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Cognitive impairment in adult CHD survivors: A pilot study☆

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Abstract

The most common comorbidities in children with congenital heart disease (CHD) are neurodevelopmental impairments, particularly in areas of executive function, memory and attention. Limited studies have demonstrated similar impairments in CHD adults although no studies have screened specifically for mild cognitive impairment and dementia. Methods We performed a prospective cross-sectional study of CHD patients, ages 30-65 years, who were coming for clinic visits. We administered the Mini-Mental State Exam (MMSE), and scores were compared with population norms adjusted by age and education level. Results A total of 125 patients were recruited (55% male). The median age was 40 years (range 30-65). More than a half (80%) had some college education or advanced degrees. Adjusting for age and education, CHD participants scored significantly lower than the general population (median 1 point lower, $p<0.001$) on the MMSE. The greatest impairments occurred in recall and orientation. Five percent of the total cohort met the general threshold for mild cognitive impairment (MMSE < 24). Clinical factors associated with this degree of cognitive impairment were duration of cyanosis ($p=0.005$) and decreased systemic ventricular function ($p=0.003$). Conclusions Our pilot study showed that, when adjusted for age and education level, CHD adults had significantly lower MMSE scores than the general population, with 5% meeting criteria for mild cognitive impairment. These findings suggest that subtle and early cognitive changes are present in the adult CHD population. Further studies are needed to investigate those changes that might influence long-term outcomes in the adult CHD population.

Keywords

Congenital heart defects; Cognitive impairment; Anatomic complexity

☆This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Declaration of competing interest

The authors report no relationships that could be construed as a conflict of interest.

1. Introduction

Survival in patients with congenital heart disease (CHD) has improved significantly in recent decades such that ~90% of children are expected to survive to adulthood [1,2].With an improved lifespan, adults with CHD can expect to face the sequelae of their heart disease and cardiac procedures as well as typical medical conditions of adulthood such as hypertension, heart failure, atrial fibrillation, and stroke [2-8]. Using administrative data, Bagge, et al. showed that adults with CHD have a higher prevalence of dementia diagnoses relative to the general population [9]. A few other small studies have shown neuropsychological deficits in ACHD patients including areas of memory and executive function, but no studies have evaluated specifically for cognitive impairment [10-12]. Understanding cognitive outcomes was included as a high priority research area by a recent National Institutes of Health/Adult Congenital Heart Association working group [13,14].

Multiple studies over the last two decades have shown that children with CHD, particularly those with moderate and complex disease, are at an increased risk of deficiencies in all neurodevelopmental domains [15-23]. These domains include intellect, language, attention, memory, executive functioning, fine and gross motor skills, and psychosocial maladjustment. It has been postulated that genetic and structural brain abnormalities, all play a role [24-29].

In addition, adult CHD patients can also develop acquired cardiovascular conditions that have a risk of cognitive impairment such as heart failure, stroke or the need for cardiac surgery [30-32]. These acquired cardiovascular comorbidities are postulated to have a direct effect on cerebral blood flow, cognitive decline and the development of dementia.

The purpose of this study was to evaluate the cognitive status in middle age adults with CHD compare to age and education matched general population norms. We hypothesized that ACHD patients will have a higher prevalence of cognitive deficits compared to the general population. This hypothesis is based on the known risk of impairments in neurodevelopment during childhood and the superimposed risks of ACHD general adult cardiovascular comorbidities [15-17,33]. In order to explore this hypothesis, we used a standardized test the Mini-Mental State Exam (MMSE) to evaluate different neurological domains. This test was initially developed to screen for dementia although in clinical practice is used routinely to measure general cognitive functioning due to ease and speed of administration. The MMSE also has general population norms adjusted for age and education level.

2. Methods and materials

We performed a cross-sectional study of 125 ACHD patients between the ages of 30–65 years and compared the results to the Mini Mental State Exam population norms by age and education level. The study was conducted during a single clinic visit. Elegible participants were identified from the cardiology clinic schedule prior to the visit. We included participants who had the cognitive and language abilities to complete the informed consent process and study questionnaires in English. People without structural congenital heart disease, those with cardiac surgery or other general anesthesia procedures in the preceding

6 weeks or those who were unable to complete the surveys or testing independently were excluded. Participants with known genetic syndromes were not automatically excluded from the study unless they met one of the other exclusion criteria. Permission prior the visit was obtained from the primary cardiologist to approach the participant for the study. The study was approved by the IRB at the Boston Children's Hospital.

2.1. Recruitment

We recruited participants between the ages of 30–65 years old from the outpatient clinic of our tertiary ACHD clinic at Boston Children's Hospital from July 2019 to February 2020. Eligible patients who chose to participate in the study were required to give informed consent and then the MMSE test was administered during the clinic visit.

2.2. Measures

The Mini Mental State Exam is widely used to measure cognition in clinical practice and research [34-36]. The results provide an assessment of cognitive function in the areas of orientation, memory, attention, calculation, language and visual construction. The total score measures between 0 and 30 points and a value of less than 24 suggests cognitive impairment regardless of age and education level norms. The MMSE was administered by a trained research assistant. Data on socio-demographic factors including age, gender, ethnicity, race and educational level were collected from medical records. Medical records were used to collect data about past medical history including number of heart surgeries which required cardiopulmonary bypass, number of cardiac catheterizations, actual medications, percentage of systemic ventricular function, presence of cyanosis at birth, years of cyanosis, current oxygen saturation and presence of other medical conditions.

2.3. Data analysis

MMSE scores from ACHD patients were compared to age and education specific population norms for the MMSE. Demographic and clinical characteristics were reported as means with standard deviations or medians with interquartile ranges (IQR) for continuous variables, and frequencies and percentages for categorical variables.

MMSE scores were compared for categories of demographic and clinical characteristics using Wilcoxon rank sum and Kruskal-Wallis tests. Patient characteristics were compared for subjects with and without mild cognitive impairment using Fisher's exact test.

In order to compare MMSE scores with population norms, for each study subject, a z-score for MMSE was created by subtracting the mean for the normative population MMSE of the appropriate age and education level and dividing by the standard deviation. Mean z-score was then compared to the value 0 – the mean which would be expected if adult CHD survivors have scores comparable to the general population – using a one-sample signed-rank test. All statistical tests were performed with the use of STATA version 15.

3. Results

3.1. Descriptive data

In our study sample the median age was 40 years [33,49] with 55% male participants and 98% Caucasian among those who reported race. The group was highly educated with 80% having more than a high school degree including 38% with a college diploma and 27% with an advanced degree (Table .1).

From the clinical standpoint, 8 (6%) had simple complexity, 68 (55%) had moderate complexity CHD and 49 (39%) had severe complexity (Table .1). Sixty percent had cyanosis at birth, and most had surgical repair prior 4 years of age. In addition, a majority of patients had undergone cardiac surgery or catheterization. The majority of the study group (91%) had normal systemic ventricular function, with only 4 patients having severe systemic ventricular dysfunction. Among the 125 participants, cardiac and non-cardiac comorbidities were common, and most took at least one medication. The most common cardiac comorbidities were arrhythmia (37%) and systemic hypertension (17%).

The mean MMSE score of the whole cohort was 28 [28,29]. Table 2 shows socio-demographic and clinical characteristics associated with MMSE scores. The demographic factors associated with lower than expected MMSE scores were female sex and high school or less education. Relevant clinical factors associated with low MMSE scores were low systemic ventricular systolic function and multiple (≥2) cardiac catheterizations. When the ACHD sample was compared with population norms, the mean Z score was −0.6 (SD 1.4; $p<0.001$) (Fig. 1). The areas of most difficulty were orientation where at least 22% had one question wrong, recall with >32% unable to recall at least one object, and language and praxis where 10% of the population was not able to copy the assigned object or do the 3-step command correctly (Fig. 2).

The group with mild cognitive impairment (MMSE<24) had a longer period of cyanosis although they were also older and had lower systemic ventricular function.

4. Discussion

This study is the first to evaluate a middle-age cohort of ACHD patients with a specific dementia screening test. Even in this highly educated patient cohort, the ACHD population had significantly lower scores than an age and education matched general population, and 5% scored in the mild cognitive impairment range overall. Studies have demonstrated that many children and adolescents with CHD have neurodevelopmental disabilities and struggle with academic requirements and social and vocational skills with a large proportion requiring remedial academic services, occupational therapy and special education [17,22,37]. Limited studies highlight that neurocognitive challenges are also present in the adult population with CHD and there may be a risk of early dementia [3,5,9,10,33]. In addition to the known neurodevelopmental deficits from childhood, most of the known cardiovascular comorbidities associated with early dementia or the development of mild cognitive impairment such as hypertension, atrial fibrillation, heart failure, exposure to cardiopulmonary bypass, and stroke are also common in the ACHD population. These risks

factors in addition to a possible genetic basis share similar mechanism to affect the cognitive function which includes cerebral hypoperfusion, reduced brain volumes, microbleeds, and neuroinflammation.

Our MMSE results support previous data seen in children, particularly those with moderate and complex disease, with neurocognitive deficiencies in language, attention, memory, and executive function [9,16,17,20-23]. Higher risk for impairment in ACHD patients was seen with decreased systemic ventricular function and multiple procedures, suggesting that early brain injury from procedures and hypoxemia or lower perfusion from decreased systemic ventricular function may contribute. Lower MMSE scores were also seen in women and high-school or less educated patients; similar results have been reported in other studies in participants without CHD [38,39]. A study of more than 18,000 participants showed than MMSE scores are influenced by age and education [36]. The reason for the gender difference it is still controversial where some authors have found no difference, others more robust difference in specific items of the test and other have correlated with a higher prevalence of less education.

The MMSE is a well validated measure of screening for cognitive functioning, with similar reliability statistics to more comprehensive cognitive measures, although full assessment of cognitive function is limited. MMSE has limited specificity with respect to an individual clinical syndrome or disorder such as Alzheimer disease, vascular dementia among others [34,35,40]. It is well known that results can be influenced by age and educational level. In order to avoid this bias, we standardized our results by age and education level for comparison. The actual diagnosis of cognitive impairment and dementia requires an extensive evaluation beyond a screening test.

There are some limitations to our study. The study was conducted in a tertiary level specialized ACHD clinic, which may limit generalizability of the findings. Most of our population has a high school diploma or higher degrees, which in general could affect the MMSE scores. Also, they are in close ACHD care, which may also influence overall cardiovascular health which can affect cognitive performance. However, our pilot data show findings consistent with the cognitive phenotype identified in childhood CHD, even in highly educated patients. In addition, we did not perform a psychosocial evaluation in our study which can influence the performance of the MMSE. Other studies have shown a higher prevalence of depression and other psychosocial problems in the ACHD population which could cause lower scores [11,41].We also recognize that our sociodemographic and past clinical data was based on record review. There were several cases without or with limited old records about operative reports and past procedures for which we were not able to know if patients were placed on cardiopulmonary bypass or had more cardiac catheterization as an infant which in our study were found as risks for lower MMSE scores.

In conclusion, our findings suggest that early cognitive changes are present in the adult CHD population. This significant finding underscores the importance of identifying early cognitive impairment changes as well as assoiated psychological and clinical factors that may be amenable to intervention. Cognitive impairment can impact well-being, self-care, decision making capacity, compliance with treatment, morbidity and mortality. Further

studies are needed to more deeply investigate cognitive changes, and potential disease modifying therapies that might influence long-term outcomes and quality of life in the adult CHD population.

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Abbreviation:

MMSE	Mini-Mental State Exam
ACHD	Adult Congenital Heart Disease.

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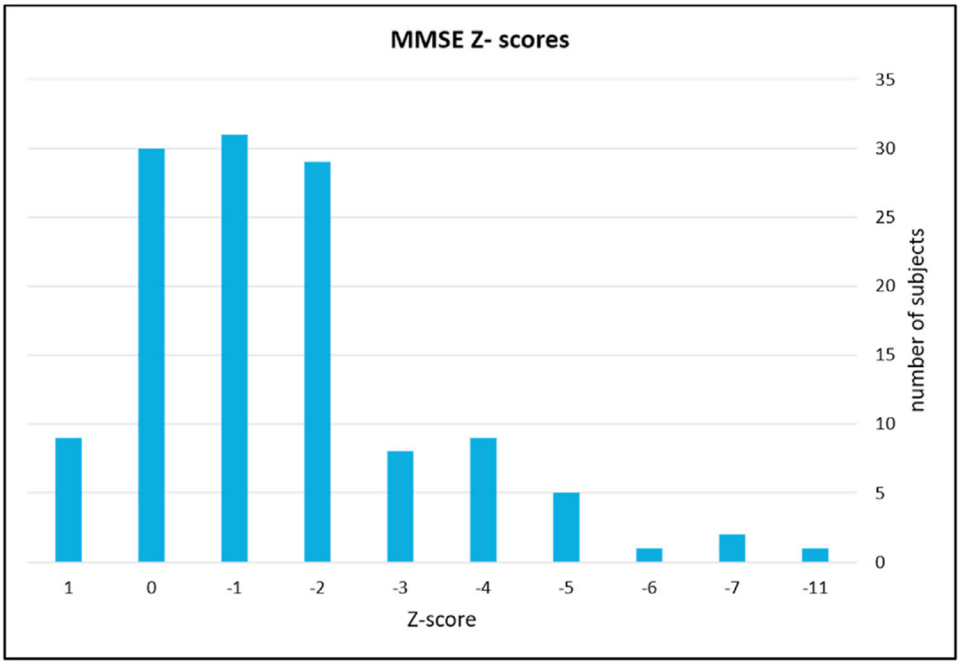

Fig. 1.
MMSE score deviations from population norms by age and education.

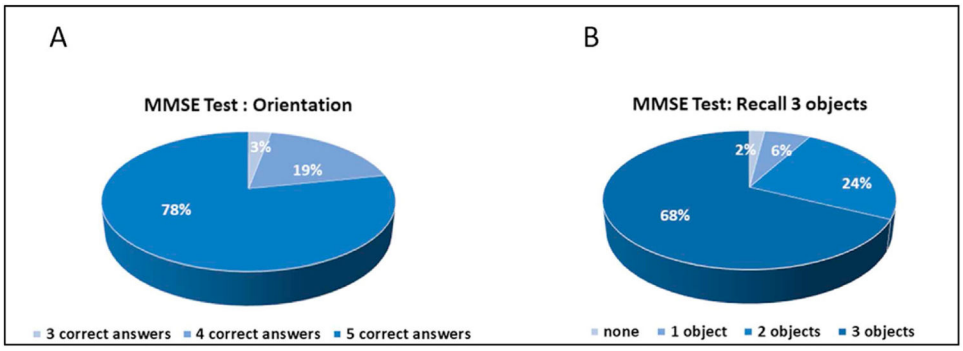

Fig. 2.

MMSE Test: Percentage of subjects who have the questions correct. (A) Orientation (B) Recall 3 objects.

Table 1

Social-demographic and Clinical Characteristics and MMSE scores.

	Congenital Heart Disease Group n = 125
Age	
Median age [IQR]	40 [33, 49]
Sex at Birth	
Male	69 (55%)
Race	
White or Caucasian	98 (78%)
Other races	2 (2%)
Not reported	25 (20%)
Ethnicity	
Non-Hispanic/Latino	72 (58%)
Not reported	45 (36%)
Education Level	
Less than high school	4 (3%)
High school graduate	21 (17%)
Vocational school or higher degree	100 (80%)
Anatomic Complexity	
Simple	8 (6%)
Moderate	68 (55%)
Severe	49 (39%)
Duration of Cyanosis	
0–4 years	42 (60%)
5 years or more	27 (39%)
Unrepaired	1 (1%)
Number of Surgeries Requiring Cardiopulmonary Bypass	
0	42 (34%)
1	49 (39%)
2 or more	34 (27%)
Number of Cardiac Catheterizations	
Less than 2	65 (52%)
2 or more	60 (48%)
Systemic Ventricle Systolic Function	
≥41%	114 (91%)
≤40%	11 (9%)
Most Recent Oxygen Saturation, Day of the Appointment	
≥85%	123 (98%)
<85%	2 (2%)
Any Medications	
Yes	96 (77%)
No	29 (23%)

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	Congenital Heart Disease Group n = 125
Number of Comorbid Conditions	
None	10 (8%)
1	23 (18%)
2 or more	90 (72%)
None	2 (2%)
MMSE Score	
24-30: No cognitive impairment	119 (95%)
18-23: Mild cognitive impairment	6 (5%)
0-17: Severe cognitive impairment	0 (0%)
Median MMSE score with IQR	28 [28, 29]

Table 2

MMSE score by socio-demographic and clinical characteristics.

	Mean ± SD	P Value
Age		
30-44	28.0 ± 1.9	0.27
45-54	28.5 ± 2.1	
55-65	28.0 ± 2.5	
Gender		
Female	27.8 ± 2.0	0.039
Male	28.3 ± 2.0	
Education Level		
Less than high school, high school graduate	26.3 ± 2.4	<0.001
More than high school	28.5 ± 1.6	
Anatomic Complexity		
Simple	28.6 ± 1.7	0.30
Moderate	28.2 ± 2.0	
Severe	27.8 ± 2.1	
Cyanosis at Birth		
Yes	27.8 ± 2.3	0.11
No	28.5 ± 1.6	
Duration of Cyanosis		
0–4 years	28.2 ± 1.7	0.43
5–10 years	28.0 ± 1.9	
>10 years	26.3 ± 3.4	
Number of surgeries requiring cardiopulmonary bypass		
0	28.3 ± 1.7	0.78
1	28.0 ± 2.3	
2	27.6 ± 2.3	
≥3	28.4 ± 1.4	
Number of Cardiac Catheterizations		
0	28.6 ± 1.3	0.051
1	28.3 ± 2.6	
2 or more	27.7 ± 2.0	
Systemic Ventricular Systolic Function		
≥50%	28.4 ± 1.6	0.028
41–49%	27.2 ± 2.5	
30–40%	26.7 ± 3.0	
<30%	25.8 ± 2.9	