Original Article
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Medical Journal of the Islamic Republic of Iran (MJIRI)
Iran University of Medical Sciences

Attention deficit hyperactivity disorder in children with early stages of chronic kidney disease

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Received: 2 January 2014 Accepted: 9 April 2014 Published: 17 February 2015

Abstract

Background: Attention Deficit Hyperactivity Disorder (ADHD) is the most common childhood neurological disorder. This disorder is more prevalent in some chronic diseases. The aim of this study was to investigate ADHD in children with early stages of chronic kidney disease (CKD) and to compare it with healthy children.

Methods: Seventy five 5-16-year-old children with early stages of CKD (stage 1, 2 and 3) and 75 healthy children without CKD were included in this case – control study as case and control groups, respectively. The participants were selected from those children who were referred to the pediatric clinic of Amir Kabir Hospital of Arak (Iran) in the form of simple probability and based on inclusion and exclusion criteria. ADHD was diagnosed using Conner's Parent Rating Scale – 48 (CPRS-48) and DSM-IV criteria and was confirmed by a psychologist consultant. Data were analyzed by Binomial test in SPSS18.

Results: ADHD inattentive type was observed in 8 cases (10.6%) with CKD and 2 controls (2.6%) (p= 0.109). Moreover, in the case and control groups, 7 (9.3%) and 6 (8%) children were affected by ADHD hyperactive-impulsive type (p= 0.997), and 9 (12%) and 12 (16%) children were affected by ADHD mixed type (p= 0.664), respectively.

Conclusion: No differences were found between the prevalence of ADHD in the children with early stages of CKD and the control group. However, due to the importance of the relationships between different types of psychiatric disorders and CKD and lack of enough evidence concerning the relationship between ADHD and different stages of CKD in children, conducting further studies in this field is recommended.

Keywords: Attention Deficit Hyperactivity Disorder, Children, Chronic Kidney Disease.

Cite this article as: Yousefi Chaijan P, Sharafkhah M, Salehi B, Rafiei M. Attention deficit hyperactivity disorder in children with early stages of chronic kidney disease. *Med J Islam Repub Iran* 2015 (17 February). Vol. 29:181.

Introduction

Chronic kidney disease (CKD) is defined as a slow and steady damage of kidney function in an irreversible manner, which is ended in end-stage renal disease (ESRD) (1, 2). This chronic disorder is one of the serious health problems with a high prevalence in adults and children. It causes mortality, complications and high costs due to poor prognosis and high medical diagnosis of patients (1, 2). The causes of CKD are very different in children than in adults. In a recent North American Pediatric Renal Transplant Cooperative Study (NAPRTCS), congenital causes including congenital anomalies of the kidney and urinary tract (CAKUT) (48%) and hereditary nephropathies (10%) were the most common causes of CKD in children (3). Based on the previous studies, such a chronic disorder impairs quality of life of children due to developing various clinical symptoms, especially developmental disorders and psychiatric disorders (4-6). CKD clinical manifestations in children are manifested as edema, hypertension, hematuria and pro-

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teinuria and during the neonatal period as weight gain disorder, polyuric dehydration and urinary tract infection (7). In addition to the mentioned symptoms, this chronic disorder may lead to a type of hyperactivity and CNS dysfunction (especially sympathetic function) (8).

Based on the literature, the prevalence of cognitive disorders, such as memory disorder, and different psychiatric disorders such as different kinds of anxiety disorders (ADs), depression and adjustment disorders in children with different levels of CKD was significantly higher compared to the group of healthy children and children with early stages of CKD (9-12). Based on the available literature, patients with CKD who develop psychiatric and cognitive disorders, experience longer hospitalization and more complications and mortality compared to other patients at the same stage without these disorders (11, 12). Therefore, better and further diagnosis of psychiatric disorders in these patients is of paramount importance. One of the disorders whose relationship with CKD in children has not been considered yet is attention deficit hyperactivity disorder (ADHD). ADHD is the most common neurobehavioral disorder of the childhood period. As per DSM-IV (statistical manual of mental disorders, fourth edition) criteria, it includes ADHD inattentive type, ADHD hyperactive-impulsive type and ADHD mixed type (13). ADHD affects 5-10% of school- aged children (14). The causes of ADHD in children are not clearly known; however, some evidence recognizes underlying genetic defect and CNS dysfunction as its main causes (15). ADHD can be significantly associated with a variety of childhood chronic diseases (16-18), depression (18), behavioral, emotional, language and hearing disorders (19,20) and even such illnesses as epilepsy (16,17) and abnormal EEG in children (21). Similar to CKD, ADHD can be affected by such associated disorders in terms of response to treatment and clinical course of disease. (22-24) With respect to the prevalence of CKD and ADHD in children and the importance of the relationship between CKD and psychiatric disorders (12-9) and the relationship between ADHD and chronic diseases in childhood (22-24), the hypothesis concerning the relationship between ADHD and CKD in children was discussed. As no study has been conducted on the relationship between ADHD and CKD in children, the aim of this study was to investigate ADHD in children with early stages of CKD and compare it with healthy children.

Methods

This case-control study was performed on 150 male and female children in the age bracket of 5-16 years old who were referred to the pediatric clinic of Amir Kabir Hospital in Arak (Iran) in 2013. Of the 150 children, 75 children with early stages of CKD as the case group and 75 healthy children without CKD as the control group were included in the study based on the inclusion criteria. The sample number was calculated with regards to the prevalence of cognitive disorders due to CKD (α= 0.05%, β= 0.2%).

CKD was defined as a presence of kidney damage (for example, any structural or functional abnormality involving pathological, laboratory or imaging findings) for ≥3 months or a glomerular filtration rate (GFR) < 60 ml/min/1.73 m2 for ≥3 months (2). In this study, as per CKD definition (2), children with early stages of CKD (Stage 1, 2 and 3 CKD) who were with CKD due to renal and urinary - genital tract anomalies such as obstructive uropathy, renal dysplasia, reflux nephropathy, etc. were included in the case group. Those children who had CKD due to the reasons other than renal and urinary - genital tract anomalies and those children with stages 4 and 5 CKD were excluded from the study. Stage 1, 2, 3 and 4 CKD were defined as kidney damage with normal or increased GFR (GFR ≥90 cc/min/1.73m2), kidney damage with mild decreased GFR (GFR=60-89 cc/min/1.73m2), kidney damage with moderately decreased GFR

(GFR=30-59 cc/min/1.73m2) and kidney damage with severely decreased GFR (GFR=15-29 cc/min/1.73m2), respectively (25). ESRD or stage 5 CKD was defined as the amounts of GFR<15cc/min/1.73m^2 which are an indicative of the start of dialysis (25-27).

Clinical interviews were carried out with children and their parents to study the inclusion/exclusion criteria. This was done to study the confounding factors that, based on the previous studies, could contribute to ADHD in children (13, 28, 29), and they are as follows:

1. History of major depressive disorder (MDD), ADs, schizophrenia, autistic disorders (ASD), Tourette's disorder, bipolar disorder (BD), ADHD (in the case group, before developing CKD) and other considerable psychiatric disorders
2. Congenital and chromosomal abnormalities such as Down syndrome and Fetal alcohol syndrome, birth weight less than 1,500 gr or very low birth weight (VLBW), major and chronic maternal diseases in pregnancy, the use of teratogenic drugs, alcohol, substance and smoking by the mother during pregnancy (particularly in the first 3 months)
3. Substance abuse, mental retardation (MR)
4. Epilepsy, asthma, diabetes, immune deficiency, organ transplantation, a history of moderate to severe head trauma and other considerable or chronic medical disorders
5. History of chronic medication use in children
6. Family history (first-degree relatives (parents and siblings)) of major psychiatric diseases such as AD, schizophrenia, depression, ADHD, etc.
7. Low socioeconomic status, parental consanguinity and separation or death and children whose parents were unwilling to participate in the study

Those participants who had any of the above cases were excluded.

Schizophrenia, different types of ADs (post-traumatic stress disorder, panic attacks and etc.) MDD, ASD, Tourette's disorder and BD were defined according to DSM-IV criteria (30-34). MR was defined as the intelligence quotient (IQ) of 70 or less (35); epilepsy was defined as a history of recurrent seizures for which no cause can be identified in clinical studies (17) and chronic drug use was defined as a history of at least one year of continuous use of one or more types of medications. History of moderate to severe head trauma was defined as a trauma that causes Glasgow coma scale (GCS) <12 and symptoms such as dizziness or persistent confusion, behavioral changes, loss of consciousness, neurological symptoms or coma (36). Moreover, the low socioeconomic status was considered as family income less than 5,000,000 Rials (for a family of 3 to 5) and parental education lower than diploma.

Clinical, laboratory and imaging studies were carried out on those children who had CKD at least for 3 months with respect to the clinical histories of their parents and their medical records (if available). The clinical, laboratory and radiologic studies of children with CKD consisted of history and thorough examination, GFR measuring and imaging studies including abdominal and pelvic ultrasonography, voiding cystourethrograms (VCUG) and computed tomography (CT) scan. The etiology and CKD stage were determined based on the diagnostic workup, GFR levels, symptoms of children with CKD such as urinary tract infections (UTIs), proteinuria (30-100 mg), edema, hypertension and etc. According to the CKD definition (2), children with stages 1 to 3 CKD were entered into the study as the case group. Control group members were selected from children who referred to the hospital for common cold, abdominal pain and etc. as outpatients. The matching method was used to select the control group, and children were matched into two groups with respect to age, gender, developmental level, economic status, number of family members, place of residence (in terms of floor and area) with a standard deviation of ±2. After the primary evaluation

considering the exclusion/inclusion criteria and obtaining informed consent from children's parents for participating in the study, basic information (age, sex) was recorded.

ADHD was defined according to DSM-IV criteria as the presence of disease symptoms for at least 6 months continuously and in two separate environments (both at home and at school) without any organic causes (19), and it was diagnosed by Conner's Parent Rating Scale – 48 (CPRS-48).

After CPRS-48 was completed by the parents, and children were identified with different types of ADHD, they were then referred to an expert psychiatrist as the project administrator for the confirmation of ADHD diagnosis using clinical interview and based on DSM-IV diagnostic criteria (13).

Conner's Parent Rating Scale (CPRS) was standardized by Conners et al. in 1999. It has two 93-item and 48-item versions. In this research, the 48-item version has been used. This version of Conners Questionnaire evaluates 5 factors of conduct, psychosomatic - impulsivity, hyperactivity, anxiety and learning problems and has 4 choices scored from 0 (never) to 3 (very high). The score of each article is converted into t scores with the average of 50 and standard deviation of 10. If the t scores of 12 standard deviations are higher than the average, the individual has a problem (37). Abdekhodaie Z et al. reported the sensitivity and specificity of this form of Conner Questionnaire for the diagnosis of children with ADHD to be 90.3% and 81.2%, respectively (38). It should be mentioned that ADHD diagnosis for children with this disorder was confirmed by evaluating its differential diagnoses such as hyperthyroidism (by measuring TSH and FT4) and lead poisoning (Blood Lead Level (BLL)> 5-10 µg/dl) (39).

The collected data were analyzed with SPSS software (Statistical Package for the Social Sciences, version 18.0, SPSS Inc, Chicago, Ill, USA) and descriptive statistics methods for frequency determination. Moreover, Binomial test were used for data analysis. P values less than .05 were considered significant. This study was confirmed by The Ethics Committee of Arak University of Medical Sciences. Furthermore, we were loyal to Helsinki declaration principles in all stages of this study, and we obtained written consent from all the participants and they were free to exit the study by their will.

Results

The mean age of children in the case and control groups was calculated at 7.92±2.56 and 8.25±2.21, respectively (p=0.39). There were 31 (41.3%) boys and 44 (58.6%) girls in the case group and 39 (52%) boys and 36 (48%) girls in the control group (p= 0.19).

Of the 150 (100%) children in both groups, 10 (13.3%), 13 (17.1%) and 21 (27.6%) children were affected by ADHD inattentive type, ADHD hyperactive-impulsive type and ADHD mixed type, respectively.

There were no significant differences between the two groups with respect to the prevalence of ADHD inattentive type (p=0.109), ADHD hyperactive-impulsive type (p= 0.997) and ADHD mixed type (p=0.664) (Table 1).

The results of this study revealed no significant relationship between ADHD inattentive type (p = 0.344), ADHD hyperactive-impulsive type (p= 0.997) and ADHD

Table 1. Frequency of Children with any Form of ADHD in the Case and Control Groups

ADHD Inattentive Type		p	ADHD Hyperactive-Impulsive Type		p	ADHD Mixed Type		p
Case[a] (n=75) N (%)	Control[b] (n=75) N (%)	0.109	Case (n=75) N (%)	Control (n=75) N (%)	0.997	Case (n=75) N (%)	Control (n=75) N (%)	0.664
8(10.6)	2(2.6)		7(9.3)	6(8)		9(12)	12(16)	

[a] Children Group with Early Stages of CKD, [b] Healthy Children Group

Table 2. Gender Distribution of the Children with ADHD Inattentive Type, ADHD Hyperactive-Impulsive Type, and ADHD Mixed Type in both Groups

Gender	ADHD[b] inattentive type (n=10) N (%)	ADHD hyperactive-impulsive type (n=13) N (%)	ADHD mixed type (n=21) N (%)
Male	7 (70)	6 (46.1)	7 (33.3)
Female	3 (30)	7 (53.8)	14 (66.6)
p-value[a]	0.344	0.997	0.189

[a] p-values less than .05 Were Considered Significant, [b] Attention Deficit Hyperactivity Disorder

mixed type (p= 0.189) and the gender distribution of children in the two groups (Table 2).

Discussion

Our study showed no significant relationship between the disorders (ADHD inattentive type, ADHD hyperactive-impulsive type and ADHD mixed type) and early stages of CKD in the affected children; in the study, the prevalence of ADHD in children with CKD did not exceed the control group.

However, no study has been done on the relationship between ADHD and CKD in children, but different studies have been conducted on psychiatric disorders in children with various stage of CKD. Bakr A (9) studied 19 children with CKD who did not need dialysis and 19 other with ESRD for psychiatric disorders in 2007. Based on the evidence, it was indicated that 18.4%, 10.3%, 7.7%, 5.1% and 2.6% of the participants suffered from adjustment disorder, depression, cognitive disorder, anxiety disorders and elimination disorder. The prevalence of the above disorder was calculated at 68.4% and 36.8% in dialysis and non-dialysis groups, respectively. In another study by Fukunishi I et al. (10) on 30 children with ESRD, 30 children who had undergone renal implantation and 33 healthy children, a significant difference was found in the prevalence of adjustment disorder between children in the 3 groups; the prevalence of this disorder was the highest and lowest in the dialysis and control groups, respectively. Also, Slickers J (11) found a significant relationship between a decline in cognitive functions and the severity of CKD in children with different stages of CKD. In the two studies on children with ESRD and healthy children, Fukunishi I (40) and Eisenhauer G (41) indicated that the prevalence of anxiety disorders and depression in children with ESRD undergoing dialysis is significantly higher than healthy children group. According to the results of our study, the hypothesis on the relationship between ADHD and early stages of CKD in children was rejected.

Among the limitations of our study, we may point to the lack of cooperation of some parents to complete the ADHD questionnaire and the psychiatric examination of the participants which was performed by a psychiatrist. Although this criterion resulted in excluding some eligible children, we attempted to remove such limitation by encouraging the parents for possible usefulness of the study and help them fill in the questionnaire.

Finally, according to similar studies, it seems that the prevalence of different kinds of psychiatric disorders such as depression, ADs and adjustment disorder in children with the final stages of CKD or ESRD who need dialysis is considerably higher than children with the preliminary stages of CKD. However, due to the importance of the relationships between different types of psychiatric disorders and CKD (9-12) and lack of enough evidence concerning the relationship between ADHD and different levels of CKD in children, conducting further studies in this field is recommended.

Conclusion

Based on the current study, there were no differences between the prevalence of ADHD in children with early stages of CKD and control group. However, due to

the importance of the relationships between different types of psychiatric disorders and CKD and lack of enough evidence concerning the relationship between ADHD and different stages of CKD in children, conducting further studies in this field is recommended.

Acknowledgments

The research team wishes to thank the vice chancellor of the research for the financial support and they are also grateful to the children and their parents who participated in this research.

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