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Attention-Deficit/Hyperactivity Disorder symptoms in children with surgically corrected Ventricular Septal Defect, Transposition of the Great Arteries and Tetralogy of Fallot

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Abstract

Background: Children with complex congenital heart disease are at risk for psychopathology such as severe Attention-Deficit/Hyperactivity Disorder symptoms after congenital heart surgery.

Objective: To investigate if children with Ventricular Septal Defect, Transposition of Great Arteries, or Tetralogy of Fallot have an increased occurrence of Attention-Deficit/Hyperactivity Disorder symptoms compared to the background population and to investigate differences between the three congenital heart defects in terms of occurrence and appearance of Attention-Deficit/Hyperactivity Disorder symptoms.

Method: A national register-based survey, including children aged 10-16 years with surgically corrected congenital heart defects without genetic abnormalities and syndromes. The Attention-Deficit/Hyperactivity Disorder-Rating Scale questionnaires were filled in by parents and school teachers.

Results: In total 159 out of 283 questionnaires were completed among children with congenital heart defects and compared with age- and sex-matched controls. Children with congenital heart defects had significantly increased inattention scores (p=0.009) and total Attention-Deficit/Hyperactivity Disorder scores (p=0.008) compared to controls. Post hoc analyses revealed that children with Tetralogy of Fallot had significantly higher inattention scores compared to both children with Ventricular Septal Defect (p=0.043) and controls (p=0.004).

Conclusion: Attention-Deficit/Hyperactivity Disorder symptoms and inattention symptoms were significantly more frequent among children aged 10-16 years with congenital heart defects, in particular in children with corrected Tetralogy of Fallot.
Keywords; Congenital Heart Defects, Attention-Deficit/Hyperactivity Disorder, Questionnaires, Children, Adolescents, Ventricular Septal Defect, Transposition of the Greater Arteries, Tetralogy of Fallot.
Introduction

Neurodevelopmental impairment is recognised as one of the major morbidities associated with complex congenital heart defects (CHD) (1) can be present as cognitive impairments, impaired social interaction and communication skills, as well as inattention and impulsive behaviour, and executive dysfunctions (1-3). Previous studies have suggested that attention and hyperactive symptoms are more frequent in children with CHD (4, 5) and the risk of fulfilling the diagnostic criteria of Attention-Deficit/Hyperactivity Disorder is three-four times higher than in the general population (6).

Attention-Deficit/Hyperactivity Disorder is one of the most common mental health disorders and is characterised by a persistent and age inappropriate pattern of inattention and /or hyperactivity/impulsivity causing significant impairments throughout life (7). During childhood, adolescence, and adulthood Attention-Deficit/Hyperactivity Disorder is associated with increased risk of other psychiatric disorders, educational and work failure, accidents, social problems, addictions, and early death (8). If undiagnosed and untreated, the prognosis later in life may worsen (6). Attention-Deficit/Hyperactivity Disorder symptoms arise early in childhood and 3-5 % of Danish pre-schoolers in the background population show significant Attention-Deficit/Hyperactivity Disorder symptoms and impairments in cognitive, social and family functioning (9).

International studies have investigated the prevalence of Attention-Deficit/Hyperactivity Disorder in different subtypes of CHD (4, 5, 7) and the risk for Attention-Deficit/Hyperactivity Disorder may be 3-4 times higher in children with complex CHD compared to the prevalence in the general population (4). However, the aforementioned studies are either based on relatively minor groups of children or focused on a single cardiac lesion (4-6, 10).

The primary aim of this study was to investigate the occurrence of Attention-Deficit/Hyperactivity Disorder symptoms in a mixed group of children with biventricular cardiac repair, including Ventricular Septal Defect, Transposition of Great Arteries, and Tetralogy of Fallot compared to community controls. The secondary aims were to compare severity of Attention-Deficit/Hyperactivity Disorder symptoms across the three subgroups of CHD and finally to characterize the Attention-Deficit/Hyperactivity Disorder presentation in each of the three CHD diagnostic groups.
Methods

Participants

All children who underwent surgery for simple Ventricular Septal Defect closure, Transposition of Great Arteries, or Tetralogy of Fallot from January 1st, 2001 to December 31st, 2007 in two tertiary paediatric cardiac surgery centres at Aarhus University Hospital, Denmark and at Rigshospitalet, Copenhagen University Hospital were recruited to the study. Children were identified by means of the Danish National Patient Register. Inclusion criteria were: surgically corrected Ventricular Septal Defect, Transposition of Great Arteries, or Tetralogy of Fallot in Denmark, age 10-16 years at the time of the completion of the questionnaire, and Danish speaking parents. Ethics approval was gained. Exclusion criteria were presence of syndromes-, genetic-, or neurological abnormalities or other chronic diseases. Patients were either contacted by mail or asked to participate in the survey at a routine follow-up visit at the outpatient Paediatric Cardiac Clinic at Aarhus University Hospital or at Rigshospitalet, Copenhagen University Hospital. All families received a letter with two identical (parent and school teacher) Attention-Deficit/Hyperactivity Disorder-Rating Scale (9) and a total of 159 questionnaires were returned by parents in a pre-stamped envelope enclosed in the invitation letter, including the school teacher’s evaluation.

Control group

A control group of 317 community sample children and adolescents was acquired from an existing national Attention-Deficit/Hyperactivity Disorder-Rating Scale dataset from the Department of Child and Adolescent Mental Health Odense. This dataset was part of previously published data from the Danish Attention-Deficit/Hyperactivity Disorder-Rating Scale standardization study (9). All control subjects with a completed parent and a school questionnaire were selected and randomly matched 2:1 with respect to gender and age (10-16 years) to the individual participant in the CHD group. In the control group, the school questionnaires were returned directly to the Department of Child and Adolescent Mental Health, Odense, Denmark and not via parents.

Attention-Deficit/Hyperactivity Disorder-Rating Scale

The Attention-Deficit/Hyperactivity Disorder-Rating Scale is a behaviour rating scale and has favourable psychometric properties as reliability and validity (14) and widely applied to measure Attention-Deficit/Hyperactivity Disorder symptoms as well as symptoms of Oppositional Defiant Disorder in school-aged children (6 to 16 years) (11). The Attention-Deficit/Hyperactivity Disorder-Rating Scale consists of 26 items rated by parents and teachers and scored across three separate subscales; the inattention subscale (9 items), the hyperactivity/Impulsivity subscale (9 items) and the behaviour problem subscale (8 items). The
questionnaire is valid and clinically feasible in a Danish setting (9, 12). The Attention-Deficit/Hyperactivity Disorder-Rating Scale includes the 18 Attention-Deficit/Hyperactivity Disorder symptoms as defined in the DSM-5 (13) to be rated on a four-point Likert scale ranging from 0 (the symptom is never/rarely present) to 3 (the symptom is very often present) (14). The eight additional items cover Oppositional Defiant Disorder symptoms. The scale is designed to generate an inattention score (0-27 points), a hyperactivity/impulsivity score (0-27 points), and a total Attention-Deficit/Hyperactivity Disorder score (0-54 points), which is the sum of the inattention and hyperactive/impulsive scores. The present study included the parents- and school teacher version of the Danish Attention-Deficit/Hyperactivity Disorder-Rating Scale-IV (15). The raw scores of all patients were transformed to T-scores with the usage of Danish normative data of 781 children, stratified on age and gender (12). A T-score of 50 is the normative mean (considering their age and gender) with a standard deviation (SD) of ten points. A T-score of 40-60 indicates a normal score, a T-score of 61-70 (>1 SD) indicates a moderate risk of Attention-Deficit/Hyperactivity Disorder and while a T-score >70 (>2 SD) indicates a high risk of Attention-Deficit/Hyperactivity Disorder presentation (16).

Based on the T-score, if a child presented with a high risk of Attention-Deficit/Hyperactivity Disorder, the child was grouped into only one of the three high-risk Attention-Deficit/Hyperactivity Disorder presentations; inattention, hyperactivity/impulsivity or combined (13).

Quality of life

The Paediatric Quality of Life (PedsQL™) version 4.0 generic core module surveys in Danish were applied to investigate the quality of life of the children with CHD (17, 18). The survey is composed of parallel Child Self-Report (8-12 years) and Adolescent Self-Report (13-16 years). The survey contains 23 items that contribute to four subscales in 1) physical-, 2) emotional-, 3) social- and 4) school functioning. A five-point Likert-scale from 0-4 estimates the degree to which the participants (child/adolescent) have experienced difficulties during the last month. The points were reversed and transformed to a 0-100 scale as previous described (33).

Statistical analyses

The Attention-Deficit/Hyperactivity Disorder ratings from the CHD groups were analysed as follows; if one item in a subscale of the Attention-Deficit/Hyperactivity Disorder-Rating Scale questionnaire was missing, the mean value of all the remaining items was imputed. If more than one item was missing in a subscale, the respective subscale score and the total score for the specific individual was omitted from the analysis.

Data from the Attention-Deficit/Hyperactivity Disorder-Rating Scale questionnaires were treated as continuous variables with ordinal numbers. Continuous variables were summarized as mean ± standard deviation. Categorical variables were summarized by percentage.
All non-normally distributed variables were pursued to approximate a normal distribution with equal variances by data transformation (logarithm, square root, cube root). The homogeneity and variance of all non-transformed and transformed data were visually inspected for variance and tested with the Levene’s test for equal variances (‘car’ package v.3.0-2). A p-value <0.05 in the Levene’s test for equal variances was interpreted as a significant difference in variance. The normal distribution was inspected visually by histograms and QQ-plots. If normal distribution and equal variance were achieved after data transformation, data were analysed with unpaired t-test or ANOVA/regression analysis models between group comparisons as appropriate. A statistically significant ANOVA test was subsequently followed by a post-hoc Tukey Honest Significant Difference (HSD) test. Binomial data were analysed with Chi-square/Fisher’s exact test. All non-normally distributed data or data with unequal variances were analysed with non-parametric test such as Mann-Whitney U-test or Kruskal-Wallis H-test in group comparisons, significant intergroup differences in the Kruskal-Wallis H-test were explored with stepwise Mann-Whitney U-test. All analyses were two talled and were performed separately for the parent and the school teacher’s version.

A p-value <0.05 was considered statistically significant in all primary outcomes due to the usage of post-hoc Tukey in the analysis. Equally, p-values <0.05 in all secondary outcomes were considered statistically significant. Analyses were performed using R studio 1.1.4 and R studio 3.4.4 (19).
Results

Demographics

Of the 419 children with surgically corrected Ventricular Septal Defect, Transposition of Great Arteries and Tetralogy of Fallot, 283 were eligible for inclusion. Forty-five children did not meet the inclusion criteria, 27 were excluded due to syndromes, 42 were lost due to emigration, 13 did not consent, and nine children had died. Parents of 159 children (56%) responded on the Attention-Deficit/Hyperactivity Disorder-Rating Scale questionnaire, whereas only 123 teachers of the CHD children (43%) responded (Figure 1).

The CHD group comprised 159 children, 55% male; with a mean age of 13.0 ± 1.8 years, and they were compared with 317 age- and sex-matched controls. Demographics on individual CHD subgroups (Ventricular Septal Defect, Transposition of Great Arteries, and Tetralogy of Fallot) and controls are displayed in Table 1.

Attention-Deficit/Hyperactivity Disorder

The parental Attention-Deficit/Hyperactivity Disorder-Rating Scale ratings of the CHD and the control group showed an overall statistically significant difference in the total Attention-Deficit/Hyperactivity Disorder mean score (p= 0.008) (Table 2a). Post hoc analysis showed that the difference between CHD children and background population was primarily driven by the difference in severity of inattention symptoms. The mean scores were significantly higher in the Tetralogy of Fallot group compared to controls with a mean score difference of 3.90 (standard deviation difference=3.4) as seen in Table 2 (p=0.005). The Tetralogy of Fallot group also had significantly higher mean scores in inattention symptoms than children in the Ventricular Septal Defect group (p=0.043) (data not shown). Equally, the Tetralogy of Fallot group had a significantly higher total Attention-Deficit/Hyperactivity Disorder mean score compared to the control group (p=0.004) (data not shown). The school teacher ratings of CHD children and controls were comparable without any significant differences between groups (Table 2).

The Oppositional Defiant Disorder subscale mean scores based on both the parent and school teacher ratings were not significantly different between the CHD group and controls (Table 3).

The frequency of individuals with an Attention-Deficit/Hyperactivity Disorder score in the clinical range (i.e. T-scores > 70) is displayed in Figure 2. In children with Tetralogy of Fallot, the rate of scores in the clinical range of inattention was almost six times more frequent than in the controls and the occurrence was three times higher than in children with Transposition of Great Arteries and Ventricular Septal Defect, respectively. In contrast, clinical range of hyperactive/impulsivity scores were comparable in children with Transposition of Great Arteries- and Ventricular Septal Defect as well as controls whereas high
hyperactivity/impulsivity scores were completely absent in children with Tetralogy of Fallot. Severe combined Attention-Deficit/Hyperactivity Disorder symptoms were mainly seen in children with Transposition of Great Arteries and Tetralogy of Fallot. Consequently, clinical range of Attention-Deficit/Hyperactivity Disorder symptoms occurred almost three times more frequently in children with Tetralogy of Fallot compared to controls (p=0.007). The occurrence of high scoring individuals was not statistically significantly different between the remaining two CHD groups and controls.

When comparing ratings by parents who returned only their own rating (n=36) with parents who returned both their own and teacher’s rating (n=120), the first group reported significantly worse mean inattention symptoms T-score (p=0.043). No significant inter-group differences were found in hyperactivity/impulsivity symptoms severity (Table 5).

Quality of life and Attention-Deficit/Hyperactivity Disorder

To explore if clinical range of Attention-Deficit/Hyperactivity Disorder scores were associated with lower quality of life, we analyzed previously published quality of life data (33) for associations with the Attention-Deficit/Hyperactivity Disorder scores. Among children with Tetralogy of Fallot, a high Attention-Deficit/Hyperactivity Disorder symptom score (T-score >70) was significantly associated with lower scores in quality of life within each sub-score (physical, emotional, social, school and total) within the group of Tetralogy of Fallot children (p<0.029) (Supplementary Material). Similar correlations were seen in the Transposition of Great Arteries group (p<0.008), whereas in children with Ventricular Septal Defect less clear associations were present (Supplementary Material).
Discussion

Children with surgically corrected CHD had significantly increased inattention- and total Attention-Deficit/Hyperactivity Disorder symptom scores compared to controls. Children with Tetralogy of Fallot had significantly increased total Attention-Deficit/Hyperactivity Disorder symptom scores- as well as worse inattention symptoms compared to the control group and children with Ventricular Septal Defects. Our findings confirm previous observations, showing a higher occurrence of predominantly the psychometrically defined Attention-Deficit/Hyperactivity Disorder inattentive presentation in children with complex CHD (1, 5) (4). However, we did not observe significantly worse hyperactivity/impulsivity symptoms among children with CHD compared to controls, which previously has been reported in children with various complex CHDs (4, 5). These diverging observations may relate to that fact the children with single ventricular physiology (5) were not included in the present study and since we included older children between 10 to 16 years, while previous studies focused on children in the age span between 5-10 years (4) and 7-15 years (5), respectively. Finally, it is important to emphasize that the severity of hyperactivity/impulsivity symptoms in general decreases with age (9).

There is accumulating evidence that the behavioral changes observed in children with CHD are related to hypoxic-ischemic white matter injury seen on brain magnetic resonance imaging (20). In children with Transposition of Great Arteries, the risk of developing white matter injury has been shown to increase with time between birth and surgery (21). The underlying pathophysiology is likely related to the fact that cerebral oxygen extraction increases during the preoperative period in neonates with Transposition of Great Arteries, but without a concomitant increase in the oxygen delivery (20). Whether this is the same in children with Tetralogy of Fallot has to be explored, but overall it is well known that children with cyanotic CHD have an increased risk of impaired neurodevelopmental outcome through school age and into adolescence (1, 4, 22). Of importance, it has been described that preoperative hypoxemia in infancy due to cyanotic CHD is likely to be associated with impaired attention functioning compared to acyanotic CHD- and healthy children (5). Hypoxemia can cause injury to the prefrontal cortex and corpus striatum of the brain (23). These regions are highly oxygen sensitive and have been associated with impaired executive control network of attention (19). Both children with Tetralogy of Fallot -and Transposition of Great Arteries have prenatally been exposed to lower cerebral oxygen levels compared to healthy fetuses. A study on brain magnetic resonance imaging has shown a lower cerebral tissue oxygenation in fetuses with complex CHD (including Transposition of Great Arteries and Tetralogy of Fallot) compared healthy fetuses (24).

Children with Tetralogy of Fallot have postnatally a varying intensity of cyanosis based on the degree of blood flow obstruction to the lungs (25). Children with Ventricular Septal Defects, Transposition of Great...
Arteries and Tetralogy of Fallot all carry a risk of perioperative brain injury due to circulatory instability and the associated occurrence of acidosis, hypoxemia and hypoxic-ischemic injury, but perioperative events have not shown any strong association with neurodevelopmental outcome, indicating that the prenatal- and preoperative periods are stronger determinants for neurodevelopmental outcome (21, 25).

We found that parents to the Tetralogy of Fallot children reported significantly more inattention symptoms compared to parents of Ventricular Septal Defect children. In line with our findings, it has been shown that Tetralogy of Fallot children with preoperative cyanosis had increased risk for attention dysfunction in the field of executive control compared to acyanotic children with Ventricular Septal Defect (23). However, we did not observe any statistically significant difference in parent rated Attention-Deficit/Hyperactivity Disorder symptoms severity between the other cyanotic CHD (Transposition of Great Arteries) in the present study and the controls. Nevertheless, the Transposition of Great Arteries children presented a markedly higher inattention symptom load and almost twice as many Transposition of Great Arteries children (15%) were in the clinical range of Attention-Deficit/Hyperactivity Disorder symptoms compared to the controls, although the difference was not statistically significant. In accordance, DeMaso et al found by clinical evaluation a similar proportion (16%) of children with surgically repaired Transposition of Great Arteries fulfilled the diagnostic criteria for Attention-Deficit/Hyperactivity Disorder (6).

It has been shown that the children with a prenatal diagnosis of Transposition of Great Arteries have less preoperative brain injury and more robust microstructural brain development than children with a postnatal diagnosis (26). Children with Transposition of the Great Arteries who undergo CHD surgery later than two weeks after birth have been shown to be associated with impaired brain growth and delayed development of language skills compared to children who undergo surgery during the first two weeks of life. The mechanisms are uncertain, but the prolonged period of cyanosis combined with pulmonary overcirculation may contribute to the impaired growth of the brain and thereby delayed neurodevelopment (27). The prenatal screening program was introduced in 2004 in Denmark with more than 95% of women scanned in their pregnancy, increasing the number prenatal diagnosis of CHD from 4.5% in 1996 to 71% in 2013 (28). This may have led to an optimized management with planned delivery at a specialized cardiac center, enabling prompt administration of prostaglandin and balloon atrial septostomy (if required) for the Transposition of the Great Arteries, thereby minimizing the risk of preoperative circulatory collapse and risk of cerebral damage. Our study cohort was born between 2001-2007, indicating that the majority has been diagnosed prenatally (28), which may have contributed to the less prominent Attention-Deficit/Hyperactivity Disorder symptoms in these children.
It is well known that Attention-Deficit/Hyperactivity Disorder carries a high rate of psychiatric comorbidities like Oppositional Defiant Disorder (29), delinquency and poor educational achievement (1, 30). It has previously been described that up to 39% of Tetralogy of Fallot children with 22q11 deletion syndrome have Attention-Deficit/Hyperactivity Disorder and an increased prevalence of other psychiatric disorders (10). We did not identify any significant differences in Oppositional Defiant Disorder symptoms between the CHD children and the controls. In particular, we did not observe an increased occurrence of Oppositional Defiant Disorder in the Tetralogy of Fallot group, which may be related to the fact that children with a 22q11 deletion syndrome were excluded from the present study. The different pattern of comorbidity in children with CHD and Attention-Deficit/Hyperactivity Disorder symptoms could implicate that the pathogenesis of their Attention-Deficit/Hyperactivity Disorder is different from children with idiopathic Attention-Deficit/Hyperactivity Disorder (10, 31).

The marked discrepancy between parents and teachers’ rating was seen both in children with CHD and among controls, although the difference was less obvious in controls due to the overall lower Attention-Deficit/Hyperactivity Disorder symptoms scores. It is evident that levels of Attention-Deficit/Hyperactivity Disorder symptoms perceived by parents are above the levels by teachers as previously reported in both children with idiopathic Attention-Deficit/Hyperactivity Disorder (32, 33) and in CHD children with Attention-Deficit/Hyperactivity Disorder (4, 5, 22, 34).

The inattention symptoms are among others increased distractibility, forgetfulness, and reduced sustained attention (29, 35). Since children with CHD predominantly had the DSM-5 Attention-Deficit/Hyperactivity Disorder inattentive presentation in the present study, it could indicate that the symptoms may easily have been ignored or misinterpreted in a teaching setting. In contrast, children with hyperactivity/impulsivity symptoms, who display more negative behavior in a teaching setting are easier to discover (35). Teachers may have had a higher threshold for deviant attention functioning than the parents, or the inattention symptoms may have been less noticeable in a class room setting to teachers as suggested by another group (5). Parents, who only returned their own ratings, scored their children’s Attention-Deficit/Hyperactivity Disorder inattentive symptoms higher than parents who returned both their own and the teacher's rating, which could either indicate that the parents deliberately avoided to involve the teacher or that the teacher of the child with more severe Attention-Deficit/Hyperactivity Disorder symptoms did not respond.

Unfortunately, we cannot discriminate between the two causes.

Attention-Deficit/Hyperactivity Disorder can impair accomplishment in school, education, or work functioning and disturb the quality of life (36). We have recently investigated the quality of life in children with CHD and found that all three subgroups of CHD had decreased quality of life scores compared to
healthy controls (37). A clear association between clinical range of Attention-Deficit/Hyperactivity Disorder symptoms load and lower quality of life scores were seen in all sub-scores in the Tetralogy of Fallot group, and to some degree a similar association was seen in the Transposition of Great Arteries group. These findings are in line with other studies (38, 39) and highlight the importance of early identification and treatment of Attention-Deficit/Hyperactivity Disorder in CHD, in order to improve quality of life for these children and their families (40).

The Attention-Deficit/Hyperactivity Disorder-Rating Scale measures Attention-Deficit/Hyperactivity Disorder in children from 6 to 16 years and is feasible to be used in a clinical setting as a screening tool (41); for example in a CHD population (4, 6, 10, 42). Since symptoms of Attention-Deficit/Hyperactivity Disorder often become clinically evident at 5 to 6 years, it could be recommendable to screen at this time-point also in the CHD population to have the possibility to intervene both in the family and in school setting at this early stage. If the child comes up with a score in the clinical range (a T-score >70), it is recommended to refer for a clinical assessment by a school psychologist or in the Child and Adolescent psychiatric services. Attention-Deficit/Hyperactivity Disorder-Rating Scale has a high correct classification proportion in distinguishing Attention-Deficit/Hyperactivity Disorder cases from non-cases as shown in resent Japanese studies (43, 44). If a child scores in the sub-threshold range (T-score 60 to 70), one would recommend screening the child again one year later or observe the child for Attention-Deficit/Hyperactivity Disorder symptoms.

**Limitations**

Attention-Deficit/Hyperactivity Disorder is a clinical DSM-5 diagnosis, requiring thorough clinical assessment. Therefore, evaluation based solely on questionnaire data (i.e. a purely psychometric definition of Attention-Deficit/Hyperactivity Disorder) must be cautiously interpreted.

Combined parent and teacher’s scores on Attention-Deficit/Hyperactivity Disorder rating scales gave a lower number of CHD children with clinical range Attention-Deficit/Hyperactivity Disorder scores than solely based on parents’ rating. We cannot exclude selection bias in the present study. Parents who had a suspicion of Attention-Deficit/Hyperactivity Disorder potentially were more compelled to complete the questionnaire or it may have been the other way around. The response rate was 56%, which preferentially should have been higher. Fewer school teachers than parents participated, which may be a consequence of the study design, since the teacher questionnaires were sent to families with a child having undergone CHD surgery and not directly to the school. Since we were unable to retrieve further response, despite several mails, we cannot rule out that the non-responders may have been a potential source of bias as well. It
would have been preferable to investigate if the CHD responders were representative in terms of perioperative courses, but unfortunately, the Danish Patient’s Act does not permit us to track information from the medical records without informed consent from the parents, which still only would be available from the parents returning the questionnaires.

Conclusion

In conclusion, children with surgically corrected CHD had significantly increased Attention-Deficit/Hyperactivity Disorder scores compared to controls; the difference in inattention symptoms was mainly driven by the Tetralogy of Fallot group.

In children with CHD presenting cognitive and/or self-regulatory concerns, a neurocognitive- and psychiatric assessment is recommended to assess the neurocognitive- and psychiatric signature of an individual child. It is important to screen children with CHD since inattention symptoms are more likely to be misinterpreted and overlooked.

The intervention possibilities are many depending on age and health, ranging from academic or school interventions, parent/family skills training, psycho-education and medication (1). The value of early intervention in this vulnerable group remains to be evaluated in future clinical studies (1).

Acknowledgments

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Conflicts of Interest: None

Ethical Standards

The authors assert that all procedures contributing to this work comply with ethical standards of the relevant Danish national guidelines on human questionnaires and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by institutional committees at Copenhagen University Hospital Rigshospitalet, Denmark.
References


19. www.r-project.org


ADHD-RS

Assessed for eligibility (n=419)

Excluded (n=136)
- Not meeting inclusion criteria (n=45)
- Lost to follow up (n=42)
- Syndromes (n=27)
- Dead (n=9)
- No consent (n=13)

Eligible (n=283)

No response (n=124)
- VSD n= 58
- TGA n= 28
- TOF n= 38

Responders (n=159)

Parents rating (n=156)
Did not return form (n=3)

Both parents and school rating (n=120)

School rating (n=123)
Did not return form (n=36)

Enrolment
August 2017 –
December 2018
# Table 1. The participant’s characteristics. All data are shown as mean ± SD. NA: Not Available.

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<th>Patient population</th>
<th>VSD n=61</th>
<th>TGA n=46</th>
<th>TOF n=52</th>
<th>CHD n=159</th>
<th>Control n=317</th>
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<tbody>
<tr>
<td>Male sex, n (%)</td>
<td>29 (47.5%)</td>
<td>26 (56.5%)</td>
<td>33 (63.5%)</td>
<td>88 (55.3%)</td>
<td>174 (54.9%)</td>
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<tr>
<td>Age (years)</td>
<td>12.9 ± 1.6</td>
<td>12.9 ± 2.0</td>
<td>13.3 ± 1.7</td>
<td>13.0 ± 1.8</td>
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<td>Birth weight (kg)</td>
<td>3.2 ± 0.7</td>
<td>3.4 ± 0.6</td>
<td>2.9 ± 0.8</td>
<td>3.2 ± 0.7</td>
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<tr>
<td>Gestation (weeks)</td>
<td>39.3 ± 2.6</td>
<td>39.8 ± 1.6</td>
<td>38.1 ± 3.0</td>
<td>39.1 ± 2.6</td>
<td>NA</td>
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</table>

# Table 2. Parent- (upper) and teacher rating (lower) of two ADHD symptom dimensions in the CHD children and the controls. All data are shown as mean ± SD. * Total score is the sum score of inattention and hyperactivity/impulsivity sub-scores. RS: Rating Scale.

<table>
<thead>
<tr>
<th>ADHD symptoms – parent’s report</th>
<th>VSD n=58</th>
<th>TGA n=46</th>
<th>TOF n=52</th>
<th>Control n=311</th>
<th>ANOVA p-value</th>
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<tr>
<td>Inattention</td>
<td>4.8 ± 4.6</td>
<td>5.6 ± 5.1</td>
<td>8.0 ± 7.5</td>
<td>4.1 ± 4.1</td>
<td>0.009</td>
</tr>
<tr>
<td>Hyperactivity/Impulsivity</td>
<td>3.3 ± 4.1</td>
<td>3.8 ± 4.5</td>
<td>4.1 ± 5.9</td>
<td>3.2 ± 3.7</td>
<td>0.863</td>
</tr>
<tr>
<td>Total score*</td>
<td>8.0 ± 7.9</td>
<td>9.4 ± 9.1</td>
<td>12.1 ± 12.0</td>
<td>7.3 ± 6.8</td>
<td>0.008</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ADHD symptoms – teacher’s report</th>
<th>VSD n=50</th>
<th>TGA n=34</th>
<th>TOF n=39</th>
<th>Control n=317</th>
<th>ANOVA p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inattention</td>
<td>4.5 ± 5.3</td>
<td>3.6 ± 4.1</td>
<td>6.4 ± 7.0</td>
<td>4.5 ± 5.7</td>
<td>0.394</td>
</tr>
<tr>
<td>Hyperactivity/Impulsivity</td>
<td>2.8 ± 4.3</td>
<td>2.1 ± 3.2</td>
<td>3.4 ± 5.5</td>
<td>2.2 ± 3.9</td>
<td>0.103</td>
</tr>
<tr>
<td>Total score*</td>
<td>7.4 ± 8.6</td>
<td>5.6 ± 6.6</td>
<td>9.7 ± 11.6</td>
<td>6.6 ± 8.5</td>
<td>0.346</td>
</tr>
</tbody>
</table>
Table 3. The behavioral scores from parents (upper) and teacher (lower) of the Ventricular Septal Defect-, Transposition of Great Arteries -, Tetralogy of Fallot - and control group. Data are shown as means ± SD.

<table>
<thead>
<tr>
<th></th>
<th>VSD</th>
<th>TGA</th>
<th>TOF</th>
<th>Control</th>
<th>Overall p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ODD Behaviour</td>
<td>3.4 ± 4.3</td>
<td>3.4 ± 4.1</td>
<td>2.8 ± 3.8</td>
<td>2.5 ± 3.2</td>
<td>0.841</td>
</tr>
<tr>
<td><strong>Teacher</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ODD Behaviour</td>
<td>1.7 ± 3.1</td>
<td>1.4 ± 2.2</td>
<td>1.2 ± 2.7</td>
<td>1.3 ± 2.8</td>
<td>0.543</td>
</tr>
</tbody>
</table>

Table 4. Number (rates) of children rated in the clinical range (T-score >70 points) of Attention-Deficit/Hyperactivity Disorder presentation (parent rating). The children with combined Attention-Deficit/Hyperactivity Disorder presentation are not included in the inattentive- or hyperactive/impulsive presentation.
Figure 2. Parent rated Attention-Deficit/Hyperactivity Disorder T-scores >70 points (clinical range of Attention-Deficit/Hyperactivity Disorder) of the three different CHD subgroups and the controls.
<table>
<thead>
<tr>
<th>ADHD symptoms</th>
<th>Parents’ ratings only n= 36§</th>
<th>Parents’ and school ratings n= 120</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inattention</td>
<td>59.1 ± 17.4</td>
<td>52.9 ± 13.4</td>
<td>0.043</td>
</tr>
<tr>
<td>Hyperactive/Impulsive</td>
<td>55.3 ± 18.6</td>
<td>49.9 ± 11.7</td>
<td>0.151</td>
</tr>
<tr>
<td>Total</td>
<td>58.2 ± 18.8</td>
<td>51.6 ± 12.6</td>
<td>0.063</td>
</tr>
</tbody>
</table>

Table 5. Parent’s rating of Attention-Deficit/Hyperactivity Disorder symptoms shown in T-scores. T-scores are calculated from a normative Danish sample stratified on age and gender. § 10 parents of the CHD children in high risk of Attention-Deficit/Hyperactivity Disorder symptoms did not return the teacher’s rating.
### High risk of ADHD

<table>
<thead>
<tr>
<th>School rating</th>
<th>VSD n= 50</th>
<th>TGA n= 34</th>
<th>TOF n= 39</th>
<th>Total CHD n= 123</th>
<th>Control n= 317</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inattentive presentation</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>2 (5.1%)</td>
<td>2 (1.6%)</td>
<td>14 (4.4%)</td>
</tr>
<tr>
<td>Hyperactive /Impulsive</td>
<td>3 (6.0%)</td>
<td>0 (0.0%)</td>
<td>2 (5.1%)</td>
<td>5 (4.1%)</td>
<td>6 (1.9%)</td>
</tr>
<tr>
<td>presentation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined presentation</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>2 (5.1%)</td>
<td>2 (1.6%)</td>
<td>4 (1.3%)</td>
</tr>
</tbody>
</table>

**SI.1.** School rating of high-risk (T-score >70 points) Attention-Deficit/ Hyperactivity Disorder symptoms. SD is calculated from a normative Danish sample stratified on age and gender. § 10 patients of high risk Attention-Deficit/ Hyperactivity Disorder on parents rating did not return school rating.

<table>
<thead>
<tr>
<th>Parents- and school rating</th>
<th>VSD n= 47</th>
<th>TGA n= 34</th>
<th>TOF n= 39</th>
<th>Total CHD n= 120</th>
<th>Control n= 311</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inattentive presentation</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>2 (5.1%)</td>
<td>2 (1.7%)</td>
<td>4 (1.3%)</td>
</tr>
<tr>
<td>Hyperactive/ Impulsive</td>
<td>1 (2.1%)</td>
<td>0 (0.0%)</td>
<td>1 (2.6%)</td>
<td>2 (1.7%)</td>
<td>2 (0.6%)</td>
</tr>
<tr>
<td>presentation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined presentation</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1 (2.6%)</td>
<td>1 (0.8%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

**SI.2.** Combined parents- and school rating of high risk (T-score >70 points) Attention-Deficit/ Hyperactivity Disorder symptoms. SD is calculated from a normative Danish sample stratified on age and gender.
### Quality of life in TOF patients

<table>
<thead>
<tr>
<th></th>
<th>Clinical range of ADHD</th>
<th>Low to moderate ADHD score</th>
<th>p-value</th>
<th>Estimated difference in median between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physical score</strong></td>
<td>62.5 (43.8 – 81.3)</td>
<td>93.8 (86.7 – 97.7)</td>
<td>&lt;0.001</td>
<td>21.9</td>
</tr>
<tr>
<td><strong>Emotional score</strong></td>
<td>50.0 (45.0 – 90.0)</td>
<td>82.5 (65.0 – 95.0)</td>
<td>0.028</td>
<td>15.0</td>
</tr>
<tr>
<td><strong>Social score</strong></td>
<td>60.0 (52.5 – 77.5)</td>
<td>97.5 (83.8 – 100.0)</td>
<td>&lt;0.001</td>
<td>25.0</td>
</tr>
<tr>
<td><strong>School score</strong></td>
<td>25.0 (17.5 – 52.5)</td>
<td>70.0 (53.8 – 86.3)</td>
<td>&lt;0.001</td>
<td>35.0</td>
</tr>
<tr>
<td><strong>Total score</strong></td>
<td>50.0 (40.7 – 67.5)</td>
<td>84.9 (74.8 – 91.4)</td>
<td>&lt;0.001</td>
<td>29.3</td>
</tr>
</tbody>
</table>

Risk of ADHD:  Low = T-score 40-60  Moderate = T-score 61-70  High = T-score > 70

### Quality of life in TGA patients

<table>
<thead>
<tr>
<th></th>
<th>Clinical range of ADHD</th>
<th>Low to moderate ADHD score</th>
<th>p-value</th>
<th>Estimated difference in median between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physical score</strong></td>
<td>79.7 (71.2 – 81.3)</td>
<td>93.8 (84.4 – 100.0)</td>
<td>0.007</td>
<td>15.6</td>
</tr>
<tr>
<td><strong>Emotional score</strong></td>
<td>55.0 (38.8 – 60.0)</td>
<td>85.0 (70.0 – 90.0)</td>
<td>0.006</td>
<td>30.0</td>
</tr>
<tr>
<td><strong>Social score</strong></td>
<td>92.5 (82.5 – 95.0)</td>
<td>95.0 (90.0 – 100.0)</td>
<td>0.213</td>
<td>5.0</td>
</tr>
<tr>
<td><strong>School score</strong></td>
<td>50.0 (36.3 – 60.0)</td>
<td>75.0 (65.0 – 80.0)</td>
<td>0.008</td>
<td>20.0</td>
</tr>
<tr>
<td><strong>Total score</strong></td>
<td>70.6 (61.8 – 71.4)</td>
<td>85.9 (76.1 – 92.5)</td>
<td>0.006</td>
<td>17.2</td>
</tr>
</tbody>
</table>

Risk of ADHD:  Low = T-score 40-60  Moderate = T-score 61-70  High = T-score > 70
<table>
<thead>
<tr>
<th>Quality of life in CHD patients</th>
<th>Clinical range of ADHD n = 25</th>
<th>Low to moderate ADHD score n = 131</th>
<th>p-value</th>
<th>Estimated difference in median between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical score</td>
<td>79.7 (63.3 – 84.4)</td>
<td>93.8 (84.4 – 100.0)</td>
<td>&lt;0.001</td>
<td>15.6</td>
</tr>
<tr>
<td>Emotional score</td>
<td>60.0 (50.0 – 82.5)</td>
<td>85.0 (70.0 – 95.0)</td>
<td>&lt;0.001</td>
<td>20.0</td>
</tr>
<tr>
<td>Social score</td>
<td>80.0 (62.5 – 90.0)</td>
<td>100.0 (88.8 – 100.0)</td>
<td>&lt;0.001</td>
<td>15.0</td>
</tr>
<tr>
<td>School score</td>
<td>42.5 (26.3 – 60.0)</td>
<td>70.0 (60.0 – 85.0)</td>
<td>&lt;0.001</td>
<td>25.0</td>
</tr>
<tr>
<td>Total score</td>
<td>69.0 (50.8 – 74.0)</td>
<td>85.8 (77.3 – 91.4)</td>
<td>&lt;0.001</td>
<td>19.3</td>
</tr>
</tbody>
</table>

Risk of ADHD: Low = T-score 40-60   Moderate = T-score 61-70   High risk = T-score > 70

<table>
<thead>
<tr>
<th>Quality of life in VSD patients</th>
<th>Clinical range of ADHD n = 6</th>
<th>Low to moderate ADHD score n = 52</th>
<th>p-value</th>
<th>Estimated difference in median between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical score</td>
<td>87.5 (84.4 – 96.9)</td>
<td>96.7 (86.7 – 100.0)</td>
<td>0.383</td>
<td>3.1</td>
</tr>
<tr>
<td>Emotional score</td>
<td>75.0 (70.0 – 75.0)</td>
<td>85.0 (75.0 – 95.0)</td>
<td>0.088</td>
<td>15.0</td>
</tr>
<tr>
<td>Social score</td>
<td>80.0 (75.0 – 80.0)</td>
<td>100.0 (90.0 – 100.0)</td>
<td>0.032</td>
<td>20.0</td>
</tr>
<tr>
<td>School score</td>
<td>55.0 (45.0 – 75.0)</td>
<td>70.0 (60.0 – 85.0)</td>
<td>0.166</td>
<td>15.0</td>
</tr>
<tr>
<td>Total score</td>
<td>74.8 (70.0 – 80.6)</td>
<td>87.5 (81.0 – 91.3)</td>
<td>0.022</td>
<td>10.7</td>
</tr>
</tbody>
</table>

Risk of ADHD: Low = T-score 40-60   Moderate = T-score 61-70   High = T-score > 70
SI.3. Clinical range of Attention-Deficit/ Hyperactivity Disorder compared to low to moderate Attention-Deficit Hyperactivity Disorder score in relation to QoL scores in Tetralogy of Fallot, Transposition of Great Arteries, Ventricular Septal Defect and the CHD group.