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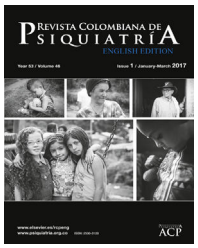

Review Article

Risk of attention deficit/hyperactivity disorder (ADHD) and other psychiatric disorders in siblings of ADHD probands☆

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ABSTRACT

Introduction: Attention deficit and hyperactivity disorder (ADHD) occurs more frequently in first-degree relatives. It is believed that this risk is not specific to this disorder but also occurs with other psychopathologies. The study of siblings of ADHD probands is an interesting field since they share common environmental factors.

Methods: This is a narrative literature review. A bibliographic search was performed on PubMed and PsychNet databases and topic-related publications were included without date of publication or study design limits.

Results: Siblings of patients with ADHD have a higher likelihood of having this disorder when compared to controls, with odds ratios (OR) ranging between 11.4 and 13.5. Among these siblings, ADHD prevalence ranges between 26 and 45.2%. Siblings with ADHD and those without ADHD have an increased risk of having other disorders, the most frequent being oppositional defiant disorder (ODD).

Conclusions: Siblings of people with ADHD have an increased risk of having the same disorder. The risk of having another psychiatric disorder markedly increases when the sibling also presents ADHD; this is especially true for ODD, substance use disorder and bipolar disorder.

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Riesgo de trastorno por déficit de atención e hiperactividad y otros trastornos psiquiátricos de los hermanos de pacientes con TDAH

Palabras clave:
Trastorno por déficit de atención e hiperactividad
Hermanos
Riesgo
Comorbilidad
Familiares de primer grado

RESUMEN

Introducción: El trastorno por déficit de atención con hiperactividad (TDAH) ocurre con mayor frecuencia en familiares de primer grado. Se cree que el riesgo no solo es específico de este trastorno, sino también de otras psicopatologías. Estudiar a los hermanos de pacientes con TDAH es un campo interesante porque comparten factores ambientales comunes.

Métodos: Revisión narrativa de la literatura. Se realizó una búsqueda bibliográfica en las bases de datos PubMed y PsychNet, y se seleccionaron los artículos relacionados con el tema sin límites de fecha de publicación o diseño.

Resultados: Los hermanos de pacientes con TDAH tienen mayor posibilidad de sufrir el mismo trastorno en comparación con controles, con *odds ratio* que varían entre 11,4 y 13,5. En estos hermanos la prevalencia de TDAH oscila entre el 26 y el 45,2%. Los hermanos con TDAH y aquellos sin TDAH están en mayor riesgo de sufrir otros trastornos, de los que el más frecuente es el trastorno de oposición desafiante (TOD).

Conclusiones: Los hermanos de personas con TDAH tienen mayor riesgo de padecer el mismo trastorno. El riesgo de otro trastorno psiquiátrico aumenta marcadamente cuando el hermano también tiene TDAH; esto es aplicable especialmente al TOD, el trastorno por uso de sustancias y el trastorno bipolar.

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Introduction

Attention deficit/hyperactivity disorder (ADHD) is a neurodevelopment disorder; its cardinal symptoms are: inattention, hyperactivity and impulsivity.[1] Some authors propose that the affected domains actually correspond to attention and impulse control, and that hyperactivity is secondary to impulsivity.[2,3] There are three ADHD presentations: inattentive, hyperactive-impulsive and mixed or combined.[1]

ADHD affects 3–12% of children and adolescents, with a global prevalence of 5.3%. Although the disorder is predominant in childhood, it has been found that it can also persist into adulthood (4–5%)[4]; in the USA, 7–10 cases are recorded per 100 children in primary education and it is more common in males than females, with a ratio of 9:1.[5] According to the last national study performed in 2015, the prevalence of ADHD in the Colombian population is 2.3%, with a greater frequency of the hyperactive subtype (1.3%), followed by the inattentive (0.8%) and combined (0.2%) forms.[6] Moreover, it presents high rates of comorbidity with other psychiatric disorders (60%).[5] The risk of an ADHD patient also suffering from bipolar affective disorder (BAD) is increased up to 10-fold, with rates of 57% to 93%[7,8]; comorbidity with oppositional defiant disorder (ODD) and other conduct disorders ranges from 40% to 70%,[9] and with depressive and anxious disorders, from 30% to 40%.[5,7]

Heritability is estimated at 60% to 90% (mean, 75%), making ADHD one of the most hereditary psychiatric disorders.[10] It has been found that, in 50% of children with ADHD, at least one of their parents also had this diagnosis.[2] Moreover, the siblings of children with ADHD have a 3–5 times greater risk of the disorder than siblings of controls; in turn, monozygotic twins have a greater risk (50–80%) than dizygotic twins (33%).[11] First-degree blood relatives also have an increased risk of other behavioural and affective disorders. The objective of this article is to review the literature on the risk of ADHD and other psychiatric disorders in siblings of ADHD probands.

Methods

This is a narrative literature review. A search was performed on the PubMed and PsycNet databases, with no time limit, using the following keywords: “siblings” OR “family members” AND: “attention deficit disorder”, “attention deficit hyperactivity disorder”, “oppositional defiant disorder”, “behaviour disorder”, “anxiety disorder”, “generalised anxiety”, “major depressive disorder”, “bipolar affective disorder”, “obsessive compulsive disorder”, “substance use disorder” and “schizophrenia”. This review included articles related to the topic with no design limit.

Results

Risk of ADHD in the siblings of affected patients

In Iran, a study was performed which determined the risk of ADHD in siblings of patients with this disorder.[12] The authors compared three groups: 200 patients diagnosed with ADHD, all treated with methylphenidate with no dose alteration during the study, 200 of their siblings and 200 controls (aged 8–14 years). Diagnoses were made based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) and they carried

out semi-structured interviews on parents administering the ADHD rating scale-IV and Conners' Parent Rating Scale, a direct assessment of the children and a review of their school reports. Adjustments were made for age, sex and the presence of other psychiatric disorders, and patients with a history of central nervous system diseases and psychiatric disorders such as autism, depression, anxiety and ODD were excluded. Ultimately, they found that the risk of ADHD in siblings of patients with ADHD is greater compared to the controls (odds ratio [OR] = 13.50; 95% confidence interval [95% CI], 3.15–57.94). It was also discovered that children with ADHD whose siblings had the same diagnosis presented higher scores for oppositional behaviour, anxiety, perfectionism and psychosocial and psychosomatic problems than children with ADHD and siblings without, thereby indicating greater severity. However, in the total ADHD rating scale-IV score, there were no significant differences between the index cases and affected siblings as regards impulsivity and hyperactivity.

Yang et al.[13] took 136 children from Taiwan with a diagnosis of ADHD as per the DSM-IV-TR (mean age, 12.8 years), 136 siblings and 136 controls of similar ages. Children with autistic spectrum disorders, psychosis or an intelligence quotient (IQ) < 80 were excluded. The authors assessed all of the subjects using the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children, Epidemiologic Version (K-SADS-E) and classified the siblings as either affected or unaffected by the following disorders: ADHD, conduct disorder (CD), major depressive disorder (MDD), ODD, sleep disorders and substance use disorders (SUD). The percentage of siblings found to have ADHD was 34.6%.

A previous study published by Faraone et al.[14] in 1996 compared 174 siblings of ADHD patients and 129 siblings of controls. All of the subjects were Caucasian and aged 6–17. Adopted children, subjects who presented neurodegenerative diseases, psychosis, autism or an IQ <80 were excluded, as well as those from low socioeconomic classes (to avoid confounding due to psychosocial adversity). After the initial assessment, follow-up at one year was performed (retention: 169 index case siblings and 135 control siblings) as well as at four years (retention: 169 index case siblings and 143 control siblings). They were diagnosed according to the DSM-III-R, administering the K-SADS-E interview to parents and patients (except for children younger than 12 years of age, who were not directly interviewed). The authors found that 26% of the index population's siblings had the same diagnosis at four years, compared to 10% of the control population's siblings ($p = 0.01$).

In concordance with previous studies, in 2014 Lino Palacios et al.[15] published a study performed on the Mexican population in which they assessed 84 biological siblings (aged 13–19 years) of ADHD patients undergoing psychiatric follow-up. Twins, patients diagnosed with a chronic CNS disease and those who had a previous psychiatric diagnosis or who were receiving psychiatric medication or psychotherapy were excluded. A mental health professional (clinical psychologist with a Master's degree or psychiatrist) carried out the assessments and, to diagnose any form of mental disorder, the following criteria were used: DSM-IV and the Brief Psychiatric Rating Scale for Children (BPRS-C), 25-item Mexican version, which includes four more aspects than the original scale: (a) elimination disorders; (b) hyperthymia; (c) use and abuse of alcohol, tobacco and other drugs, and (d) psychological and sexual abuse. Moreover, each case assessed underwent diagnostic confirmation by another certified expert psychiatrist. Variables such as severity of ADHD symptoms, functioning in various areas (school, social and family) and psychosocial adversity were measured. It was found that 45.2% of the siblings also had ADHD, most of which had the combined subtype (68.4%), with the rest having the inattentive subtype. On the other hand, 17.9% of these siblings had no psychiatric disorder. These figures are striking given the study's inclusion criteria: only siblings who had not asked for professional help.

Based on these four studies, we can conclude that, although the risk of ADHD in siblings of patients with this diagnosis is variable, they all agree that these siblings have an increased risk compared to the general population. This confirms the influence of both genetic and environmental or psychosocial variables on ADHD risk.

Risk of other psychiatric disorders in the siblings

The siblings of ADHD patients are not only more at risk of ADHD, but other types of psychiatric disorders too. In the study by Yang et al.[13] it was found that the frequency of any other psychiatric disorder (ODD, tics, anxiety and CD) stood at 82.4% in the index patients; 72.3% in siblings with ADHD; 42.7% in siblings without ADHD; and 33.1% in the control subjects. On comparing index cases to unaffected siblings, the risk of suffering another psychiatric disorder was high (OR = 6.38; 95% CI, 3.43–11.88). This was also the case compared to the control population (OR = 9.60; 95% CI, 5.31–17.34). Moreover, said disorders were more common in siblings with ADHD than siblings without ADHD (OR = 3.58; 95% CI, 1.61–7.98) and control subjects (OR = 5.38; 95% CI, 2.5–11.6). By specific psychiatric disorders, the frequency of ODD was 44.7% among siblings with ADHD, 11.4% among siblings without ADHD and 9.6% in control subjects. The frequency of CD was 21.3% among siblings with ADHD, 2.4% among siblings without ADHD and 2.9% in control subjects. With respect to tics, the frequency was 8.5% among affected siblings and 2.9% in the control population. As regards affective disorders, the subjects with MDD were 10.6% of the siblings with ADHD, 8.2% of the siblings without ADHD and 10.3% of the controls. The frequency of generalised anxiety disorder (GAD) was 4.3% among affected siblings, 1.2% among unaffected siblings and 0.7% in control subjects. Greater rates of alcohol abuse were also found in siblings with ADHD than in the control population (61.7% versus 41.2%), a risk which is comparable to the index cases.

In the publication by Faraone et al.,[14] three groups of subjects were compared: siblings of patients with ADHD with the same disorder, siblings without ADHD and control subjects. A greater prevalence was found in the first group: CD (25% versus 6% versus 4%), ODD (59% versus 19% versus 2%), MDD (36% versus 10% versus 8%), BAD (25% versus 3% versus 4%), anxiety disorders (32% versus 20% versus 10%) and psychoactive substance use (25% versus 17% versus 16%).

Palacios[15] found that only 17.9% had no psychiatric disorder at the time of the study and that over 40% of the ADHD patients' siblings had two other mental disorders besides ADHD. Nevertheless, when adjusted for gender, age

and number of psychosocial adversities, only ODD was statistically significant (OR = 2.98; 95% CI, 1.8–10.9). Moreover, it was also shown that the siblings with a ADHD diagnosis had a greater frequency of learning difficulties (OR = 5.09; 95% CI, 1.28–20.28) even after adjustment for the abovementioned variables. Impaired self-concept and social and family relationships were also observed, but with no statistical significance ($p = 0.288$).

Schuler et al.[16] described the psychopathology of subjects with ADHD and their affected siblings in a genetically isolated population from Costa Rica's Central Valley. They selected a sample of 95 index cases and 62 siblings aged between 6 and 26, whom they divided into two groups: children (6–12 years) and adolescents (13–26 years). The subjects were assessed according to the DSM-IV diagnostic criteria, for both ADHD and any other psychiatric disorder, and it was found that the most associated comorbidities in the index cases were anxiety disorders (55.9%), tics (34%), mood disorders (11.7%) and conduct disorders (30.9%); only 16% did not have psychiatric comorbidities. On assessing the disorders individually, it was found that ODD was the most common (26.6%), followed by a specific phobia and social phobia (each 17.2%), Tourette's syndrome (17%), GAD (14%) and separation anxiety (12.9%). Generally speaking, there were no differences between the age groups, except for disruptive disorders which were more prevalent in children than adolescents, a difference that is largely due to ODD (35% versus 16.2%; $p = 0.03$). On comparing the index cases to their siblings, it was found that they did not differ significantly in terms of comorbidities except for tic disorders, which were more common in the former (31.9% versus 11.5%). Moreover, a greater proportion of siblings were found to have no psychiatric comorbidities (26.3% versus 16%), although the difference was not statistically significant ($p = 0.12$). There was also a significant concordance between anxiety disorders and mood disorders, which indicates heritability in these families; for anxiety disorders this heritability estimate was 0.81 and, for mood disorders, 0.49. Anxiety disorders were also more common if the index case had said comorbidity (OR = 6.39; 95% CI, 1.65–24.7). These data contradict other study series in which comorbid ODD or SUD are more common, thus indicating that certain genetic, environmental and sociocultural factors specific to this sample might have an impact on the subjects' psychopathology.

Milberger et al.[17] searched for a relationship between ADHD and SUD in index case siblings and control population siblings. A sample of white, non-Hispanic males aged 6–17 was selected. A group of 140 index cases and their 174 siblings (referred to as high-risk siblings) were compared to a group of 120 controls and 129 siblings. Adopted children and those with major CNS disorders, psychosis, autism or an IQ < 80 were excluded, as well as children from a low socioeconomic class in order to minimise the potential confounding of social adversity. Diagnoses were made using a semi-structured Kiddie SADS-E interview based on the DSM-III-R criteria, with a psychiatric assessment also performed to establish alcohol and drug abuse or dependence. Parents and children were interviewed separately, except for children younger than 12 years of age, who were not directly interviewed. The high-risk siblings were found to have significantly higher rates of ADHD than the control group siblings (18% versus 5%). Moreover, four groups were compared: (a) high risk + ADHD; (b) high risk without ADHD; (c) control siblings + ADHD; (d) control siblings without ADHD. No significant differences were found in the prevalence of substance use between the high-risk population and control siblings (17% versus 16%). However, marked differences were observed between siblings with ADHD and without ADHD, regardless of the degree of risk (36% versus 15%). The prevalence of SUD in all siblings with ADHD was 41%, compared to 16% among siblings without ADHD, with high scores in all categories of abuse or dependence in the first group. No significant differences were found in the preferred drugs of the high-risk siblings and siblings with ADHD. The drug most frequently used in all groups was marijuana; 92% of the siblings with drug abuse or dependence also had a history of tobacco or alcohol use and, of these, 88% were dependent on cigarettes or alcohol alongside drug abuse or dependence. The age at onset of substance use was also compared, but no significant differences were found between the high-risk siblings and those of the control group. However, siblings with ADHD generally had an earlier onset of all categories of SUD compared with siblings without ADHD. These results were also adjusted for different variables and high-risk status was not found to be a significant predictor of SUD (hazard ratio [HR] = 0.6; $p = 0.1$), whereas having ADHD at baseline (HR = 2.7; $p = 0.01$), CD (HR = 4.7; $p = 0.001$) and anxiety disorders (HR = 2.2; $p = 0.04$) were. In addition, siblings with ADHD and a comorbid CD had significantly higher rates of SUD (89%), with an earlier onset of substance use (13.6 years), compared to ADHD siblings without CD (24%), who had an age at onset of 15.6 years.

Steinhausen et al.[18] published a study with the objective of determining the behavioural profile of children with ADHD and of their siblings with and without the disorder. They used a sample of 172 children aged 8–16 (69 index cases, 32 siblings with ADHD and 35 siblings without ADHD, compared to 36 controls). All of the index cases had ADHD combined type, while the siblings had any subtype, and there were no significant IQ differences between the groups. The Conners' Rating Scale was used for the assessment, as well as the Strengths and Difficulties Questionnaire (parent and teacher version) and the Child Behaviour Checklist; diagnoses were made according to the DSM-IV. The authors found that, with the exception of hyperactivity, which was marked among the index cases, there were no differences between the index subjects and their siblings with ADHD on any scale. Moreover, scores on the Conners' Rating Scale were similar in siblings without ADHD and control subjects across all the domains. However, siblings without ADHD scored significantly higher than the controls on other scales measuring anxiety, shyness, perfectionism and emotional lability. The index subjects and their affected siblings had equal scores for social withdrawal, somatic complaints, affective problems (anxiety and depression), thought problems and delinquent behaviour, but index children scored higher than their affected siblings for inattention and aggression.

Biederman et al.[19] examined the relationship between ADHD and obsessive-compulsive disorder (OCD) by means of a familial aggregation study. The authors used a sample of index subjects (6–17 years): 256 with ADHD but without OCD, 12 with both ADHD and OCD and 235 controls; they also included their

first-degree blood relatives (parents and siblings): 791, 33 and 716, respectively. They found that the risk of ADHD was similarly elevated among relatives of ADHD patients with and without OCD (19.9% and 20.1%) compared to the control group (4.6%), but that the risk of OCD was only significantly elevated in relatives of subjects with ADHD and OCD (13%) versus the controls (0.5%). Moreover, they also discovered that relatives with ADHD had a greater risk of OCD than unaffected relatives (7.4% versus 1.3%), thus indicating co-segregation between these disorders.

Finally, a Swedish study[8] explored the risk of ADHD, BAD and schizophrenia in first- and second-degree blood relatives. A sample of 61,187 patients with ADHD was identified and matched by gender and age with a group of control subjects without ADHD (aged 7–65 years) and their respective first- and second-degree relatives. Diagnoses were made according to the criteria of the eighth, ninth and tenth editions of the International Classification of Diseases (ICD), and patients who already had a history of either of these two disorders were excluded. In the relatives of patients with ADHD, the authors found a stronger history of BAD in 51% of parents (OR = 1.84; 95% CI, 1.72–1.97), 12% of children (OR = 2.54; 95% CI, 1.92–3.35) and 23% of siblings (OR = 2.22; 95% CI, 1.98–2.50), and a stronger history of schizophrenia in 16% of parents (OR = 2.22; 95% CI, 1.99–2.47), 5% of children (OR = 1.89; 95% CI, 1.13–3.15) and 13% of siblings (OR = 1.71; 95% CI, 1.44–2.04). This risk was lower among second-degree blood relatives.

Discussion

This article is a literature review with regard to the risk of psychopathology in siblings of ADHD probands. There are only four studies that address the specific topic of ADHD risk and eight on the presence of other psychopathologies.

Generally speaking, the studies show that these siblings have a greater risk of ADHD than the general population and siblings of control subjects. The studies mentioned were conducted in Iran, Taiwan, Mexico and the USA,[12–15] and the ADHD prevalence in these siblings ranged from 26% to 45.2%. In other words, when one has a sibling with ADHD, the risk of suffering from the same disorder increases by 11.4–13.5 times in relation to the control population.[12,13]

Comorbidity in ADHD subjects is more the rule than the exception, and there are various studies documenting greater frequencies of other psychopathologies such as ODD, CD, OCD, MDD, GAD and SUD. It is important to highlight that siblings both with and without ADHD had a greater risk of suffering from other disorders.[13–15] The most common psychopathology is ODD, with a greater frequency among siblings diagnosed with ADHD, followed by unaffected siblings. This frequency pattern was also found in GAD. As regards CD and MDD, there is no clear trend. The Mexican study[15] stands out in this review, where the analysis was adjusted for different variables, including the number of psychosocial adversities, with statistical significance only being observed after the ODD adjustment.

With regard to psychoactive substance use, Faraone et al.[14] found a greater risk of SUD in siblings of subjects with ADHD than in the controls, while Milberger et al.[17] found no differences in the group of siblings overall, although the risk was greater for siblings affected by ADHD than for unaffected siblings. Likewise, siblings of individuals with ADHD who have other psychiatric disorders, such as CD or anxiety disorder, have a greater risk of psychoactive substance use and/or earlier SUD.

There is only one familial aggregation study on ADHD and OCD, which highlights that, in families with both disorders, the risk of inheriting either or both is greater than in family groups with only one of the two disorders and than in the control families.[19] It is hoped that this finding will be repeated in future studies and that, in turn, variables such as the presence of anxiety and tic disorders will be controlled.

The evidence on the risk of BAD in siblings of ADHD subjects is derived from two studies with different methodologies. One of them, carried out in Sweden,[8] found that siblings of patients with ADHD were at least twice as likely to have BAD than the control subjects, regardless of whether they had ADHD; the other, by Faraone et al.,[14] found that the frequency of BAD is equal in siblings and the control group, and that said BAD frequency is only higher when the siblings have ADHD. In the latter case, it should be taken into account that the risk is not only due to the family history of a sibling with ADHD, but may also be attributable to the comorbidity effect of ADHD with BAD.

There is only one study that assesses the risk of schizophrenia among relatives of ADHD probands, a familial aggregation study that indicates a risk increase of 13% for first-degree relatives.[8]

Although the few studies found in the literature highlight that siblings have a greater risk of ADHD and other conditions, these findings should be regarded with caution. Moreover, they were carried out in geographical regions which could entail different genetic and environmental components, and some studies did not adjust their analysis for said variables.[14,15,17] Confidence intervals are also very wide, which may be due to samples of insufficient sizes. The studies were conducted in different periods, with diagnostic criteria from different versions of the DSM, the diagnostic sensitivity of which fluctuates. Finally, in some studies, prevalence rates were calculated at a specific time[8,12,13,15–19] while others carried out follow-up over several years.[14] Thus, future studies should include larger sample sizes and more sensitive diagnostic criteria for the disorder, clearly defining that the control population comprises siblings of individuals without ADHD and not just the general population.

Conclusions

Although the literature on the topic is limited, it highlights that siblings of ADHD probands have a greater risk of suffering from the same disorder. The risk of suffering another psychiatric disorder increases considerably when the sibling also has ADHD; this is especially applicable in cases of ODD, SUD and BAD, whereas other disorders require further evidence. Future studies on the genetic risk of ADHD should consider adjusting for the presence of other disorders and environmental factors. Studying this at-risk population is essential for proper prevention, timely care and to ensure the best prognosis.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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