# Attention Deficit Hyperactivity Disorder (ADHD) in Patients With Congenital Heart Disease (CHD)

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**Research**

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# Abstract

Background

It is established that children with congenital heart disease (CHD) are more susceptible for suffering deficiencies in intellectual functioning, developmental problems, and academic performance difficulties. Neurodevelopmental disabilities, particularly executive function impairments, are currently the most prevalent long-term morbidity in the population with CHD. The aim of this study was to investigate the frequency of Attention deficit hyperactivity disorder (ADHD) in children with CHD.

Methods

This was a retrospective cohort study, which was performed between 2002-2018 in patients with CHD referred to Imam Reza hospital, Mashhad, Iran. Using the census method, all files for which ADHD diagnosis has been made according to DSM-IV or DSM-V criteria should be included in the study. Diagnosis of CHD was performed clinically and using an echocardiographic machine 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. Demographic, clinical and para-clinical data of patients as well as the type of heart intervention were collected and analyzed.

Results

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

Conclusion

This study demonstrated that children born with CHD are at increased risk of suffering from ADHD.


# Introduction

Congenital heart disease (CHD) is the most common birth defect worldwide, affecting millions of newborns every year (1). The mean 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 5 years (1). In order to improvement in CHD management, most of patients can be survived to higher age in childhood or even more. There is now challenges related to quality of life and long-term development in these patients.

It is established that children with CHD are more susceptible for suffering deficiencies in intellectual functioning, developmental problems, and academic performance difficulties (2, 3). Children with CHD are

in higher risk of several cognitive disorders, which can showed problems in school like to patients with disorders of attention (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 serve to coordinate and organize actions towards a goal, allowing the individual to adapt to new or complex situations (7). Impairments in executive function manifest as behavioral dysregulation and 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 is IQ, predicts both 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 rare 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 higher incidence of ADHD (11, 15, 21), this literature is limited by reliance on parent- and self-report measures. The aim of this study was to investigate the prevalence of ADHD in children with CHD referred to Imam Reza hospital between 2002 and 2018.

## Methods

This was a retrospective cohort study, which was performed between 2002–2018 on patients with CHD referred to pediatric cardiology clinic of Imam Reza hospital, Mashhad, Iran.

# Inclusion criteria

In this study, we enrolled children and adolescents aged less than 18 years who were diagnosed with CHD (ICD-9-CM codes: 745, 746, 747.1–747.4) by pediatrician, cardiologist, or cardiac surgeons. Patients with histories of a psychiatric disorder (ICD-9-CM codes: 290–319) before enrollment, were excluded from this study. Confirmed diagnosis of an autism spectrum disorder that would prevent successful completion of the planned study testing; scheduled to undergo major cardiac interventions in the 6 months following enrolment were excluded from the study, too.

# CHD definition

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

1. a) Age less than 18 years at baseline assessment;
2. b) Had received cardiovascular care at Imam Reza Hospital, Mashhad; and

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 dimentional, doppler and color Doppler echocardiography performed on (Vivid 7 GE, USA and Resona7, Mindray, China) using 3–5 MHz transducer by an experienced pediatric echocardiographist in the department of pediatric and congenital cardiology, Imam Reza hospital Structural defects and cardiac function 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.

# Ethics

This study was approved by the institutional review board 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.

# Statistics

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

## Results

During the period of study, 136 patients were enrolled in the study. The mean age of participants in the study was 59.12 ± 45.84 months at time of diagnosis. Twenty-nine of them 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) gr | 3075 ± 603.51 |
| Birth weight group (n, %) | |
| SGA | 24, 17.6 |
| NL | 104, 76.4 |
| LGA | 8, 5.9 |
| New Weight (mean, SD) kg | 31.25 ± 15.78 |
| Premature (n, %) | 5, 3.7 |
| Consanguinity (n, %) | 48, 35.3 |
| Delivery (n, %) | Cesarean (74, 54.4)<br>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 show 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 CXR (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 |
| ENT 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 UTI (1.5%). Cardiac abnormality is listed in Table 4.

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 |

Electrocardiogram(ECG) abnormality was reported in 12 cases that is listed in Table 5.

Table 5
ECG abnormalities

| Characteristics | |
|---|---|
| QRS WIDENESS > 0.16 Sec | 1, 0.7 |
| Right bundle branch block(RBBB) | 5, 3.7 |
| PAC, PVC (INFREQUENT) | 1, 0.7 |
| SINUS ARRYTHMIA | 3, 2.2 |
| RAD&RVH | 2, 1.5 |
| Left bundle branch block (LBBB)& ST-T changes | 1, 0.7 |
| Tachycardia | 1, 0.7 |
| RAH | 1, 0.7 |

Abnormal 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 and in their last follow-up, 96 of them were stable and 40 of them were missed 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 not more significantly in any sex ($P > 0.05$). There was significant correlation between prematurity and developmental delay ($P = 0.01$). The mean of age was significantly different in patients with minor rather than patients with major cardiac disorder ($P < 0.05$).

# Discussion

Our study showed that ADHD was prevalent in CHD patients (31.6%) toward 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 significant correlation between prematurity and developmental delay and the mean of age was significantly different in patients with minor rather than patients with major cardiac disorder.

Although our study was not in a casualty design, prior investigations have suggested that CHD can be a risk factor for both 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 suggests that the prevalence of ADHD symptomatology was significantly higher in this group with CHD (11.8%) when compared to the estimated prevalence in children (5%) (21). In one study, it was demonstrated that the mean ADHD score in patients with CHD was as the same in general population with ADHD (23). Razzaghi et al. found that the chance of ADHD and autism were higher in children with CHD than control group (24). In another study, it was determined that the number of children with clinically significant ADHD scores among a patients with CHD was 3–4 times higher than that observed in the general population (25). Primary investigations mentioned that patients with CHD usually manifested by unusual hemodynamic changes (26, 27). This can lead to impairing cerebral blood flow (27) and abnormality in neurodevelopment (28–30), and with immunological dysregulation (31, 32), which has been important role in the development of ADHD and autism (33, 34). It was found in another study, that the risk of ADHD and Autism spectrum disorder(ASD) was higher in children with developmental delay (35). 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 (36). Moreover, Perna and Loughan (32) reported that young children with EDD were more likely to be subsequently diagnosed with ADHD.

According to previous studies, children with CHD are at higher risk development and intelligent delay, with higher incidence of gross and fine motor abnormalities as well as lower mean IQ scores, compared with the age-matched controls (37, 38). Marino et al. clearly 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 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 was exponentially increased by 16.59 times (35). These results suggested that existence of CHD, can predispose the brain areas to dysfunction.

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

An increased incidence of ADHD in CHD patient population may be because of higher prevalence of genetic syndromes in children undergoing heart surgery than 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 (25). 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 sub-group analysis can help to calculating hazard ratio by Kaplan Mayer test to achieve more practical tool for predicting ADHD in CHD patients.

# Conclusion

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

# Abbreviations

CHD
congenital heart disease
ADHD
Attention deficit hyperactivity disorder
EEG
electroencephalogram
RBBB

Right bundle branch block
LBBB
Left bundle branch block
ASD
Autism spectrum disorder
ECG
Electrocardiogram

# Declarations

### Conflict of interest

There is no conflict of interest.

### Declarations

### Ethics approval and consent to participate:

This study was approved by the institutional review board at Mashhad University of Medical Sciences, Mashhad, Iran (IR.MUMS.MEDICAL.REC.1397.743). All parents or guardians were requested to complete the written consent form for enrolling in the study.

### Consent for publication:

This manuscript doesn't contain any individual person's data.

### Availability of data and materials:

The datasets during and/or analyzed during the current study available from the corresponding author on reasonable request.

### Competing interests:

There is no conflict of interest.


### Funding:

Mashhad University of Medical Sciences, Mashhad, Iran


### Authors' contributions

HM proposed and designed this research, and performed assessment of patients diagnosed with CHD. AH analyzed and interpreted the patient data regarding the CHD and ADHD comorbidity. ME was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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