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A REVIEW ON COGNITIVE IMPACT OF SCHOOL-AGE CHILDREN IN THE BACKGROUND OF HYPO-/ HYPERGLYCAEMIA

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Abstract

Cognitive impairment in children with type 1 diabetes has been intensively analyzed and studied in a number of studies and then meta-analyzes, with not succeed or understanding the impact of glycemic control concerning cognitive performances in children with diabetes, both in hypoglycemia, and hyperglycemia, being known that to adult, diabetes leads over time to permanent cognitive impairment, neurodegeneration or Alzheimer's disease. At children, presence of diabetes overlap to the most active periods in their brain's development and cognitive functions as well, which can lead to concern that these children are exposed to the cognitive risk as secondary effects. Children with diabetes have a greatly increased risk of manifesting mild neurocognitive dysfunction. Because the level of glycemic control is crucial for the risk of future complications, we are very interested in finding out the effects of glycemic variation on cognitive development in children in both the short and long term. When we talk about diabetes, we must refer to two main goals: preventing complications and ensuring a quality of life close to healthy people. Early detection of cognitive deficits in different areas can facilitate effective treatment options and can help reduce adverse effects on diabetes management and disease outcomes.

Keywords: *diabetes, neurocognitive, hypoglycemia, hyperglycemia, children.*

1. INTRODUCTION

Diabetes is one of the most serious chronic diseases and also, a medical problem that we must take care of, given its prevalence, through both the increase the risk of disability and mortality (World Health Organisation, 2020). Diabetes causes effects in the whole body, irreversible structural changes, but also brings changes to the psychological sphere of a patient. Diabetes is a condition characterized by elevated or instability of blood glucose levels due to reduced

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insulin secretion. Diabetes represents a major risk for brain damage. It causes slow, asymptomatic, but significant damage into the body. Research has shown that diabetes can directly damage the brain through insulin resistance, memory loss or even Alzheimer's disease. If the harmful effects of diabetes on the retinal, renal, cardiovascular and peripheral nervous systems are widely recognized, less attention has been paid to the effect of diabetes on cognitive function (Kodl and Seaquist, 2008; Rizeanu, 2015).

Both type 1 and type 2 diabetes have been associated with poor performance in many areas of cognitive function. Brain damage is associated with acute and chronic hyperglycemia, insulin resistance, hyperinsulinemia, diabetic ketoacidosis and hypoglycemic events for diabetic patients. Hyperglycemia is a cause of cognitive impairment, neurodegeneration, brain atrophy and dementia at the diabetic patient (Moheet, Mangia & Seaquist, 2015).

Type 1 diabetes occurs in childhood, including infants, but is more common in older children, aged between 6 and 13 years. It is an autoimmune disease, the cause of which is an attack of the immune system on the cells of the pancreas that produces insulin. More than 240 mg/dl is considered an over glycaemic amount (hyperglycaemia) and can be considered dangerous by severely affecting of the eyes, heart function, kidney function, blood vessels, but also of the brain. If there is a very low level of blood sugar (hypoglycaemia), the brain does not function normally, and the child may be confused, irritable, and almost always hungry. If the blood sugar decrease under 40 mg/dl, the child's brain receives too little glucose for functioning and both the judgement and muscle coordination will be affected (American Diabetes Association, 2020).

Cognitive dysfunction in type 1 and type 2 diabetes has many similarities, but there are important differences. Both conditions are associated with mental and motor retardation and similar decreases in attention skills and executive functioning. In addition, both types are characterized by neural slowing, increased cortical atrophy, microstructural abnormalities in the white matter tract, and similar, but not identical, changes in the brain (McCrimmon, Ryan et al., 2012).

Regarding of children with diabetes, exposure to the glycemic extremes (severe hypoglycemia, chronic hyperglycemia and diabetic ketoacidosis) overlaps the period of time most active in the brain development and the cognitive functions, which may lead to the concern that these children are exposed to the cognitive risk as secondary effects (Cato & Hershey, 2016).

2. EVIDENCES

Diabetes mellitus was associated with decrements in cognitive function and changes in brain structure. Diabetes is associated with a significantly increased risk of cognitive decline and an increased risk of dementia on long-term. Type 1

diabetes is commonly diagnosed during childhood and adolescence. This is a period of rapid developmental changes in the central nervous system and there has been concern that the younger brain may be more susceptible to extremes of glycemia. Both types of diabetes have been associated with poor performance in several areas of cognitive function and evidence of abnormal and structural and functional brain MRI (Moheet, Mangia & Seaquist, 2015). Neurophysiological, cerebrovascular, and neuroimaging studies also show evidence of CNS abnormalities (Ryan, 2009). Cognitive deficits can occur in the earliest stages of diabetes and are exacerbated by the duration of diabetes and glycemic control, but it is not yet possible to predict what is the greatest risk of developing cognitive impairment (Zilliox, Chadrasekaran et al., 2016).

The human brain depends on glucose as a source of energy, and acute hypoglycemia results in subsequent cognitive impairment. In general, performance on complex cognitive tasks deteriorates when blood glucose drops below 48 mg/dL (Ryan, 2009).

Hyperglycemia has the strongest association with the risk of developing cognitive impairment (Dik, Jonker et al., 2007).

And if, type 2 diabetes is associated with a 50% increase in the risk of dementia (Biessels, Staekenborg et al., 2006) and has been associated with deficits in attention, information processing, motor speed, executive functioning and verbal memory (Monette et al., 2014; Palta, Schneider et al, 2014; Wong et al., 2014), we propose to find out the impact of type 1 diabetes on cognitive functions in formation to the children to prevent cognitive impairment.

The first 5 years of life are considered a particularly critical period for brain development: special sensitivity to changes in glucose levels characteristic of diabetes could lead to an increased probability of structural and functional brain deficiencies and neurocognitive deficits (Berg and Linton, 2009).

Children diagnosed early in life, before 7 years of age, appear to be most vulnerable, showing impairments on virtually all types of cognitive tests, with learning and memory skills being particularly affected (Ryan, 2009).

A study has shown that in children with diabetes before 7 years there was a reduction in intellectual performance and a mild atrophy of the brain compared to adults with the same duration of diabetes or children who later developed diabetes (Ferguson, Blane et al., 2005).

The children who developed diabetes very early in life, diagnosed before the age of 2, had a significantly increased risk of not finishing school, compared to diabetic patients diagnosed after that age or with the reference population. (Ryan, 2009)

Results from several meta-analyses for more of 15 cross-sectional pediatric studies suggest that there are 2 distinct phenotypes associated with diabetes age at onset (Gaudieri, Chen et al., 2008). The children between 4 to 6 years of life (the early onset phenotype) show small to medium standardized effect sizes in

comparison with non-diabetes children in almost all cognitive domains, including learning and memory (d = -0.5), attention and executive functions (d = -0.4), psychomotor speed (d = -0.37), and verbal intelligence (d = -0.35). The differences may be clinically significant and may have an impact on performance in the classroom (Biessels et al., 2006; Gaudieri et al., 2008). Diabetic children are more likely to perform more poorly than their nondiabetic peers in the classroom and earn lower scores to school performance and verbal intelligence (Ryan, 2009). Specialized neuropsychological testing reveals evidence of dysfunction in a variety of cognitive domains, including sustained attention, visuoperceptual skills, and psychomotor speed. On the other hand, those diagnosed after the age of 6 years (later onset phenotype), show much smaller differences on a more limited set of cognitive domains, when compared to the healthy children's (d < 0.2) For these individuals, verbal intelligence and psychomotor speed are most consistently affected, while executive functions are only sometimes affected, and learning and memory are usually intact (Van Duinkerken and Ryan, 2020).

There are studies suggesting that a severe hypoglycemia has a negative impact on specific neuropsychological functions, such as intelligence, verbal and spatial memory, verbal, fluency, visuomotor and visuospatial skills, and information processing speed. This impact may be related to the duration of the disease, the frequency of severe hypoglycemia (Perantie et al., 2008). More rapid cognitive decline is associated with a longer duration of diabetes (Gudala, Bansal, et al., 2013).

Few studies that have tracked subjects over time have noted that verbal IQ scores tend to decrease as the duration of diabetes increases (Northam et al., 2001). These effects appeared to be more pronounced in boys and children with an earlier onset of diabetes (Schoenle et al., 2002).

Researchers found a link between hypoglycemia and poor results on verbal IQ, poorer performance of focused attention and cognitive inhibition (Northam et al., 2009), poorer results on updating information (Naguib et al., 2009) and spatial information (Perantie et al., 2008). Previous studies have consistently shown that the early onset of diabetes predicts poorer cognitive function and most researchers have hypothesized that hypoglycemia played a key role in initiating cerebral dysfunction (Abraham, Jones et al., 2018).

Another meta-analysis of 24 studies published between 1980 and 2005 regarding the neuropsychological performance in young people under 19 with type 1 diabetes was focused on performance of seven cognitive domains. The result was statistically associated with poor visuospatial performance (d = -0.29), motor speed (d = -0.26) and writing (d = -0.28), sustained attention (d = -0.21), and reading (d = -0.23). Smaller effects were identified on complete IQ (d = -0.14), on overall Performance (d = -0.18) and verbal IQ (d = -0.15). Severe hypoglycemia was associated with short-term verbal memory deficits (d = -0.14). The conclusions of this meta-analysis indicated that children with type 1 diabetes have mild cognitive

impairments and a subtly reduced overall intellectual functioning (Naguib, Kulynskaia et al., 2009).

The adverse effects of diabetes on reading and writing may be a direct consequence of the basic visuospatial abnormalities, of the reduced motor speed, and weak sustained attention identified in children with diabetes. Recent reports do not identify the problem that may affect cognition in children with diabetes. However, the significance of the slight decreases in reading and writing reported in this meta-analysis requires clarification (Naguib, Kulynskaia et al., 2009).

Weaker motor speed in children with diabetes can be attributed of slow mental capacity in the childhood, which, together with reduced flexibility, was the main finding in the meta-analysis of cognition in adults with diabetes (Brands, Biessels et al., 2005).

The scientific search engines identified 33 other studies that analysed the cognitive function of children with diabetes. The meta-analyses and studies was performed indicated a decrease in cognitive performance in children with diabetes, compared with groups of healthy children, recording negative results in a number of areas, as follows: complete IQ (d = -0.7), information processing speed (d = -0.3), psychomotor efficiency (d = -0.6), sustained attention (d = -0.3), cognitive flexibility (d = -0.5), visual perception (d = -0.4), visuospatial ability (d = -0.29), verbal IQ (d = -0.15). In this case, poor cognitive performance in diabetic patients appeared to be associated with the presence of microvascular complications, but not with the occurrence of severe hypoglycaemic episodes or poor metabolic control (Brands, Biessels et al., 2005).

These studies considered the premise that in patients with type 1 diabetes, cognitive dysfunction is characterized by a slowdown in mental speed and a decrease in mental flexibility, also learning and memory are reduced. A decrease in mental efficiency occurs with hypo- and hyperglycaemic glucose fluctuations that occur naturally in children with type 1 diabetes (Gonder-Frederick, Zrebiec et al. 2009).

A recent systematic review showed that cognitive dysfunctions commonly seen in patients with type 1 diabetes are associated with low information processing speed, psychomotor efficiency, attention, memory, learning, problem solving skills, motor speed, vocabulary, video construction, visual perception, somatosensory examination, motor power, mental flexibility and executive function. Among these areas, the slow speed of information processing, psychomotor efficiency, attention, visuoconstruction and mental flexibility were strongly supported by the results. Type 1 diabetes is associated with chronic hyperglycaemia and exposure to severe hypoglycaemia. The long-term brain effects of these consequences of diabetes have been poorly supported (Hye-Geum, 2019).

However, the contribution of these variables, respectively the episodes of hypoglycemia and/or hyperglycemia are difficult to decide.

The human brain is influenced on the continuous availability of glucose and rapid malfunctions during hypoglycemia, but recovers quickly; a single episode of hypoglycemic coma temporarily affects intellectual function, but no permanent effect on cognitive ability is evident after 36 hours. But chronic hyperglycemia can affect the structure and function of the brain (Ferguson, Blane et al., 2003).

A meta-analysis for a group of 2.144 children, of which 1.393 subjects with type 1 diabetes and 751 control subjects from 19 studies regarding pediatric diabetes, concluded that type 1 diabetes was associated with slightly lower general knowledge (-0.13), with small differences compared to control subjects on a wide range of domains, excluding learning and memory, which were similar for both groups. Learning and memory skills, both verbal and visual (-0.28 and -0.25), were more affected for children with diabetes early onset than diabetes with late onset, along with attention skills and executive function (-0.27). Comparing with nondiabetic control subjects, the effects in children with diabetes at the beginning were higher, especially for learning and memory (-0.49). The effect sizes tends to range from ~ 0.4 to 0.5 for learning, memory and attention skills, but are even smaller for other cognitive areas (Gaudieri, Chen et al., 2008).

3. CONCLUSIONS

Children with diabetes presented deficits in a wide range of neuropsychological tests compared to nondiabetic subjects. Comparative neuropsychological findings among children with and without diabetes showed negative effects on overall results. These gaps were not very important, but they can put children with diabetes at a disadvantage compared to their peers, especially in difficult educational environments.

Pediatric diabetes generally refers to slightly lower cognitive scores in most cognitive areas. The most pronounced and pervasive cognitive effects for children with early onset diabetes show a moderately lower performance compared to control subjects. The magnitude of these effects tends to be relatively modest, with estimates generally being around 0.2 or less, although there is much variation between different studies (Gaudieri, Chen et al. 2008).

The conclusions of the studies so far are inconsistent and inhomogeneous, they have not reached a common denominator in terms of cognitive impairment of children with diabetes and have failed to fully explain the comparative differences between children with diabetes and non-diabetic children.

The wide variation in cognitive abilities addressed has made it difficult to draw a conclusion about the pattern of existing cognitive deficits.

There is a valid presumption that many other factors may be involved in the onset of cognitive impairment in children with diabetes, such as very specific medical conditions, response to treatment, obesity, emotional problems or other.

Not all early-onset diabetic children had registered cognitive dysfunction and not all tests in a particular cognitive field differentiated the diabetics from the non-diabetics. Why some tests are more sensitive to diabetes related variables than others remains unknown and unexamined (Ryan, 2009).

Therefore, in order to explain and prevent these problems, it is important to conduct in-depth research on each aspect.

Because diabetes affects planning and coordination, which are so important in the overall management of the disease and for many daily activities, executive function may suffer. Therefore, it is very important to prevent cognitive decline. Evidence obtained from neurocognitive assessments suggests that cognitive dysfunction should be listed as one of the many complications of diabetes.

It is important also, to certainly clarify the impact of metabolic control on cognitive functions from an early age and to facilitate adequate psychological, educational and medical support.

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