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Assessment of cognitive performance among Mexican children and adolescents afflicted by simple to complex congenital heart diseases. Preliminary study☆

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ABSTRACT

Among patients afflicted by congenital heart diseases (CHD) diverse, and complex neurological alterations are commonly observed. These have neither been completely identified nor understood. With the aim of identifying specific neurocognitive alterations among children and adolescents afflicted by CHD we investigated the possible presence of cognitive disorders related to the presence of cardiovascular disease with the aid of a sample of 20 patients (12 teenagers and 8 school-age children). Taken altogether, 9 of them were afflicted by simple and 11 by complex pathologies (respectively, CHDs/c). The Neuropsychological Test for Memory and Attention (Neuropsi), standardized for Mexico by Ostrosky et al. (2004), was individually applied to all participants. The information of cognitive performance was obtained in relation to the categories attention and memory, and the same areas allowed us to assess global performance. CHDc subjects performed significantly poorer compared to CHDs in i) attention and executive function, ii) memory and iii) attention and memory. Likewise, among CHDc subjects a significantly higher proportion of cases were diagnosed as abnormal in the same variables. Also a significant and negative correlation was determined between CHD severity and neuropsychological scoring. Children and adolescents afflicted by CHD are at high risk of developing cognitive function alterations including aspects of memory, attention and executive functions, alterations which are likely to be worst among those cases carrying CHDc conditions.

1. Introduction

The incidence of moderate to severe congenital heart disease (CHD) has been estimated at approximately 6–8 per 1000 children born alive, constituting in itself the second most frequent disease in infancy [1]. In México, Mendieta-Alcántara et al. [2] inform of an incidence of 7.4 per 1,000 children born alive. In the last decades, owing to progress in intervention strategies and surgical treatments the long-term survival among neonates suffering from CHD has substantially increased. Nowadays, due to the fact that the survival expectancy is high among a high percentage of cases, the condition is now considered as a life-long or chronic disease [3]. In parallel to this, the interest has now importantly progressed towards the identification of possible CHD-correlated afflictions. This is, to functional co-morbidities evolving from neonatal stages to adolescence, and adulthood. Of specific interest are the possible alterations which might appear along brain development due to altered blood perfusion. Reduced tissue oxygenation throughout development may lead to considerable insufficiencies in terms of cognitive performance.

The biological circumstances, either biochemical or physiological, underlying the neurological injuries in CHD patients appear to be many, varied and not entirely clear. These frequently include hypoxia-ischemia events triggered by hypoperfusion, and this either due to the pathology itself or resulting from cardiac surgery. A multiplicity of other factors comprising genetic, prenatal, as well as pre- and post-operative influences may contribute to the alterations observed among these patients [4,5].

Some forms of CHDc lead to atypical brain development features, and these are observed as early as 25–30 weeks of intrauterine life [6]. Also, high ratios of microcephaly, and hypotonia, and other alterations

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have been determined by neuroimaging [7]. Other specific lesions include periventricular leukomalacia, present in up to 59% of cases before surgery [8].

Lags in neurodevelopment constitute the most frequent co-morbidity conditions among school-age children carrying CHD alterations [9–11]. In general, IQ is well preserved as it has been determined among these children. Nevertheless, a significant proportion of cases show alterations in motor skills, and in the cognitive traits of attention, memory, and language. Low academic achievement and deficient social development are also typical manifestations [4,10,12–14].

Commonly, the studies carried among CHD children have centered focused their attention on early infancy or early school ages. Recently, Cassidy et al. [15] studied executive function performance among school-age children and adolescents (10–19 years old) exhibiting cyanotic CHD. They reached the conclusion that the condition constitutes in itself an important risk factor for the optimal development and acquisition of executive functions.

Taken altogether, children and teenagers CHD patients, are ostensibly at high risk of presenting diverse neurocognitive alterations. Among them minor skills are often intact although in parallel to the increased severity of the disease the patients progressively show increased difficulties in integrating and coordinating those skills so as to achieve higher order goals [16]. According to Bellinger et al. [16–18], among the most noticeable deficits observed are those related to non-verbal skills, together with alterations in social cognition, and executive performance. The severity of the condition, particularly amid complex cardiopathological cases, poses serious threats to brain development and the acquisition of optimal cognitive abilities.

Considering that the studies related to the outcome and development of CHD-associated afflictions among these patients are still limited, particularly in Mexico where the comorbidity aspects of CHD are insufficiently acknowledged, the present work was carried out with the aim of identifying some of the main cognitive alterations among Mexican children and adolescents afflicted by CHD (simple and complex) through the application of the neuropsychological test Neuropsi.

2. Materials and Methods

2.1. Ethical Considerations

The present research protocol was approved in advance by the Bioethics Committee of the School of Medicine, State of Mexico Autonomous University, in compliance with the Declaration of Helsinki [19]. In every instance, both parents and participating children were informed in advance in relation to the aims and procedures of this study as well as of possible risks and benefits. At the same time, it was clearly explained that all information was going to be kept confidential and the results delivered free of charge to the parents of participating minors. All considerations were included both in the oral explanation as in the informed written consent. After approval, this last one was signed by parents and participating children and teenagers.

2.2. Sample

This consisted of 20 patients (9 females and 11 males) of ages between 7 and 16 years, 12 teenagers and 8 under 13 years old. Of the whole sample 9 cases were afflicted by uncomplicated CHD conditions, this is, free of hemodynamic compromise and hereby named simple (CHDs) and 11 by complex (CHDc) pathologies involving either reduced blood flow, reduced blood oxygenation or both. All cases studied were patients gathered from the Child's Hospital, belonging to the Institute for the Mother and Children from the State of Mexico (IMIEM), Toluca City, Mexico. All cases were diagnosed and assessed by a medical doctor specializing in pediatric cardiology and of the total sample, 10 cases had not undergone surgical treatment at the moment of assessment. These data are summarized in Table 1.

Table 1
Types of congenital heart diseases diagnosed in the studied sample.

Cardiopathy	n	Type	Previous surgery
Coarctation of aorta	1	CHDc	Yes
Ventricular septal defect	1	CHDc	Yes
Atrial septal defect	3	CHDs	Yes
Patent ductus arteriosus	3	CHDs	No
Patent oval foramen	3	CHDs	No
Severe pulmonary stenosis	1	CHDc	Yes
Ebstein anomaly	1	CHDc	No
Tetralogy of Fallot	1	CHDc	Yes
Pulmonary atresia	1	CHDc	Yes
Common arterial trunk	1	CHDc	No
Atrial septal defect and Ebstein anomaly	1	CHDc	No
Tricuspid atresia	1	CHDc	No
Transposition of the great arteries and single ventricle	1	CHDc	Yes
Coarctation of aorta + secondary systemic arterial hypertension	1	CHDc	Yes

CHDs: simple congenital heart diseases; CHDc: complex congenital heart diseases.

2.2.1. Inclusion Criteria

Children and teenagers of ages between 7 and 16 years afflicted by simple or complex CHD.

2.2.2. Exclusion Criteria

Personal or family background of central nervous system (CNS)-related alterations including a background of CNS perinatal risk or damage; genetic conditions which might involve CNS risk or damage; any physical complaint not allowing them to take the tests; development or acquisition of new or correlated pathological alterations along the course of the study.

2.3. Procedures

Neuropsi (Neuropsychological Test for Memory and Attention) had been previously standardized for Mexico by Ostrosky et al. [20] was applied individually to all participants. The instrument includes a base of normative data for people between the ages of 6–85 years. Neuropsi was designed to assess in a detailed manner and independently of each other attention and memory processes as well as to complete a global estimate among psychiatric, geriatric, neurologic and other patients presenting diverse medical conditions. Specifically, in this study, the different areas examined covered various attention subcategories including orientation, selective attention, sustained attention and attentional control. Also, diverse subtypes of memory were evaluated. Among them working, verbal and visuospatial short and long-term memories. The test provided qualitative and quantitative estimates from both raw and normalized data. Separately, Neuropsi provided information of performance in the cognitive categories of attention and memory, and in this area of global performance too. The subdivision of the test in categories and subcategories allows the clinician or research worker to precisely identify the presence of attention or memory deficits in the patient under examination (see Table 2).

2.4. Statistical Analysis

To investigate the existence of differences between groups (CHDs vs. CHDc) and due to the size of the sample, a non-parametric and multivariate permutation test was applied [21,22]. This method does not require a normal distribution of data due to the construction of its own empiric distribution. Thus, the global test was calculated applying the permutation distribution of the Student's *t*-test maximum (tmax). After applying the permutation technique, the estimated distribution of tmax served to set the levels of significance, a procedure which at the same time controls and avoids increasing type I error. Using the Student's *t*-

Table 2
Neuropsi general profile.

Items		Sub-items
ORIENTATION		Time
		Space
		Person
ATTENTION & CONCENTRATION		Digits retention (progression)
		Visual detection (hits)
		Full digit detection
		Successive series
MORY	Working memory	Digits retention (regression)
		Regression cubes
	Codification	Average volume memory curve
		Average volume associated pairs
		Average logic history memory
		Semi-complex figure
		Faces
	Emotion	Full spontaneous verbal memory
		Full key verbal memory
		Full verbal memory recognition
		Full associated pairs
		Average logic history memory
		Semi-complex figure
		Full face recognition
EXECUTIVE FUNCTIONS		Categories formation
		Full semantic verbal fluency
		Full phonologic verbal fluency
		Full non verbal fluency
		Full motor functions
		Stroop interference (time)
		Stroop interference (hits)

test, multiple comparisons were carried out by computing all paired-wise comparisons. Thus, the global hypothesis stating CHDs is different from CHDc was applied to evaluate the differences between groups simultaneously. Therefore this test is particularly useful because it takes into account each item, and from this it determines if there is a global and statistically significant difference between groups. Marginal hypotheses were used to test differences per variable. The test was applied to assess the mean differences among the data obtained from the next globally tested neuropsychological pairs of variables: a) groups CHDs and CHDc; b) age groups, i.e., children and adolescents; c) subjects with or without previous surgery.

Nevertheless, in order to be stricter we proceeded as follows. This comparative study although it shows there are significant differences between groups both globally and in specific variables, it doesn't tell us whether there are individuals showing abnormal cognitive scoring within any of both groups (CHD simple and complex), neither it informs us about the percentage of abnormal cases within each group. Considering that Neuropsi has been standardized in Mexico, standardization allowed us then to determine normal and abnormal performance per group, and the percentage of normal/abnormal cases within each group (CHDs/c). The statistical significance of the differences between these percentages was determined by employing the software Statistica 8.

On the other hand the statistical software SPSS (version 21) was used to assess any possible correlation between the severity of the heart disease condition (simple or complex) and the neuropsychological results obtained.

3. Results

3.1. Neuropsi Test

By applying the multivariate permutation test [22] a highly significant global probability ($p < 0.001$) was found, indicating the existence of considerable and significant differences between the groups CHDs and CHDc. This global result may only be obtained after determining statistical differences of individual items between groups. As can be appreciated here next, there are items which show highly significant differences between CHDs and CHDc patients. These include attention and executive function ($p = 0.01$); memory ($p = 0.001$), and; attention and memory ($p = 0.001$). These global variables themselves summarize the results obtained from statistically different subitems (see below), and all of these obtained in a similar way to the IQ Waiss Intelligence Test design.

The statistically different subitems between groups were orientation ($p = 0.02$); attention and concentration ($p = 0.001$); working memory ($p = 0.001$); memory codification ($p = 0.001$); spontaneous verbal memory ($p = 0.001$), and; executive functions ($p = 0.001$). No significant differences were found, however, when comparisons were made taking into account age groups (children vs. adolescents), and neither between cases who had or not undergone cardiovascular surgery before this study.

3.2. Test of Proportions Differences

After determining performance within each global item tested, the final score was allocated a “normal” or “abnormal” category if, respectively, the result attained was within or under the rating corresponding to the Neuropsi test given standards of “normality.” A hypothesis test of proportions differences was then applied. Group CHDc showed a significantly higher proportion of cases diagnosed as abnormal in aspects of attention ($p = 0.003$), memory ($p = 0.003$), and attention and executive function ($p = 0.03$) compared to CHDs.

3.3. Spearmen Correlation Test

Finally, the Spearman test of correlation was applied to compare the severity of the individual cardiopathology to the results determined for each psychometric variable (Table 3). Neuropsi showed a highly significant and negative correlation concerning the severity of the disease (CHDc) in all items tested.

4. Discussion

4.1. CHDc vs CHDs

In the present study, 20 Mexican children and adolescents carrying CHD, of whom 45% of them were diagnosed as simple and 55% as complex, were assessed concerning their neurodevelopment through the application of the psychometric battery test Neuropsi. Of the two groups presenting CHD, they either did not show hemodynamic compromise (CHDs) or this was present (CHDc), and between them presented significant differences in traits of attention and executive functions ($p = 0.006$), memory ($p = 0.001$), and in memory and attention ($p = 0.0001$). These results, obtained among a sample of Mexican patients are similar to those found by Miatton et al. [12]. These authors

Table 3
Spearman Correlation Test between neuropsychological variables and congenital heart diseases.

Neuropsi	Cardiopathy	p <
ATFE	-0.614	0.009
MEM	-0.869	0.0001
ATMEM	-0.831	0.0001
ORIENTATION	-0.605	0.01
ATT-CONC	-0.868	0.0001
WM	-0.869	0.0001
CODIFICATION	-0.867	0.0001
EVOC-MEM	-0.858	0.0001
EXEC-FUNC	-0.856	0.0001

ATEF: attention and executive functions; MEM: memory; ATMEM: attention and memory; CHD: congenital heart diseases; ATT-CONC: attention and concentration; WM: working memory; EVOC-MEM: evocative memory; EXEC-FUNC: executive functions.

determined the cognitive profile of school age children afflicted by CHD after surgery by applying an abbreviated intelligence scale and assessing their neuropsychological development. Within group CHD the authors found significantly lower scores in the full scale of estimated IQ. The neuropsychological evaluation also revealed lower scores in the cognitive domains of sensorimotor performance, language, attention, executive functions and memory, and increased impulsiveness compared to a group of healthy peers.

Executive functions constitute a set of superior neurocognitive abilities related to the coordination and organization of actions towards specific goals, allowing the individual to adapt to new and complex situations. These cognitive skills are critical for the accomplishment of social and academic tasks. A deterioration of executive functions in cases of CHDc was one of the findings of our study. It has been and is still of particular interest to other authors because it appears to be a specific area of cognitive weakness among children suffering from congenital heart disease [5,15,23,24]. Although deficiencies in diverse aspects of neurodevelopment are widespread among CHD children, these may not be apparent until school age is reached. In this sense, Calderon et al. [5] studied longitudinally (3 years) executive functions (EF) among a group of 45 children of ages of 5–7 years afflicted by transposition of the great arteries. Compared to a control group of healthy children the results showed that most EF impairments had an early onset at a preschool age. The alterations persisted and continued to have an impact, from moderate to substantial, later in life. Coinciding with Calderon et al. [5,23], in our study both CHDc children and adolescents showed lower scores in items concerning to executive function.

Alterations of EF among CHD children and adolescents have also been found by other authors. Cassidy et al. [15] studied 463 CHD children and teenagers and compared them to a control group of healthy individuals (111 participants). The degree of EF deterioration, according to the application of different tests, was higher among CHD patients compared to the control group. According to the conclusions of these authors, CHD represents a severe threat to EF development in direct correlation to the severity of the disease. In the present study, and in agreement with observations by other authors, among CHDc patients, we found deficits in attention, memory, and executive functions. In this sense, Shillingford et al. [25] investigated the presence of attention disturbances among a group of 5–10-years old children afflicted by CHDc. According to the Attention Deficit and Hyperactivity Disorder-IV Rating Scale, 30% of CHD children observed high-risk scores of inattention and 29% of them high-risk scores of hyperactivity. Several studies have applied tests of attention to CHD children, evidencing among them deficiencies in this domain.

Bellinger et al. [9] assessed the ability of sustained attention applying a continuous performance test to a group of 8 years old children with transposition of the large arteries, and among them found more omissions and mistakes, as well as multiple responses, and longer than average reaction times. Concurring with the above mentioned authors, we found a worsened performance in memory tests within group CHDc, evidencing a deterioration of various forms of memory. It is important to note that in all the hereby cited studies, the authors compare neuropsychological performance between cases bearing congenital heart disease to healthy controls. In the current study, all comparisons were made between CHD cases, simple vs. complex. To our knowledge, this is the first study among young CHD patients doing this type of assessment.

Postoperatively Miatton et al. [12] identified significantly lower scores in a CHD group compared to their healthy counterparts in the cognitive domains of sensorimotor functioning, language, attention and executive function, and memory. CHD children also showed increased impulsive behavior in the applied tests, all of which also coincides with our results. Recently Sanz et al. [24] determined the profile and prevalence of executive dysfunction in a sample of school-age children with CHD, concluding that school-age children with CHD have a higher prevalence of this trait, and in particular, difficulties with working memory and flexibility compared to a control group of healthy peers.

4.2. Normal vs. Abnormal Neurocognition Within Each Group

In this work, another piece of evidence supporting the higher risk of developing cognitive dysfunction among CHDc cases includes the presence of a higher proportion of people diagnosed as cognitively “abnormal”. It is important to note that categorizing a particular test result as “cognitive abnormality” is not an exclusive feature of the most complex CHD cases, as it was also observed among CHDs individuals. One of the most important conclusions of our work is related to the need of early assessing neuropsychologically and neurodevelopmentally all CHD cases (simple, and severe) in order to take appropriate medical and neuropsychological action.

4.3. CHD and Its Severity

Neither age nor surgical treatment appeared to influence the cognitive traits studied here. Specifically designed studies would have to be devoted to any of both aspects. In our study the main and strongest influence for the presence of cognitive disturbances, or neurodevelopment lags is the cardiopathology itself and the extent of its severity. Nevertheless, this is a preliminary result which for further and more comprehensive conclusions would require a larger sample. The present study by far has been constrained by the number of cases dealt with by the local Hospital for the Child who are routinely captured.

4.4. Spearman Correlation Test

We found a very high and significant negative correlation between the severity of CHD and neurocognitive performance. Other authors have only found correlation between CHD severity and performance in executive function. Calderon et al. [23] point out that the greater the severity of CHD, the worse is the determined performance in those tasks exploring executive functions. In parallel, CHD children and adolescents face increased risks of speech/language, attention, memory, and visual-spatial skills deficits [26,27]. In our work we consider important to establish a relationship between the dependent variables (Neuropsi items) and the independent one (severity of heart disease) among cases of CHD, simple and complex. We have corroborated among children and adolescents with CHD (simple and complex) that as a group they are likely to show greater neuropsychological deterioration in direct relationship to the severity of heart disease.

In summary, children, and adolescents afflicted by congenital heart disease show alterations in aspects of cognitive functions including memory, attention and executive functions, alterations which were more noticeable among those cases carrying the complex conditions. This is, those patients presenting severe hemodynamic compromise, and this regardless of age or medical treatment, including surgery. Although subject to further investigation, those alterations in cognition and behavior most like are the result of an atypical brain development present since fetal stages up to late infancy due to cardiological and systemic complications.

Current medical and technical progress has increased the survival rate of children suffering from congenital heart disease thereby allowing a higher number of patients to surpass infancy and reach adulthood. Thanks to these advances, a higher probability of normal integration into family and social life exists. Nevertheless, in spite of attaining an overall body condition of physical bodily health, there may be present underlying CNS alterations which have to be looked after. Taking into account the results of this study and observations by other authors, the neurocognitive complications resulting from CHD are likely to carry wider and long lasting adverse effects.

Finally, we consider essential to note that in Mexico few studies investigate the presence of neuropsychological alterations in children and adolescents with CHD. This study not only presents patients from

Mexico but also and importantly compares neurocognitive performance among CHD patients suffering from a simple to a severe heart pathology, being both novel aspects and contributing thus to the growing literature on this topic.

Author Contributions

All authors contributed to the concept/design, data acquisition, analysis and interpretation, drafting of the article, its critical revision, and final approval.

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