ABSTRACT

Objective: to investigate the neuropsychological abilities in children and adolescents with type 1 diabetes mellitus. Method: this is an literature review by searching the PEPSIC, which includes the databases: LILACS, IBICS, MEDLINE, Cochrane Library and Scielo using the descriptors type 1 diabetes, cognition, cognitive ability, neuropsychological. Results: the studies shows that Type 1 DM is a disease that can promote impact on neuropsychological functioning, especially considered three specific variables: age at diagnosis, exposure to hypoglycemia and exposure to hyperglycemia. Conclusion: the studies on the neuropsychological findings and Type 1 DM controversies regarding the variables that possibly affect cognitive functioning. It should be noted, in general, that for variables considered, such as childhood is a time of vulnerability to the impact of Type 1 DM in neuropsychological skills. A significant part of researches suggest lower cognitive performance, though slight, in most areas studied. Descriptors: Diabetes Mellitus Type 1; Child Development; Cognition.

RESUMO

Objetivo: investigar habilidades neuropsicológicas en niños y adolescentes portadores de diabetes mellitus Tipo 1. Método: trata-se de revisão da literatura por meio de busca no PEPSIC, o qual inclui as bases: LILACS, IBECS, MEDLINE, Biblioteca Cochrane e Scielo, utilizando-se os descritores diabetes tipo 1, cognição, cognitive ability, neuropsychological. Resultados: os estudos encontrados apontam que o DM Tipo 1 pode promover impacto sobre o funcionamento neuropsicológico, em especial quando são consideradas três variáveis específicas: idade ao diagnóstico, exposição à hipoglicemia e à hiperglicemia. Conclusão: os estudos acerca dos achados neuropsicológicos e o DM Tipo 1 apresentam controvérsias no tocante a variáveis que alteram o funcionamento cognitivo. Destaca-se que para as variáveis consideradas, a infância é referida como momento de vulnerabilidade ao impacto do DM Tipo 1 na habilidades neuropsicológicas. Parte significativa das pesquisas realizadas sugere desempenho cognitivo inferior na maioria dos domínios estudados. Descriptors: Diabetes mellitus Tipo 1; Desenvolvimento Infantil; Cognição.

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INTRODUCTION

The Type 1 Diabetes Mellitus (DM type 1) - which is focused in this study - included about 5 to 10% of the total of DM cases and starts characteristically in childhood or adolescence. However, this disease can also be present in adulthood, something which is observed in about 30% of the DM type 1 cases.¹

Concerning the clinical condition of the disease, the DM is characterized as a disorder of the intermediary metabolism, especially regarding the carbohydrates, which leads to the increase of the serum glucose levels and acute metabolic complications with a fatality potential, besides a series of chronic multisystemic complications.² With respect to the DM type 1 treatment, it is pointed out that a strict therapeutic diet is demanded, with the glycaemia monitoring and daily insulin injections.²

The DM type 1 has as a particularity the deficiency or complete lack of insulin, and this is an important hormone for the glucose homeostasis control in the body. The glucose has fundamental acting for the brain development and functioning, as the brain primarily needs glucose in order to function in a great level and provide the maturation of the cortical areas involved in different cognitive activities. The glucose is the main source of energy for the body, and it is almost the only one for the brain. Due to the DM etiology, the factors that contribute to the hyperglycemia can be the reduction of the insulin secretion, as well as the decrease of use and increase of glucose production.³

This way, it is questioned how the DM in childhood can influence the brain activities, notably in sensitive periods of the nervous system development, something which points to the necessity of investigating about how the manifestation of the disease in childhood can interfere in the neurodevelopment and, consequently, in the cognitive functioning of the clinical subgroup. Once it is found that the brain development is extended from intrauterine life until about 12/14 years old and as the glucose is the brain nutrient element by excellence, it is indicated that children with atypical glycaemic patterns can present neuropsychological impairments resulting from these alterations.⁴

Then, the objective of this article is to investigate the neuropsychological abilities in children and adolescents who have the type 1 DM, pointing the nature and the extension of possible neuropsychological impairments resulting from the presence of glycaemic alterations along the stages of the neurodevelopment. We intend to contribute towards the understanding of the neuropsychological functioning which is characteristic of this population, benefiting them, the other professionals who work with these children and adolescents, especially the school which can offer a profile of activities and evaluations that are adequate for the especial needs of this group, and the family who can better understand some cognitive alterations that can be consequence of the disease process.

METHOD

During the mentioned investigation, it was performed a literature integrative review through the search motor PEPSIC (Psychology Electronic Periodicals), using the option “all the sources”, which includes the data bases: LILACS, IBECS, MEDLINE, Cochrane Library and Scielo.

Among the descriptors used for the title, abstract, keywords and text, it was found: Diabetes type 1, cognition, cognitive ability, neuropsychological. The search was delimited by the age of the researched groups - Childhood (birth to 12 years old) and Adolescence (13 to 17 years old), during the last five years, with fully available electronic articles.

It was found 22 articles, from which it was excluded the texts which did not fit the indicated age group, as well as the ones that dealt with a subject different to the one proposed here. After this restriction, it was selected 17 articles.

RESULTS

The first 5 to 7 years of life are a crucial period associated with the cognitive decline in individuals with type 1 DM. The called ‘precocious beginning’ - an important predictor of worse cognitive performance - mediated by the adverse effects resulting from events of severe and serious hypoglycaemia, suggests the association of the age of the child importance in the diagnosis moment with the presence of peaks of low glycaemia, and this is one of the most supported propositions by several studies. On the other hand, the bad glycaemic control does not seem to present consistent relations with the cognition.⁵ Regarding the suggestion of factors interaction for the concurrence of impacts in the neurodevelopment, it is indicated a greater vulnerability of children aging less than five years old to identify the hypoglycaemia, due to the lack of awareness...
or verbal abilities to report the symptoms. This way, the authors speculate that the factor precocious beginning of the disease would be secondary to the preponderant factor of the exposure to severe hypoglycaemia.6

The absence of association between the glycaemic control and the presence of cognitive deficits in adolescents with type 1 DM corroborates the association of the mentioned deficits with the precocious beginning of the disease, supporting the previously mentioned findings. In a study performed with 70 children and adolescents, who were divided into groups of acceptable and non-acceptable glycaemic control, it was carried out an evaluation through the application of patterned battery of psychological tests, including neuropsychological and psychological measures. Before this procedure and aiming to prevent the impact of hypoglycaemia and hyperglycaemia, the blood glucose level was checked, as well as the participants were trained to report hypoglycaemia symptoms during the evaluation process performance. As a result, it was observed some damage of the executive functions in all the children, independently of the glycaemic control level.5,7

The precocious beginning of the disease effect about the cognition was also studied, especially in relation to the basic and academic verbal abilities, aiming to explore the mechanisms of learning deficits and the dyslexia incidence. For this, it was constituted a sample with 51 children with precocious beginning of the disease and ages between 9 and 11 years old, who was compared with a group of 92 children without DM. The children were evaluated with tasks of phonological processing, short-term memory, rapid automatised naming, reading, spelling and mathematics. The researchers found that the children with type 1 DM had an inferior performance in relation to the other group in the phonological processing, in the spelling precision and in mathematics. Besides, the data indicated that the children with DM started reading later, but the reading performance and the dyslexia incidence was the same for both groups. Considering the results, the study concluded that the children with precocious beginning of the disease are prone to present phonological processing deficits, causing some difficulties with the learning in the first school years.8

There is some consistent finding indicating a worse cognitive performance with the children who had precocious beginning of the

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type 1 DM, although there is not yet a clear distinction between the studies concerning the beginning of the disease, associated to the presence of frequent or severe events of hypoglycemia and to a greater exposure of time to the disease. This observation is important so that it is performed a critical analysis about the carried researches and an adequate discussion about their results.9

It is suggested that the hyperglycaemia plays a smaller role than the hypoglycaemia factors and the precocious beginning of the disease, concerning the impact on the central nervous system development. Neuropsychological profiles of a cohort of young people with type 1 DM were examined; they were studied since the disease diagnosis - 12 years before. When compared to the control group, this young people had a worse performance in the working memory. The precocious beginning of the disease was related to some damage to the sustained and divided attention, new learning and mental efficiency. The hypoglycaemia was associated with the adverse effects in the verbal abilities, working memory and non-verbal processing speed; the hyperglycaemia was only associated with the damage to the working memory.10

Considering the struggle between hyperglycaemia and hypoglycaemia, a group of researchers carried out a study aiming to examine if the experience of hypoglycaemia or hyperglycaemia during the brain development would affect the hippocampus volume. In a similar way to previous studies, it was found some qualitative differences regarding the exposure to the mentioned glycaemic patterns. The obtained data through images of magnetic resonance with type 1 diabetic patients, aging between 7 and 17 years old, reveal that the severe exposure to hypoglycaemia was associated with the hippocampus expansion; the hyperglycaemia was not linked to the hippocampal volume.11

In the same understanding line, it was performed a study aiming to quantify the magnitude and patterns of effects associated with the precocious beginning of the type 1 DM and severe hypoglycaemia, as well as the cognitive functioning difficulties in children with this pathology. Through the performed analysis, it was concluded that the severe hypoglycaemia is related to a cognitive performance a bit inferior in the majority of the specific domains.12

As it is shown in the studies, the occurrence pattern of hypoglycaemic events and consequent cognitive dysfunctions appear in an insidious way among children. In 2008, it
was published a study which included, 18 years after, young people who entered the Diabetes Control and Complications Trial between 13 and 19 years old. However, in contrast to the high severe hypoglycaemia rates which were found, the cognitive function did not show alterations. This study suggests that the hypoglycaemia occurrence upon the adolescents with type 1 DM seems not to promote impacts on the cognitive functioning.\textsuperscript{13}

Taking into consideration the study of the relation between the type 1 DM and school, another study used a different research method compared to the previous ones, which used evaluation data of teachers and school records, as well as several medical variables - age at the beginning of the disease (considering it as precocious when the diagnosis happened before the seventh birthday), type of treatment (conventional or intensive) and glycaemic control level (last value of the glycated hemoglobin). The participants of the study were selected according to criteria: being type 1 DM patient at school age; having a teacher in class who is aware of the diagnosis; having a healthy sibling registered at school and aging between 5 to 18 years old; and, both - patient and sibling - without mental retardation, blindness or deafness.\textsuperscript{14}

For the evaluation of the school variables and its relation to the DM, the researchers created a questionnaire, which presented items regarding the abilities, working habits and attention: academic development (reading, arithmetic and writing) in relation to the school level of the student; barriers in the classroom functioning, in which the teachers classified how many times the student presented difficulties in areas such as memory and attention; variability of the daily performance, considering the performance in a typical week; and attention in class measure through the inattention dimension of the ADHD Rating Scale - IV: School Version.\textsuperscript{14}

The study results mentioned above point that, in relation to the age at the beginning of the treatment, it was not found statistically significant differences between precocious or late diagnosis in the evaluated school domains, data which match several studies, as it is previously shown. Concerning the type of treatment, those ones who received intensive therapy presented less absenteeism and had a better classification in mathematics by the teachers. However, when compared to the patients who received conventional therapy, the intensive therapy patients were evaluated by their teacher as having a difficult performance for the academic success. Regarding the variability of the daily performance and the attention in class, it was not found differences related to the type of adopted therapy. The glycaemia stability was related to all the academic evaluations, and particularly to the evaluations of the teachers of the attention in class, as well as it was positively associated with the variability of the daily performance. The authors concluded that the type 1 DM affects the child at school, but the effects do not seem to be regular both in school academic and non-academic aspects.\textsuperscript{14}

Still interested in the effects of the type 1 DM at schooling, the above research published a literature review about this theme, finding that although several studies already performed point that the pathology is associated with problems about the school frequency, cognition, school performance and interpersonal relations, it is necessary well controlled studies for elucidating the nature and the severity of the school problems.\textsuperscript{15} There was still the preoccupation of investigating the effect of a specific treatment for the type 1 DM - continuous subcutaneous insulin infusion (CSCII) - upon the cognition, mood and behavior, through a pilot study, with the participation of 32 children and adolescents aging between 6 and 16 years old. For the evaluation of cognitive aspects, it was used comprehensive group with intelligence, attention, processing speed and executive functions measures. The psychological and glycaemic evaluations were administered a week before the beginning of the CSCII and 6 to 8 weeks after its beginning. The obtained data suggest some improvement on the performance after the beginning of the CSCII in the perceptual reasoning tasks, selective attention, divided attention, cognitive flexibility and working memory. On the other hand, it was not observed any changes in the vocabulary tasks, sustained and divided attention, planning and organization, new learning and verbal fluency. The found data is in accord with the information obtained from other studies, which claim that in subtle alterations of the brain functions, the presence of neuropsychological deficits is less likely in tasks that require simple and automatic responses, and it is more likely in complex tasks that demand higher order cognitive abilities. Although the performed research does not enable a direct association between the findings and the reduction of the blood glucose variation, the data suggest that the improvement of the glycaemic control with the beginning of the CSCII was related to

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the improvement in the more complex executive tasks, mood and behavior.  

The effect of a specific treatment for the glycaemic control of the type 1 DM upon the cognition - specifically upon the attention in class - and similar results were found in other researches, being observed 4 children with the type 1 DM and glycaemic instability in class during 10 days; after the glucose stabilization, through the insulin pump, the children were observed again for 10 days. The study revealed that all the children had some improvement on their behavior in class concerning the attention; however, it was not found attention alterations when it was used classifications through the laboratory scales and measures. So, besides demonstrating the association between the glycaemic control and the attention in class, this study suggests that the use of direct observation techniques can be important in the investigation of effects of chronic diseases about the functioning of children at school.

In a recent study it was compared the cognitive functioning of children with precocious beginning of the type 1 DM (diagnosis before 6 years old) with healthy children (without chronic diseases). It was also aimed to examine among the children with type 1 DM the existing relation between the neurocognitive functioning and the glycaemic control - this was obtained through the access to the medical records of the children. The neurocognitive abilities were evaluated through a group of instruments that evaluated three domains: intellectual capacity, language and fine motor functioning. Before the evaluation, the blood glucose level was checked to verify its adequacy, considering it as low when it was lower or equal to 70 mg/dL and high when it was higher than 200 mg/dL, taking appropriate measures, if necessary, in order to avoid significant hypoglycaemia or hyperglycaemia during the evaluation. The data did not reveal differences of the group of children with type 1 DM and the ones of the control group - healthy, being both groups under the average. Among the children of the DM group, those ones with bad glycaemic control were related to a smaller general cognitive ability; slower fine motor speed and, smaller punctuation in the tasks that evaluated the receptive language. The authors concluded that this data show that young children with type 1 DM already present some negative effects in association with the chronic hyperglycaemia; the severe hypoglycaemia was not associated with any neurocognitive functioning measures. These results, then, are dissonant from the ones found by other researchers, who found a significant relation between the severe hypoglycaemia and the cognitive performance.  

The factor glycaemic control was also associated with the cognition, precisely with the visual memory, examining the impact of risk factors of the type 1 DM (bad metabolic control, severe hypoglycaemia, long duration of the disease and age at the diagnosis) upon the long-term visual and verbal memories, through an accelerated longitudinal design and the analysis of the individual growth curve. The individual growth curve analysis allowed the participation of all the available patients combined according to their ages, which was about 9 and 17 years old.

The participants and caregivers answered psychosocial and socio demographic evaluation questionnaires. The first ones were also submitted to the Wide Range Assessment of Memory and Learning (WRAML) in the initial consultation and two years later, it was also used, in this second moment, an additional cognitive battery. Besides this evaluation, it was also measured the metabolic control, hypoglycaemia crises, age at the diagnosis and duration of the DM. After the analysis, it was identified a significant negative effect of the bad metabolic control (elevated levels of glycosylated hemoglobin) upon the scores of visual memory along the time. It was also found significance about the gender, as the girls presented more gains of visual and verbal memory that the boys. On the other hand, the other mentioned factors did not reveal impact on the performance of the evaluated memories, highlighting that the verbal memory was not affected in any hypothesis. However, the study suggests as the only association, the presence of chronic hyperglycaemia and the decrease of the scores in tasks of visual memory along the time.

Using a differentiated technique from the other studies, some data support the proposition that the natural occurrence of events of acute hyperglycaemia and hypoglycaemia during the daily routine can be associated with cognitive-motor interruptions in students (6 to 11 years old) with type 1 DM. The researchers provided the study participating families with a technology called Digital Personal Assistant, which enabled the realization of brief cognition tests in the moment that preceded the glucose measurement done at home. It was performed from 3 to 5 trials a day, during 5 to 6 weeks, accounting for 70 trials, with tests related to
tasks of mental calculation and reaction time; after the test realization, the glucose measurement was done. It is highlighted that the decrease of the tests performance was observed as equivalent in the two glucose extremes, however, the decrease was only observed in the hyperglycaemia when it became really deep. Another relevant data approached by the study is that the glucose extremes in blood only affect the time of the tasks completion, but not the accuracy of them, in other words, the number of the correct responses to the tasks, something which suggests the presence of a decrease of the mental and psychomotor processing speed. It was also informed that demographic variables such as age and gender did not interfere in the individual differences.20

These findings are compatible with a study, which was about the disease effects, notably about the brain structural volumes, evaluated through magnetic resonance images. It was also found some differences between the research subjects who developed severe hypoglycaemia or a greater exposure to hyperglycaemia.21

In the same direction of the mentioned researches, or, trying to correlate the type 1 DM in children and the possible cognitive consequences, being based on neuropsychological and neuropathological evidences and neuroimages, it was raised the hypothesis that the exposure to hyperglycaemia and hypoglycaemia would be able to affect different aspects of the cognitive functioning of these individuals. For this, it was performed a study with young people aging between 5 and 16 years old who were submitted to cognitive tests, aiming to evaluate the spatial and verbal intelligence, the spatial and verbal memory and the processing speed. The group was characterized in relation to the amount of hypoglycaemic events (none, 1 to 2 events and 3 or more); in relation to the first hypoglycaemia event (before or after 5 years old;) and concerning the beginning of the diabetes (precocious before the fifth birthday and late afterwards). The exposure to the hyperglycaemia was estimated with the glycated hemoglobin average, adjusted for the duration of the diabetes for each subject. The results indicated some different qualitative effects between hypoglycaemia and hyperglycaemia in the cognitive functioning, such as the hypothesized. These effects were partly associated with the exposure time during the development. Among the findings it is pointed out: lower estimative of verbal intelligence in the diabetic group than in the control one; specifically in relation to the experimental group, it was also noted that there was some decrease in the verbal intelligence, with the increase of the exposure to hyperglycaemia, but not to the hypoglycaemia, and the spatial intelligence and the delayed recall were reduced only with repeated hypoglycaemia, especially when these events happened before five years old; the age at the beginning of the pathology was not associated with the results.9

Therefore, the three studies suggest that the two variables contribute towards the observed damage only when they act intensely upon the child. It is highlighted that the two last studies identify qualitative differences derived from the hypoglycaemia and hyperglycaemia, different from the studies which claim the concurrence of factors for the promotion of one or more effects, as in the case of association between the hypoglycaemia and precocious beginning of the disease.9,20-1

Finally, we emphasize the importance of defining the impact of the type 1 DM, as well as reporting the risk factors for the brain structure and functioning. For this, the author suggests that advanced image exams and also the use of comprehensive neurocognitive trial batteries in children with the type 1 DM are necessary, in order to carry prospective studies through the monitoring along the time.22

DISCUSSION

The different studies discuss about the modality and extension of possible neuropsychological impairments, caused by the presence of glycaemic alterations along the stages of the neurodevelopment. Most of them indicate that the type 1 DM is a disease that can promote significant impact upon the neuropsychological functioning. From the analysis of the selected articles, it was observed that this impact is considered due to three specific variables, which can be presented combined between them, and they are: a) age of the child at the diagnosis; b) exposure to hypoglycaemia in children with precocious beginning of the disease; c) glycaemic control and exposure to hyperglycaemia.

Regarding the impact of the variables mentioned above, the first decisive moment in the neurodevelopment happens between the birth up to five years old, something that includes the development of primary and secondary areas of the brain, highlighting the
importance of the healthy neurodevelopment at this age. However, the diabetic children with bad control of the disease tend to have a great physical and mental tiredness, low motivation, discouragement, constant inattention and drowsiness. This data emphasize the importance of considering the implications that the less active behavior can bring for the development and learning process of the subject, enabling the neuropsychological manifestations found by the listed studies.

This development can be influenced both by endogenous and exogenous factors, such as nutritional deficiency, metabolic defects or congenital hereditary and brain lesions. The alterations which happen along the development represent a dynamic of sequential organization/reorganization of cognitive functions that are subjacent to the maturation process in interface with the environment experiences.

In the meaning of suggestion of the factors interaction for the concurrence of impacts on the neurodevelopment, diabetic children with precocious beginning of the disease are more susceptible to hypoglycaemia, having as a consequence greater vulnerability to develop cognitive dysfunctions. The first five years of life constitute a critical period for the brain development, and the occurrence of hypoglycaemia associated with the neuroglycopenia and/or chronic hyperglycaemia during the critical period can induce to functional and structural abnormalities of the brain, which interfere with the normal cognitive function.

On the other hand, the hypoglycaemia is one of the common complications to the DM Picture. This situation is rarely fatal, however, the hypoglycemia picture for prolonged time can cause permanent damage to the brain, mainly in diabetic children who are dependent on insulin. In this respect, it is pointed that individuals with the type 1 DM beginning in childhood can suffer complications with the severe hypoglycaemia during periods of neural and cognitive development, which can put the brain at risk, even after the stabilization of the glucose levels.

Corroborating the controversy about the theme, some researches have suggested that differences in the intellectual ability can be a reflex of both chronic hyperglycaemia and severe hypoglycaemia, or even other organic factors of the disease. It is also highlighted that the pathogenesis of the intellectual differences associated with the precocious beginning of the disease remains uncertain.

According to what was described by the studies about the neuropsychological findings in children with type 1 DM, the literature about this theme is dissonant, and there is no unanimity in terms of the characterization and extension of the neuropsychological alterations associated with the variables mentioned here. This finding reinforces the necessity of performing studies about it, notably in national scope.

**CONCLUSION**

The studies concerning the neuropsychological findings and the type 1 DM present controversies about the variables which possibly alter the cognitive functioning; the above mentioned variables are among the most recurrent and supported in literature. It is highlighted, in a general way, that for all the considered variables, the childhood is considered as a moment of greater vulnerability to the impact of the type 1 DM on the neuropsychological abilities, being presented as a contributory factor of relevance. We still point out that a significant part of the performed researches suggests an inferior cognitive performance, which is discrete, in the majority of the studied domains.

This way, it is indispensable to know how the cognitive functioning happens in the interface with the pathology, considering different clinical variables, such as the exposure time of the child to the disease, so that new ways are found as an intervention strategy, minimizing the possible damage or even overcoming peculiar specific alterations of this clinical subgroup. It is necessary to emphasize the importance of this profile identification, so that more efficient interventions can be precociously implemented in the course of development of these children, making use of the brain plasticity this way, which is characteristic by excellence of this development stage.

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