Structure

Investigators hypothesize that deficits in cognitive function may correspond to abnormalities in brain structure. Thus, as evidence for cognitive deficits in youth-onset T2D mounts, investigation into structural differences is also underway. Technological advancements in imaging capabilities and computer software have improved the evaluation of brain structure in a number of disease states, including T2D. Investigators have employed magnetic resonance imaging (MRI) to assess volume and microstructural integrity in youth-onset T2D. Differences found in youth-onset T2D compared to controls are summarized in Table 2.

In 2010, Yau et al. [40••] evaluated brain structure in 18 adolescents with T2D. This analysis found reduced white matter volume, both globally and regionally in the frontal lobe, compared to demographically (age, sex, ethnicity, socioeconomic status) and BMI-similar youth with a significantly lower degree of insulin resistance. Yau et al. also demonstrated differences in microstructural integrity in several gray and white matter regions. The authors found no significant difference in global gray matter volume. This group also reported global cerebral atrophy, and lower hippocampal and prefrontal volumes compared to non-insulin-resistant obese adolescents [46]. They found a negative correlation between hemoglobin A1c and prefrontal volumes, and a positive correlation between HbA1c and global cerebral atrophy.

In 2015, Rofey et al. [47] reported structural differences in brain regions of interest among adolescents with T2D and obese and normal-weight controls. Although this study was limited by a small sample size ($n = 5$ per group), significant differences were found in volumes of the caudate nucleus among all three groups. Additionally, there was a significantly lower volume of the thalamus in the group with T2D compared with both the obese control and lean control groups. No difference in thalamic volume was found between the two control groups. In addition, the authors noted that the data demonstrated a non-significant downward trend in volumes of other regions, including structures in the basal ganglia, the amygdala, and the hippocampus. Evaluation of white matter microstructural integrity using diffusion tensor imaging (DTI), a technique which evaluates differences in diffusion of water through tissue, also showed differences between groups. However, these differences were no longer significant after adjusting for BMI.

Table 2 Brain imaging literature summary of structural data

Author, year, (T2D group *n* value)	Control group(s) (*n* value)	Global GMV	Global WMV	Regional volume	Microstructural integrity
Yau et al., 2010, (*n* = 18)	Obese only (*n* = 18)	No difference	Lower	Lower frontal lobe	Lower gray and white region integrity
Bruehl et al., 2011, (*n* = 18)	Obese only (*n* = 18)	n/a	n/a	Lower hippocampus and prefrontal area	n/a
Rofey et al., 2015 (*n* = 5)	Obese (*n* = 5), HWC (*n* = 5)	n/a	n/a	Lower caudate, thalamus	NS
Nouwen et al., 2017, (*n* = 15)	Obese (*n* = 21), HWC (*n* = 22)	n/a	n/a	Lower caudate and putamen vs HWC only	Lower white matter tract integrity
Redel et al., 2018, (*n* = 20)	HWC only (*n* = 20)	Lower	No difference	14 lower gray matter clusters, 6 higher gray matter clusters	n/a

HWC healthy weight controls, *GMV* gray matter volume, *WMV* white matter volume, *NS* not significant

Nouwen et al. [48•] found regional differences in gray matter volume in youth with T2D compared to lean controls but did not find gray matter differences when comparing youth with T2D to youth with obesity alone. A voxel-wise regional evaluation of gray matter found differences in the caudate and putamen between the group with T2D and lean controls. This study also found clusters of lower microstructural integrity using DTI (measured by fractional anisotropy (FA)) in nine white matter tracts in the group with T2D. Since the reduction in FA was found to arise primarily from increases in radial diffusivity with preservation of axial diffusivity, the authors concluded the loss of microstructural integrity was due to demyelination.

Recently, a study published by our group [49•] evaluated global and regional gray matter volume in obese adolescents with T2D compared to lean controls. These data demonstrated lower global gray matter volume in youth-onset T2D compared to lean controls. Additionally, a regional analysis using voxel-based morphometry found 14 clusters in which gray matter was significantly lower in the group with T2D. Most of these (9/14) were located in the temporal lobes or occipital lobes, regions previously reported in adults. Surprisingly, our analysis also found six regions in which gray matter volume was higher in T2D compared to the lean controls, with three of these located in subcortical structures including the putamen and thalamus. Such findings have not been replicated by other studies in youth-onset T2D, but it was hypothesized they may represent "compensation" for areas of volume loss.

These studies suggest global and regional differences in brain structure in youth with T2D compared to obese and healthy controls. Specifically, differences in the basal ganglia and temporal lobes have been identified in more than one study. However, some discrepancies between studies exist, including the ability to detect global gray and white matter differences across all studies. These discrepancies may be related to heterogeneity in control groups, imaging techniques, or software used in the analysis. In particular, obesity presents as an important confounder, since youth with obesity alone show structural brain differences [50].

There are additional imaging techniques which could expand insight into the possible effects of youth-onset T2D on the developing brain. T2D plausibly impacts brain structure and function through vascular compromise. Imaging using arterial spin labeling methods has shown altered regional cerebral blood flow in adults with T2D [51]. Additionally, functional MRI (fMRI) has been used to evaluate changes in brain activation. Studies have demonstrated fMRI differences associated with obesity in both youth and adults [52, 53], and with T2D in adults [54, 55]. Cognitive dysfunction in adults with T2D has been found to correlate with altered regional activation and interregional connectivity of neuronal networks [56]. Therefore, adding these

techniques to the current imaging repertoire for the study of youth-onset T2D may provide insight into the interplay between youth-onset T2D and the brain.

Conclusion

The investigation into brain differences in youth-onset T2D is still ongoing, but the available evidence is compelling. The literature strongly suggests that youth-onset T2D is associated with both cognitive and structural differences in the developing brain. The mechanisms which may be driving these differences still need to be elucidated. Proposed mechanisms include macrovascular injury altering cerebral blood flow, microvascular disease of the brain, inflammatory mediators, oxidative stress, and disruption in the hypothalamic-pituitary axis [40••, 48•, 49•]. These potential mechanisms are important to consider when designing future studies.

The cognitive and structural brain findings in youth with T2D are consistent with the adult literature, which is more robust and longitudinal in nature. However, despite the similarities with older adults, the implications of T2D on the brains of adolescents and young adults prompt even greater concern. Unlike older adults, young people with T2D have not yet completed neurodevelopment [57] and neurocognitive differences are being demonstrated after only a short duration of disease. Although long-term data is not yet available, it is conceivable that T2D may be disruptive at critical junctures in normal brain development, which could potentially lead to more severe neurocognitive deficits earlier in life.

Further investigation into the possible adverse effects of T2D on the developing brain is imperative. A number of key questions need to be addressed. (1) Are the differences observed in studies truly caused by T2D-related mechanisms or is a confounder responsible for the association? (2) Do the differences observed persist long-term, and if so, do they worsen over time or are they reversible? (3) Is there a way to predict neurocognitive deficits without cumbersome and expensive neurocognitive testing or imaging? (4) What targeted interventions might mitigate the neurocognitive deficits potentially imposed by T2D early in life? We need to address these issues by employing studies with longitudinal design, appropriate control groups, the power to identify mechanisms, and the ability to evaluate the effectiveness of interventions.

Despite limitations in the published data, recent studies strongly suggest the brain is different in youth with T2D. As with many other highly vascular end-organs, the developing brain appears susceptible to adverse effects from T2D. This prompts concern for altered neurodevelopment, and more profound neurocognitive deficits later in life. Thus, the available literature and its possible implications should provide a strong impetus to focus clinical and research efforts on preventing and limiting youth-onset T2D and its sequelae.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines.

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- • Of importance
- •• Of major importance

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