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Attention deficit hyperactivity disorder in patients with congenital heart disease

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Abstract

Introduction: Neurodevelopmental disabilities, particularly executive function impairments, are currently the most prevalent long-term morbidity in the population with Congenital Heart Disease (CHD). This study aimed to investigate the frequency of Attention Deficit Hyperactivity Disorder (ADHD) in children with congenital heart disease.

Materials and Methods: This was a retrospective cohort study, which was performed during 2002-2018 on patients with CHD referred to the pediatric cardiology clinic of Imam Reza hospital, Mashhad, Iran. Using the census method, all files for which ADHD diagnosis should be included in the study. Diagnosis of CHD was performed clinically and using an echocardiographic machine by an experienced pediatric cardiologist. Demographic, clinical, and para-clinical data of patients and the type of heart intervention were collected and analyzed. The data were analyzed through SPSS software version 16.5, descriptive statistics, and the Chi-square test.

Results: In this study, 136 patients were enrolled. The mean age of participants in the study was 59.12± 45.84 months at the time of diagnosis. An abnormal electroencephalogram (EEG) was reported in three cases (2.2%). There was a significant correlation between prematurity and developmental delay ($P= 0.01$). The mean age was significantly different in patients with minor rather than those with major cardiac disorders ($P< 0.05$). The prevalence of ADHD in the CHD population was high (31.6%).

Conclusion: This study demonstrated that children born with congenital heart disease are at increased risk of suffering from attention deficit hyperactivity disorder.

Keywords: Attention deficit hyperactivity disorder, Congenital heart disease, Neurocognitive disorder, Pediatric

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Introduction

Congenital Heart Disease (CHD) is the most common congenital disability worldwide, affecting millions of newborns yearly (1). The prevalence of CHD between 1970 and 2017 globally was 8.22 per 1000. During this period, the overall prevalence of CHD globally increased by 10% every five years (1). In order to improve CHD management, most patients can be survived to higher age in childhood or even more. There are now challenges related to these patients' quality of life and long-term development.

It is established that children with CHD are more susceptible to suffering deficiencies in intellectual functioning, developmental problems, and academic performance difficulties (2,3). Children with CHD are at higher risk of several cognitive disorders, which can show problems in school, like patients with attention disorders (4). Unfavorable effects of chronic and intermittent hypoxia on development, behavior, and academic achievement have been reported in previous studies in children with CHD (5).

Neurodevelopmental disabilities, particularly executive function impairments, are currently the most prevalent long-term morbidity in the population with CHD (6). Executive function refers to a set of higher-order neurocognitive abilities that coordinate and organize actions toward a goal, allowing the individual to adapt to new or complex situations (7). Impairments in executive function manifest as behavioral dysregulation, attention problems, impaired working memory (like the ability to keep information in mind and manipulate it over a short period), and problems with organization and planning abilities. Executive function is more strongly associated with school readiness than IQ, predicts mathematics and reading competence throughout the school years (8,9), and is strongly associated with social cognition (8). Patients with CHD display deficits in visual-perceptive skills (10-14) and executive function (10,11), ADHD symptoms (14,15), and reduced quality of life (16,17). There are rarely available data on mental health outcomes in CHD survivors in adolescence (18,19).

According to full DSM-5 criteria, the prevalence of ADHD was 3.55% in a large-scale study (20). Although long-term behavioral outcomes have been studied for various forms of CHD, the presence of ADHD

within this group of patients is rarely addressed (21). Studies conducted with heterogeneous CHD populations have reported increased risk and under-treatment of psychiatric symptoms, including anxiety and depression (19,22). However, the prevalence of psychiatric disorders in adolescents with critical CHD remains under-investigated. Although studies suggest that adolescents with critical CHD display a higher incidence of ADHD (11,15,21), this literature is limited by reliance on parent- and self-report measures. This study aimed to investigate the prevalence of ADHD in children with CHD referred to Imam Reza hospital, Mashhad- Iran between 2002 and 2018.

Materials and Methods

This was a retrospective cohort study performed during 2002-2018 in all patients with CHD referred to the pediatric cardiology clinic of Imam Reza hospital, Mashhad, Iran.

The inclusion criteria included children and adolescents aged less than 18 years who were diagnosed with CHD (ICD-9-CM codes: 745, 746, 747.1-747.4) by a pediatrician, cardiologist, or cardiac surgeon.

The exclusion criteria included patients with histories of psychiatric disorders (ICD-9-CM codes: 290-319), confirmed diagnosis of an autism spectrum disorder that would prevent successful completion of the planned study testing, and scheduled to undergo major cardiac interventions in the six months following enrollment.

CHD definition

All patients were diagnosed with pediatric and congenital cardiologists according to ICD-10 and met one of the following criteria:

a) Age less than 18 years at baseline assessment, b) had received cardiovascular care at the Imam Reza Hospital, Mashhad, and c) Diagnosis of CHD was performed clinically and using an echocardiographic machine and other cardiac imaging modalities by an experienced pediatric cardiologist. Heart diseases were divided into two important (major) and non-important (minor) categories based on the need for follow-up and intervention.

Echocardiographic assessment

All patients underwent M-mode, two-dimensional, Doppler, and color Doppler echocardiography performed on (Vivid 7 GE, USA, and Resona7, Mindray, China) using 3-5 MHz transducer by an experienced pediatric

echocardiographer in the department of pediatric and congenital cardiology of Imam Reza hospital. Structural defects and cardiac function were determined by using standard and oblique views.

Attention-deficit/hyperactivity disorder assessment

The diagnoses are based upon assessments by a psychiatrist or child and adolescent psychiatrist according to DSM-IV or DSM-V criteria.

The institutional review board approved this study at Mashhad University of Medical Sciences, Mashhad, Iran. All parents or guardians were requested to complete the written consent form for enrolling in the study.

All data were entered in SPSS software Ver. 16.5. Descriptive data were reported as count, percent, mean, and standard deviation. For comparing qualitative variables, the Chi-square test was used. P value less than 0.05 was considered significant.

Results

During the period of study, 136 patients enrolled in the study. The mean age of the participants in the study was 59.12 ± 45.84 months at the time of diagnosis. Twenty-nine were female (21.3%), and others were male (78.7%). Table 1 shows the demographic data of patients.

Table 1. Demographic data of participants

| Characteristics | |
|--------------------------------------|---|
| Age at diagnosis of CHD (months, SD) | 59.12 ± 45.84 |
| Sex (n, %) | |
| Male | 107, 78.7 |
| Female | 29, 21.3 |
| Age group (n, %) | |
| < 36 months | 44, 32.4 |
| 37-80 months | 44, 32.4 |
| 81-125 months | 37, 27.2 |
| 126-170 months | 9, 6.6 |
| >171 months | 2, 1.5 |
| Age at last visit (months, SD) | 105.63 ± 50.45 |
| Birth weight (mean, SD) (gram) | 3075 ± 603.51 |
| Birth weight group (n, %) | |
| Small for gestational age | 24, 17.6 |
| Normal | 104, 76.4 |
| Large for gestational age | 8, 5.9 |
| New Weight (mean, SD) kilogram | 31.25 ± 15.78 |
| Premature (n, %) | 5, 3.7 |
| Consanguinity (n, %) | 48, 35.3 |
| Delivery (n, %) | Cesarean (74, 54.4) Vaginal (62, 44.1) |
| Syndrome (n, %) | Down (3, 2.2), Noonan (2, 1.5) |

Table 2 shows referring causes of patients to the pediatric cardiology department, and Table

3 shows the clinical features of patients enrolled in this study.

Table 2. Referring causes of patients to the pediatric cardiology department

| Variable | |
|---------------------------|---|
| Referring groups (n, %) | Pediatrics (77, 56.6) Psychiatrists (3, 2.2) Patients (28, 20.6) Others (28, 20.6) |
| Cause of Referring (n, %) | Clinical suspicion (8, 5.9) Respiratory symptoms (47, 34.6) Abnormal Chest radiography (2, 1.5) |

| | |
|--|---|
| | ADHD (3, 2.2) |
| | Cardiovascular manifestation (75, 55.1) |
| | Other (1, 0.7) |

Table 3. Clinical features of patients

| Characteristics | |
|--------------------------------|-----------|
| Tachycardia (n, %) | 4, 2.9 |
| Click or murmur (n, %) | 120, 88.2 |
| Anemia | 2, 1.5 |
| Sweating | 4, 2.9 |
| Chest anomaly | 5, 3.7 |
| Icterus | 1, 0.7 |
| Hematologic abnormalities | 4, 2.9 |
| Gastrointestinal abnormalities | 12, 8.8 |
| Neurologic abnormalities | 24, 17.6 |
| Ear nose throat abnormalities | 4, 2.9 |
| Respiratory abnormality | 15, 11 |
| Ophthalmologic abnormalities | 3, 2.2 |
| Urogenital abnormalities | 8, 5.9 |
| Orthopedic abnormalities | 2, 1.5 |

Two patients had frequent urinary tract infection (1.5%). Cardiac abnormality is listed in Table 4. Electrocardiogram (ECG)

abnormality was reported in 12 cases in Table 5.

Table 4. Major and minor cardiac abnormalities of patients

| Major abnormalities | N, % |
|--|----------|
| Septal defects | |
| Ventricular septal defect | 27, 19.9 |
| Atrial septal defect | 4, 2.9 |
| Atrioventricular septal defect | 2, 1.5 |
| Arterial abnormality | |
| Patent ductus arteriosus | 8, 5.9 |
| Right sided obstructive lesions | |
| Tetralogy of Fallot | 6, 4.4 |
| Pulmonary valve stenosis | 5, 7.1 |
| Pulmonary atresia (n, %) | 1, 0.7 |
| Pulmonary vessel abnormality | |
| Pulmonary hypertension | 2, 1.5 |
| Left sided obstructive lesions | |
| Aortic stenosis | 7, 5.1 |
| Coarctation of aorta | 4, 2.9 |
| Myocardial abnormality | |
| Hypertrophic cardiomyopathy (n, %) | 1, 0.7 |
| Complex | |
| Double Outlet Right Ventricle (DORV) (n, %) | 2, 1.5 |
| Transposition of great arteries (n, %) | 1, 0.7 |
| Heterotaxia (n, %) | 2, 1.5 |
| Tricuspid valve abnormality | |
| Ebstein anomaly (n, %0) | 1, 0.7 |
| Minor abnormalities | N, % |
| Floppy mitral valve and/ or mitral valve prolapse without mitral regurgitation | 56, 41.1 |
| Patent foramen ovale | 12, 8.8 |
| Persistent left superior vena cava | 4, 2.9 |

Table 5. Electrocardiogram abnormalities

| Characteristics | |
|--|--------|
| QRS wideness > 0.16 Sec | 1, 0.7 |
| Right Bundle Branch Block (RBBB) | 5, 3.7 |
| Premature Atrial Contraction (PAC), Premature Ventricular Contraction (PVC) (Infrequent) | 1, 0.7 |
| Sinus arrhythmia | 3, 2.2 |
| Right Axis Deviation (RAD) and Right Ventricular Hypertrophy (RVH) | 2, 1.5 |
| Left Bundle Branch Block (LBBB) and ST-T changes | 1, 0.7 |
| Tachycardia | 1, 0.7 |
| Right Atrial Hypertrophy (RAH) | 1, 0.7 |

Abnormal electroencephalogram (EEG) was reported in three cases (2.2%). Neuropsychiatric disorders were reported in 34

cases (25%). Table 6 shows the prevalence of these disorders.

Table 6. Neuropsychiatric disorders of patients

| Characteristics | |
|---------------------|--------|
| Bruxism | 1, 0.7 |
| Learning disorders | 3, 2.2 |
| Autism | 1, 0.7 |
| Anxiety | 3, 2.2 |
| Enuresis | 1, 0.7 |
| Development delay | 15, 11 |
| Behavioral disorder | 4, 2.9 |
| Hysteria | 1, 0.7 |
| Tic | 3, 2.2 |
| Sighing | 3, 2.2 |
| Speech delay | 5, 3.7 |
| Seizure | 2, 1.5 |

One hundred five patients underwent medical treatment (77.2%), one of them underwent cardiac catheterization (0.7%), and 30 of them underwent surgery (22.1%). We followed the patients; in their last follow-up, 96 were stable, and 40 were missing the follow-up. There was no significant correlation between ADHD and congenital cardiac anomaly or malformation in

our study population ($P > 0.05$). ADHD in CHD patients was less significant in any sex ($P > 0.05$). There was a significant correlation between prematurity and developmental delay ($P = 0.01$). The mean age was significantly different in patients with minor rather than those with major cardiac disorders ($P < 0.05$).

Discussion

Our study showed that ADHD was prevalent in CHD patients (31.6%) in the normal population. We also demonstrated that there was no significant correlation between ADHD and special cardiac anomalies and is not sex-dependent. Moreover, there was a significant correlation between prematurity and developmental delay, and the mean age was significantly different in patients with minor rather than patients with major cardiac disorders.

Although our study was not in a casualty design, prior investigations have suggested

that CHD can be a risk factor for ADHD and autism. In a cross-sectional study, a significant proportion of children between the ages of 7 and 15 years old with CHD had symptoms of ADHD. Their results suggest that the prevalence of ADHD symptoms was significantly higher in this group with CHD (11.8%) when compared to the estimated prevalence in children (5%). In another study, the mean ADHD score in patients with CHD was the same in the general population with ADHD (22). Razzaghi et al. found that ADHD and autism were higher in children with CHD than in the control group (23). Another study

determined that the number of children with clinically significant ADHD scores among a patient with CHD was 3-4 times higher than that observed in the general population (24). Primary investigations mentioned that patients with CHD usually manifested unusual hemodynamic changes (25,26). This can lead to impaired cerebral blood flow (26) and abnormality in neurodevelopment (27-29), and immunological dysregulation (30,31), which has played an important role in the development of ADHD and autism (32,33). It was found in another study that the risk of ADHD and autism spectrum disorder was higher in children with developmental delays (34). Flanagan et al. reported that motor delays at the age of 6 months were associated with the development of autism at the age of 36 months (35). Moreover, Sharma et al. reported that young children with early developmental disorders were more likely to be subsequently diagnosed with ADHD (31). In another study, the first logistic regression model showed that children with CHD, compared with children without CHD, had ~1.6 to 2.7 times the odds of ADHD (36).

According to previous studies, children with CHD are at higher risk of development and intelligence delay, with a higher incidence of gross and fine motor abnormalities and lower mean IQ scores than the age-matched controls (37,38). Marino et al. demonstrated that children with CHD were at increased risk of developmental disorders/disabilities and developmental delays (6). Therefore, it is important to identify the risk for ADHD and autism in a highly vulnerable subpopulation with two chronological risk factors, one present at birth and the other developing during early childhood. Indeed, the presence of one risk factor led to modest increases in risk for ADHD or autism. However, the hazard ratio for ADHD exponentially increased by 16.59 times (34). These results suggested that the existence of CHD can predispose the brain areas to dysfunction.

CHD in the neonatal period can cause neonates to suffer adverse perinatal outcomes, including perinatal infection, preterm delivery, or low birth weight (39). The potential role of these perinatal comorbid disorders that may have a negative impact on the development of ADHD (40) is still under debate. However, the current study did not show any correlation

between comorbid perinatal disorders and ADHD.

An increased incidence of ADHD in the CHD patient population may be because of a higher prevalence of genetic syndromes in children undergoing heart surgery than in the normal population. Therefore, the risk for ADHD will, unfortunately, always be higher than in the normal population. However, an additional consideration is the potential impact of interrupting cerebral blood flow during neonatal aortic arch surgery with the subsequent loss of dopamine receptor activity (24). Reduced dopaminergic activity in the striatum has been documented in ADHD patients, indicating the possibility of a link between cardiac surgery, hypoxia, and attention-deficit/hyperactivity disorder (41).

Our study was a cohort study that enrolled CHD patients and followed them up. In this study, we missed follow-up in many patients. This study could be re-analyzed, and subgroup analysis can help to calculate hazard ratios of the Kaplan-Mayer test to achieve a more practical tool for predicting ADHD in CHD patients.

Conclusion

Attention deficit hyperactivity disorder has recently received more attention and is commonly seen in congenital heart disease. Cardiopulmonary signs and symptoms, abnormal electrocardiogram findings, and other associated neuropsychiatric disorders were significantly higher in these children. This study demonstrated that children born with congenital heart disease are at increased risk of suffering from attention deficit hyperactivity disorder. Further studies with a larger sample size and more formal attention deficit hyperactivity disorder evaluation can help evaluate the prevalence and risk factors in children with congenital heart disease. A multidisciplinary approach consisting of a pediatrician, pediatric cardiologist, pediatric psychiatrist, and other related specialties is expected for timely and appropriate diagnosis and treatment.

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