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Psychosocial adversity, psychopathology, and functioning in high-risk adolescent siblings with and without attention deficit hyperactivity disorder (ADHD)

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Original article

SUMMARY

Introduction

Attention deficit hyperactivity disorder (ADHD) is a highly heritable neurodevelopmental disorder. The determination of clinical features, adversity factors and level of functioning in siblings of probands with ADHD, known as high risk (ADHD R Sib), could help us to establish the risk to which they are subjected.

Objective

To determine the frequency of ADHD and other psychiatric disorders in R Sib. Secondary objectives were to establish the psychosocial adversity factors that predict ADHD R Sib and determine the magnitude of effect on performance and other psychiatric disorders when siblings have ADHD (R Sib+) compared to those without ADHD (R Sib).

Material and methods

This multicenter study is descriptive, transversal and analytical. The sample (n=84) was formed by adolescent siblings of probands with ADHD who shared both parents.

Results

While 45.2% (n=38) had ADHD, 17.9% (n=15) had no psychiatric disorder. Being an R Sib+ increased the likelihood of having oppositional defiant disorder at least fourfold (OR=4.3, 95% CI 1.3-14.8). This data remained significant when adjusted for sex, age and number of adversities (RM 95=3, 1.8-10.9%). Being an R Sib+ increased the probability of academic dysfunction almost fivefold (OR=4.84, 95% CI 1.41-16.63). The overall average was 3.3 adversities (SD=1.4). Psychopathology in both parents was found in 51.2% of the sample (ES=0.055). Severe family dysfunction increased the probability of having ADHD in an R Sib 2.5 times (95% CI, 1.06-6.25). When comparing the groups with three or more psychosocial adversities, there were no significant differences (81.6% vs. 65.2%, p=0.14).

Conclusions

The clinical study of R Sib for ADHD is necessary due to the different implications in terms of prevention, early care and prognosis improvement of these patients.

Key words: High-risk siblings, adolescents, ADHD, psychosocial adversity, comorbidity.

RESUMEN

Introducción

El trastorno por déficit de atención con hiperactividad (TDAH) es un trastorno del neurodesarrollo altamente heredable. La determinación de las características clínicas, los factores de adversidad y el nivel de funcionamiento en hermanos de probandos con TDAH, denominados en alto riesgo (HAR), podría ayudar a establecer el riesgo al cual están sometidos.

Objetivo

Determinar la frecuencia de TDAH y otros trastornos psiquiátricos en HAR. Como objetivos secundarios, establecer los factores de adversidad psicosocial que predicen el TDAH en HAR y determinar la magni-

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tud del efecto sobre el funcionamiento y otros trastornos psiquiátricos cuando los hermanos tienen TDAH (HAR TDAH+) comparados con quienes no lo tienen (HAR TDAH–).

Material y método

Este estudio multicéntrico es descriptivo, transversal y analítico. La muestra (n=84) se conformó por hermanos adolescentes de probandos diagnosticados con TDAH que compartían a ambos padres.

Resultados

El 45.2% (n=38) tuvo TDAH. El 17.9% (n=15) no presentó trastorno psiquiátrico alguno. Ser HAR TDAH+ incrementó al menos cuatro veces más la probabilidad de presentar trastorno negativista desafiante (RM=4.3; IC 95% 1.3-14.8), dato que mantuvo significancia al ajustarse por sexo, edad y número de adversidades (RM=3 IC 95% 1.8–10.9). Ser HAR TDAH+ incrementó casi cinco veces la probabilidad de presentar disfunción académica (RM=4.84 IC 95% 1.41-16.63). El promedio general de adversidades fue 3.3 (DE=1.4). Encontramos psicopatología en ambos padres en el 51.2% de la muestra (ES=0.055). La disfunción familiar grave incrementó 2.5 veces la probabilidad de presentar TDAH en los HAR (IC 95% 1.06–6.25). Al comparar los grupos con tres o más adversidades psicosociales, no existieron diferencias significativas (81.6% *vs.* 65.2%; p=0.14).

Conclusiones

El estudio clínico de los HAR para TDAH es necesario debido a las distintas implicaciones que tiene a nivel de la prevención, la atención oportuna y la mejoría del pronóstico de estos sujetos.

Palabras clave: Hermanos en alto riesgo, adolescentes, TDAH, adversidad psicosocial, comorbilidad.

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INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is defined in the DSM-5[1] as a neurodevelopmental disorder which often starts before the age of 12 and which persists during adolescence and even into adult life. Meta-analytical and epidemiological studies indicate that at least 5.29% of children and adolescents have this disorder.[2-6] As well as the impact caused by its late recognition, these figures place ADHD as a global-level public health problem.[2]

It is one of the most heritable complex disorders, with a heritability coefficient of 76%.[7] Various studies have observed that as well as biological adversity, there is psychosocial adversity, and that in particular, it is the individual's perception and response to environmental factors[8] that increases the probability that in the gene-environment interplay, adolescent siblings of patients with ADHD will present the same diagnosis.[9,10] Various studies show that compared to controls, subjects with ADHD are found to be more exposed to stressful situations and factors related to events of psychosocial adversity.[11,12] The recurrence-risk ratio (λ) for ADHD in siblings is around 9,[13] with a higher figure (λ=26.2) for siblings of children with ADHD and comorbid psychiatric disorders, compared with siblings of healthy school-age control subjects.[14] Against this backdrop, we know that first-degree relatives of subjects with ADHD have at least four times more likelihood of being affected than relatives of control subjects.[15] This leads us to think that these individuals belong to a "high-risk" population. Based on the above and for the purposes of the present study, siblings of probands with ADHD shall be called R Sib.

Findings in siblings of children and adolescents with ADHD show an intermediate level of being affected between probands with the disorder and controls without it, in terms of the symptoms of ADHD and comorbid conditions.[14-17] However, there are some papers that have shown that non-referred affected siblings are similar to their proband siblings with the same diagnosis and that non-affected siblings are similar to healthy control subjects, except in the dimension of emotional problems or affective and anxiety disorders, depending on the dimensional or categorical view, respectively.[17,18]

The determination of clinical characteristics, including adversity factors and level of functioning, related to siblings of probands with ADHD could aid understanding of the importance of the risk to which this population is also subjected and which it shares with the affected sibling who is brought for treatment. As far as we know, this is the second specialized literature study with the aim of determining the frequency of ADHD and other psychiatric disorders in non-referred siblings, as well comparing the relationship of various psychosocial adversity factors and potential impact on different areas of functioning with the diagnostic status of ADHD between these siblings.

MATERIAL AND METHODS

With the approval of the corresponding Ethics Committees, the present study was developed in three participating centers, two of which are institutions for mental health care: a) the National Institute of Psychiatry Ramón de la Fuente Muñiz (INPRFM) and b) the Juan N Navarro Child Psychiatric Hospital (HPIJNN). The third is a civil society institution dedicated to the orientation and education of patients with ADHD and their family members: the Federico Hoth AC Foundation (FFHAC). The design of this multi-centric study was descriptive, transversal, and analytical.

The recruitment of R Sibs in the participating centers was in accordance with the following inclusion criteria: a) adolescents between 13 years and 19 years 11 months and at least one of their parents, who agreed to participate by signing an agreement and an informed consent form, respectively; b) both sexes; c) knew how to read and write; d) biolog-

ical siblings of adolescent patients diagnosed with ADHD who attended participating institutes (HPIJNN, FFHAC, or INPRFM); and e) whom the clinic did not judge to have any impairment to participating in the clinical assessment, such as a learning disability. Subjects were excluded who a) were part of a set of twins; b) who were already receiving medical or psychological treatment; c) were under psychopharmacological treatment; or d) who had a chronic-degenerative disorder that compromised the central nervous system. Subjects were eliminated if 1) they did not complete at least 75% of the clinimetric instruments or 2) they did not attend two previously-arranged appointments.

Clinical assessment

The clinical assessment of the R Sibs who participated in the study was made by a certified mental health professional (clinical psychologist with Master's or Psychiatrist) with at least five years' clinical experience. The average total duration of the assessment was two hours.

The health professionals who participated in this study carried out the diagnosis of any mental disorder in accordance with DSM-IV criteria and supported by the Mexican version of the clinical interview *Brief Psychiatric Rating Scale Child-* (BPRS-C) of 25 items developed in the Adolescent Clinic of the INPRFM. This version has four more questions than the original, which assess elimination disorders; hyperthymia; and use and abuse of alcohol, tobacco, and other drugs, as well as assessing psychological and sexual abuse. Inter-rater and test-retest reliability is r=0.824 and r=0.661, respectively. The interview lasts 30 minutes on average, and training is needed in order to apply it.

For each case assessed, diagnostic confirmation including ADHD was determined through revision and discussion by the clinician in charge of the assessment and an expert recertified psychiatrist with at least 15 years' clinical experience in child and adolescent mental health (L.P.C.).

Measurement of variables

A) Severity of ADHD symptoms

In order to determine the severity of the ADHD, the clinician-applied version of the *Attention Deficit Hyperactivity Disorder Rating Scale* (ADHD RS–IV)[19,20] was used, also called the DuPaul Scale. This scale consists of 18 questions that assess the presence and frequency of each one of the criteria cited in the DSM-IV to diagnose ADHD. Its reliability has been validated and proven in various population all over the world.[21-23] In applying this instrument, special care was taken in reporting the frequency of each behavior: "*Never*" was a maximum of once in six months; "*Sometimes*" was once a month; "*Often*" was once per week; and "*Very often*" was twice or more per week.

In order to assess the severity of the rest of the R Sibs' psychopathology, the parent version of the *Strengths & Difficulties Questionnaire* (SDQ–P; www.sdqinfo.com/)[24] was used. This instrument has shown its psychometric properties in various cultures with different cut-off points,[25-30] and its usefulness when applied in clinical[30] and community[28,29] contexts.

B) Functioning

The assessment of functioning in different areas in which R Sib can perform was carried out by means of the *Weiss Functional Impairment Rating Scale Parent Report* (WFIRS-P).[31] This scale was designed specifically to evaluate the functioning of an individual with ADHD, demonstrating more sensitivity for the assessment of populations affected by this disorder. It is a *Likert*-type scale whose values for each question range from zero to three, assessing the frequency of the dimension explored as "*never or nothing at all*" through to "*very often or a lot*". It explores six dimensions or areas: a) family, b) learning and school, c) life skills, d) the child's own concept, e) social activities, and f) risk activities. Each area includes between three and ten questions for each dimension, with a total of 50 questions. This instrument has internal consistency greater than 0.9, as well as excellent sensitivity to change over time and a greater correlation between chance and the improvement of ADHD symptoms than measurements such as the *Children´s Global Assessment Scale* (CGAS).[32] For our study, each assessed area was given the status of "dysfunctional" when at least two of the items making up each area were scored by each adolescent's mother or father as moderate to severe deterioration; in other words, with a value of two or three.

C) Psychosocial adversity

Each of the psychosocial adversity factors was questioned by the clinician and placed on the "Sociodemographic and psychosocial adversity data card" (CEDA-SOCIAL), designed especially for this investigation. The CEDA-SOCIAL collects data such as: a) starting age of ADHD, b) number of children in the family, four or more being considered a large family, c) conditions of overcrowding, d) arguments and episodes of physical violence between the parents, both current and in the past six months, e) age of the mother at the time of child's birth, and f) parents' level of education.

The parents' psychopathology (that is, having major depressive disorder, generalized anxiety disorder, ADHD, and/or antisocial personality disorder) was determined by an independent lego assessor by means of the structured diagnostic interview *International Neuropsychiatric Interview* (M.I.N.I.).[33] This assesses the most frequent psychiatric disorders according to the DSM-IV and the CIE-10, and its administration time is approximately 15 minutes. In studies of validity and reliability, this interview performed well compared with other interviews such as the CIDI, and very high inter-rater and test-retest reproducibility.[33,34]

In terms of family dysfunction, the family APGAR scale[35,36] was applied directly to the adolescent. Marital dis-

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cord was determined, confirming whether the parents were separated, as well as reports of arguments, both current and in the past six months, and physical and partner violence, both current and in the past six months.

Statistical analysis

Measures of central tendency and dispersion were used for the descriptive data; specifically frequencies, percentages, and standard error for qualitative variables, and averages and standard deviation for quantitative variables. For the bivariate analysis, in the case of the qualitative variables we used chi squared (χ^2) in contingency tables of 2 x 2, and the exact Fisher test when the frequency by level of variable resulted in less than five observations. In the first step of bivariate analysis, we wanted to know if the psychosocial adversity factors predicted ADHD in this sample of adolescents, the dependent variable being the diagnostic status of ADHD in the R Sibs and the independent variables being psychosocial adversity factors. In the second step, the variable of ADHD was assigned as the independent variable and the variables to be predicted separately were the presence or absence of dysfunction in each area of functioning and each one of the comorbid psychiatric disorders in accordance with the DSM-IV.

The variable sex was used as an independent variable and risk was assigned to being male. The non-adjusted odds ratios were determined for each comparison and then the adjusted odds ratios were obtained as well as their confidence interval of 95% from logistical regressions, considering sex, age, and number of psychosocial adversities as covariates as well as ADHD.

Assuming a normal distribution, for the comparison between R Sib$^+$ and R Sib$^-$, by age, severity of ADHD symp-

Table 1. Sociodemographic and Psychosocial Adversity data in high-risk adolescent siblings (R Sib, n=84)

	X (SD)	Frequency (%)	Standard error
Age	16.21(2.51)		
Sex			
Male		36 (42.9)	0.054
Adolescents at high risk			
• ADHD		38 (45.2)	0.055
• Inattentive subtype		12 (31.6)	0.076
• Mixed subtype		26 (68.4)	0.076
• ***Two or more psychiatric disorders***[a]		34 (40.5)	0.054
• ***Number of psychiatric disorders***[a]	1.5 (1.7)		
• ***No current psychiatric disorders***		15 (17.9)	0.042
Psychosocial adversity[b]			
Family characteristics			
• Severe family dysfunction		38 (45.2)	0.055
• Large family[c]		28 (33.3)	0.052
• Marital discord		72 (85.7)	0.038
• Overcrowding at home		16 (19.0)	0.043
Parents' characteristics			
• Psychopathology, both parents[d]		43 (51.2)	0.055
• Low education, both parents[e]		57 (67.9)	0.051
• History of legal problems		10 (11.9)	0.036
• Probable disorder of alcohol use[f]		33 (39.3)	0.067
• Probable disorder of substance use		12 (14.3)	0.038
• Risk age of mother at time of birth[g]		12 (14.3)	0.038
• Three or more psychosocial adversities[h]		61 (72.6)	0.049
• Number of psychosocial adversities[h]	3.3 (1.4)		

[a] Current psychiatric disorders other than ADHD.
[b] Measured by the Psychosocial Adversity Form CEDA-SOCIAL, clinical version.
[c] Considered to be four or more siblings.
[d] Assessed through the clinical interview supported by the MINI interview.
[e] Low education considered to be a maximum school level of high school.
[f] n=53.
[g] Maternal risk age under 19 or over 35 years of age.
[h] Psychosocial adversities, family dysfunction, marital discord, overcrowding, low education of both parents, psychopathology in both parents, legal problems in at least one parent, risk age of mother at time of birth, and large family.

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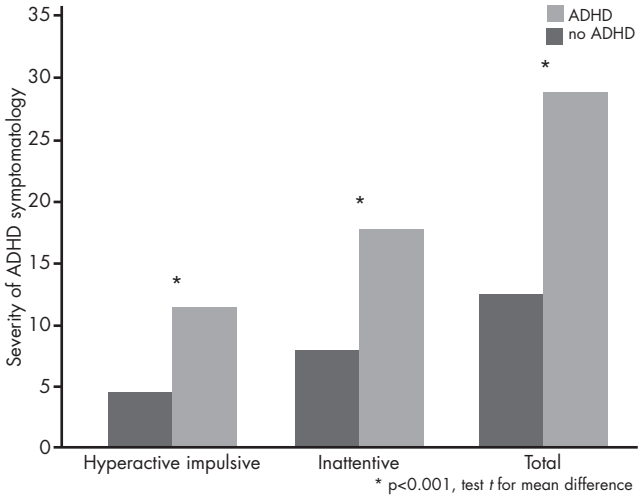

Figure 1. Comparison of the average score for severity of ADHD assessed by the ADHD RS IV in high-risk siblings with and without ADHD.

toms,[19] number of psychosocial adversities, and number of comorbid disorders, T tests were used for independent samples. An alpha level of 0.05 was adopted for all the tests. All statistical analysis was undertaken with version 20 of SPSS (*Statistical Package for Social Sciences*).

RESULTS

The final sample of high-risk adolescents was made up of 84 subjects (Table 1), and 42.9% (ES=0.054) were male. Some 53.3% (n=45) of the sample was recruited from the INPRFM's adolescent clinic, 41.9% (n=35) came from the HPIJNN, and the remaining 4.8% (n=4) came from the FFHAC.

Some 45.2% (ES=0.055) of these siblings received a diagnosis of ADHD; of those, 68.4% (ES=0.076) had the combined subtype, and the rest had the inattentive subtype. Over 40% (ES=0.054) showed more than two psychiatric disorders other than ADHD. Some 17.9% (ES=0.042) did not present any current psychiatric disorder.

As expected, the severity of ADHD symptoms (Figure 1) was significantly greater in ADHD R Sib+ *vs*. those without the diagnosis (p<0.001).

In terms of psychosocial adversity (Table 1), an average of 3.3 adversities were reported (SD=1.4). Some 72.6% (ES=0.049) of the R Sibs were exposed to three or more adversities. Regarding adverse family characteristics, 45.2% (ES=0.055) of the sample reported being in a severely dysfunctional family environment, and 85.7% (ES=0.038) reported marital discord between their parents. Psychopathology was found in both parents in 51.2% (ES=0.055) of the sample, and 67.9% (ES=0.051) reported having completed education no further than high school.

When comparing sex and age as well as psychosocial adversity between R Sib$^+$ and R Sib$^-$ (Table 2), no statistically significant differences were found between the groups, except for the presence of severe family dysfunction which, when present, increased the likelihood of having ADHD in this high-risk population more than 2.5 times (CI 95% 1.06-6.25). Adjusting for age and sex, this effect ceased to be significant (adjusted RM=2.14 CI 95% 0.87-5.28). Although the average number of psychosocial adversities was greater in

Table 2. Comparison of clinical and sociodemographic characteristics in high-risk siblings (Sib R) with and without ADHD

	Sib R (n=84)				
	ADHD n(%)/X (SD)	No ADHD n(%)/X (SD)	Statistic[b,c,d]	*P*	Non-adjusted RM (CI 95%)
Age	15.8 (2.6)	16.4 (2.5)	-1.100	0.276	
Sex (Female)	20.0 (41.7)	28.0 (58.3)	0.460	0.510	1.40 (0.59 – 3.34)
Two or more psychiatric disorders	18.0 (47.4)	16.0 (34.8)	1.368	0.271	1.69 (0.70 – 4.07)
Psychosocial adversity[a]					
• Severe family dysfunction*	22.0 (57.9)	16.0 (34.8)	4.487	**0.048**	**2.58 (1.06 – 6.25)**
• Large family	16.0 (42.1)	12.0 (26.1)	2.400	0.164	2.06 (0.82 – 5.18)
• Marital discord	34.0 (89.5)	38.0 (82.6)	0.801	0.533	1.78 (0.49 – 6.48)
• Overcrowding at home	10.0 (26.3)	6.0 (13)	2.370	0.165	2.38 (0.78 – 7.31)
• Psychopathology in both parents	21.0 (55.3)	22.0 (47.8)	0.461	0.519	1.35 (0.57 – 3.19)
• Low education in both parents	27.0 (71.1)	30.0 (65.2)	0.325	0.643	1.31 (0.52 – 3.31)
• History of paternal legal problems	6.0 (15.8)	4.0 (8.7)	–	0.337	1.97 (0.51 – 7.57)
• Probable disorder of alcohol use[e]	15.0 (62.5)	18.0 (62.1)	0.001	1.000	1.02 (0.33 – 3.11)
• Probable disorder of substance use	7.0 (18.4)	5.0 (10.9)	0.969	0.363	1.85 (0.54 – 6.39)
• Risk age of mother at the time of birth[f]	6.0 (15.8)	6.0 (13)	0.128	0.762	1.25 (0.37 – 4.25)
• Three or more psychosocial adversities	31.0 (81.6)	16.0 (65.2)	2.802	0.140	2.36 (0.85 – 6.55)

[a] Measured with the CEDA-SOCIAL instrument, clinical version.
[b] Pearson's Chi-squared.
[c] Fisher's exact t test (applied in cases where the expected value was less than five).
[d] T test for independent samples.
[e] n=53.
Risk age of mother under 20 or over 35 years of age.

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R Sib+ (3.71 SD=1.4) *vs*. R Sib- (2.9 SD=1.35; t=2.69, gl=82, p=0.009), when groups were compared by presenting three or more psychosocial adversities, there were no significant differences (81.6% *vs*. 65.2%; p=0.14).

In terms of comparison with other psychiatric disorders detected in this sample (Table 3), although all the disorders assessed were more frequent in the R Sib+ reports, only negative defiant disorder (RM=4.3, CI 95%=1.3-14.8) showed statistically significant differences in favor of the R Sib+, even after adjusting for sex, age, and number of adversities (RM=2.98; CI 95%=1.8-10.9). Although the number of other psychiatric disorders was significantly greater in the R Sib+ (1.9, SD=2.2 *vs*. 1.1, SD=1.02, respectively; F=5.24, t=2.12, p<0.02), when groups were compared by having two or more psychiatric disorders other than ADHD, a statistically significant difference was not reached (47.4% *vs*. 34.8%, p=0.271).

When comparing the frequency of cases reported with functional deterioration by area (Figure 2), the parents of R Sib+ significantly reported with greater frequency deterioration in the area of learning and school, even after having been adjusted for age, sex, and number of adversities (RM=5.09, CI 95%=1.28-20.28). Even if there was a greater report of deterioration both in the area related to self-concept (10.5% *vs*. 4.3%, p=0.403) and that related to social performance (15.8% *vs*. 6.5%, p=0.288), neither reached statistical significance.

DISCUSSION

Studying siblings of subjects with ADHD, who are also at risk of various adverse mid- and long-term consequences to their own mental health, allows knowledge to be gained of risk factors or vulnerability related to the development of the same disorder or of general psychopathology. It can even help in determining various protecting factors related to resilience. Several papers have demonstrated that siblings of patients with ADHD are a high-risk group for different outcomes such as developing ADHD or other psychiatric disorders, having poorer function, and a lower psychosocial adjustment compared with siblings of controls without ADHD.[37,38]

The main objective of this work was to determine the frequency of ADHD and other psychiatric disorders in high-risk adolescent siblings. In our sample it was found that 45.2% had ADHD; a similar figure to that reported by Steinhausen at al.,[39] who detected that 47.8% of the subjects assessed had ADHD.

Our study also found 17.9% of siblings who did not have a psychiatric disorder at the time of the clinical evalu-

Table 3. Comparison of current Psychiatric Disorders a between high-risk siblings with and without ADHD, adjusted for sex, age, and number of adversities

	Sib R (n=84) Frequency (%)				
	ADHD (n=38)	No ADHD (n=46)	Statistic[b,c]	*p*	Non-adjusted RM (CI 95%)
Major Depressive Disorder	10 (26.3)	16 (34.8)	0.698	0.480	0.67 (0.26 – 1.72)
Dysthymia	1 (2.6)	1 (2.2)	–	1.000[c]	1.22 (0.07 – 20.12)
Separation anxiety disorder	7 (18.4)	3 (6.5)	–	0.174[c]	3.24 (0.78 – 13.51)
Generalized anxiety disorder	9 (23.7)	14 (30.4)	0.477	0.624	0.71 (0.27 – 1.88)
Panic disorder	1 (2.6)	1 (2.2)	–	1.000[c]	1.22 (0.07 – 20.12)
Specific phobia	6 (15.8)	3 (6.5)	–	0.288[c]	2.69 (0.62 – 11.57)
Social phobia	5 (13.2)	2 (4.3)	–	0.236[c]	3.33 (0.61 – 18.26)
Post-traumatic stress disorder	2 (5.3)	–	–	0.202[c]	–
Non-specific anxiety disorder	5 (13.2)	1 (2.2)	–	0.087[c]	6.82 (0.76 – 61.14)
Oppositional defiant disorder	11 (28.9)	4 (8.7)	–	**0.022[c]**	**4.28 (1.24 – 14.82)**
Behavioral disorder	5 (13.2)	3 (6.5)	–	0.458[c]	2.17 (0.48 – 9.75)
Disorder of alcohol abuse	3 (7.9)	2 (4.3)	–	0.654[c]	1.89 (0.30 – 11.91)
Disorder of nicotine abuse	2 (5.3)	–	–	0.202[c]	-
Disorder of substance abuse	2 (5.3)	1 (2.2)	–	0.587[c]	2.50 (0.22 – 28.69)
Tic disorder	1 (2.6)	1 (2.2)	–	1.000[c]	1.22 (0.07 – 20.12)
Trichotillomania	1 (2.6)	–	–	0.452[c]	–
Enuresis	3 (7.9)	–	–	0.089[c]	–
Self-harm without aim of suicide	2 (5.3)	1 (2.2)	–	0.587	2.50 (0.22 – 28.69)

[a] Diagnoses obtained through the BPRS- 25 interview.
[b] Pearson's Chi-squared.
[c] Exact Fisher Test (applied in cases where the expected value was less than five).

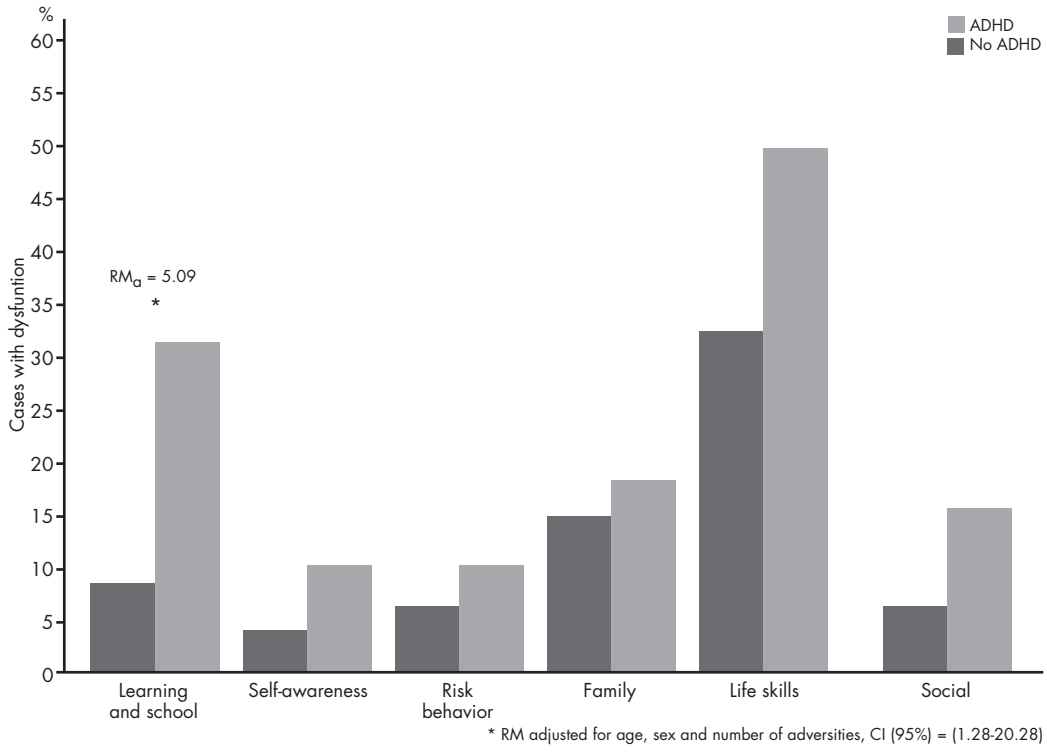

Figure 2. Comparison between high-risk siblings with and without ADHD in areas of functional deterioration, assessed by the WFIRS-P scale.

ation. Although there are papers in the literature which report the frequency of siblings unaffected by ADHD,[18,39] none of these specify whether these subjects did not have other psychiatric disorders either. This finding is relevant in light of scientific evidence which shows that generally, this type of population with shared biological vulnerability is found to be exposed to the same psychosocial adversity factors to which their already-affected siblings attending treatment are exposed. As observed in this sample of siblings, this can increase the risk of developing any psychiatric disorder, including ADHD. It is certain that studying healthy subjects whose first-degree family members have a psychiatric disorder such as ADHD can help to understand protecting factors related to the absence of psychiatric disorders.[40]

In this sample of at-risk siblings almost 43% were male. Other authors have reported frequencies which range between 37.3%[39,41] and 54%.[42] When comparing by sex between those who had ADHD *vs*. those who did not, it is notable that almost 42% of the ADHD R Sib+ were female, further to there being no differences by sex between both groups. This figure coincides with that reported by Biederman et al.[43] in a study which assessed subjects not referred with ADHD. This study found no differences by sex in terms of the subtype of ADHD, psychiatric comorbidity, or history of treatment. Furthermore, in the same study, both males and females with ADHD showed similar levels in terms of cognitive, psychosocial, educational, and family functioning. The lack of differences by sex in terms of the proportion of ADHD R Sib$^+$ in this sample of non-referred adolescent siblings agrees with previous revisions[44,45] which have indicated the concern that only females with a substantial deterioration are referred for clinical treatment. The research suggests that the referral bias leads to underestimating the diagnosis of ADHD in women, particularly young women.[46] In terms of psychosocial adversity, it is notable that 72.6% of our sample was found to be exposed to three or more adversities assessed. Within the psychosocial adversity factors studied, those related to parents stand out, especially: 1) raised frequency of reporting marital discord, 2) raised percentages of mental health problems including a history of alcohol and drug consumption disorders, and 3) a high percentage of low education found in those parents. The finding that a good proportion of these parents presented problems related with their mental health has already been indicated in other studies. In this respect, Steinhausen et al.,[47] upon assessing parents of children and adolescents with ADHD, found that in parents who also had ADHD, greater severity was observed in comorbid psychopathology. Another previous report by Ghanizadeh et al.[48] indicated that the psychiatric disorders most frequently detected over a lifetime in parents were ADHD (fathers 45.8% *vs*. mothers 17.7%) and major depressive disorder (mothers 48.1% *vs*. fathers 43%). The presence of a psychiatric disorder, especially ADHD, in parents, could raise the threshold of recognition for any

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mental health problems in their children, especially in those who are less affected, and this could in turn reduce the possibility of being treated in a timely manner. Other areas of study in mental health have indicated that when the parent has an affective episode, this affects their recognition of psychopathology in their children.[49] Still other papers highlight the importance of jointly treating parents who have psychopathology,[50] given that not treating them has been shown to negatively influence their children's prognosis on a behavioral, emotional, and social level.[51] In our report, the ADHD R Sib+ significantly had five times' greater likelihood than ADHD R Sib- of being reported by their parents as being impacted in education and achievement. That the parents had not seen sufficient reason to bring the affected adolescent siblings of patients with ADHD forward for treatment could be explained by the mediating effect of the parents' psychopathologies. Furthermore, scientific evidence shows that factors such as the presence of an externalized disorder in affected subjects could increase the probability of being brought for specialized treatment.[44,52]

Scientific evidence also indicates the importance of considering the various adversity factors and their relationship with different psychiatric disorders, primarily in children and adolescents. In our study, severe family dysfunction increased the likelihood of finding ADHD in R Sibs by 2.5 times; a finding which lost significance when adjusted for age and sex. In Mexico, studies by Benjet et al.[53-55] note that Mexican adolescents are found to be exposed to different adversities, indicating that it is the sum of these adverse events more than their individual effect which explains their relation to the start of various psychiatric disorders. In our sample, the average number of adversities found was more than three, and it was significantly greater in ADHD R Sib+ compared with those who did not have the disorder. However, no difference was found when comparing those who had three or more adversities. In this respect, Benjet et al.[55] indicated in their work that the effect of the number of adversities found was not lineal; in other words, although the probability of starting a disorder increases with an increase in the number of adversities, that probability raises in a decreasing rate, so it would seem that past a certain threshold in the number of adversities, the effect lessens in the likelihood of having a psychiatric disorder.

The study of this population of siblings of patients with ADHD highlights that not only are they exposed to the risk of developing the same disorder as the sibling, but also of presenting other psychiatric disorders such as affective, anxiety, or behavioral disorders. Except for oppositional defiant disorder, the diagnostic frequencies were shown to be very similar between R Sib+ and R Sib- when psychiatric disorders were determined in the current moment. Our finding shows that the presence of ADHD, even adjusted for sex, age, and number of adversities, increases almost threefold the likelihood of R Sibs having an oppositional defiant disorder. This confirms the findings of other studies where oppositional defiant disorder is the most frequent comorbid psychiatric disorder that can be found in subjects with ADHD.[18,48,56]

Some of the limitations of our study may be considered as follows: first, the majority of the adolescents assessed came from a clinical sample. Second, only adolescent siblings were assessed - no children were included. Third, despite the diagnosis of the psychiatric disorders being made more robust by means of the consensus, it is also certain that the recall bias could not be totally removed in our sample. Fourth, secondary analysis of some data suggests that our study could have some problems related to statistical power, especially for some of the secondary results.

The strengths of our study are related to incorporating the assessment of at least one of the parents. The clinicians who participated in the assessment were professionals with sufficient clinical experience in the area of children and adolescents, and furthermore, the diagnostic confirmation was determined by consensus with a certified psychiatrist with at least 15 years' clinical experience. Finally, the sample of adolescent siblings demonstrated independence in itself, given that except for one subject, the rest came from distinct families.

These results suggest to the clinician that when dealing with patients with ADHD, it is important to systematically consider first-degree family members within their assessment, specifically siblings. This is because they are exposed to different events related to psychosocial adversity, they can manifest the same or other psychiatric disorders, and they show important levels of impact in different areas of functioning which, if not treated, will very likely negatively affect their capacity for adaptation and functioning their entire lives. The parents of these subjects also deserve a special mention as they show raised percentages of psychiatric disorders.

CONCLUSIONS

Taking into account the likelihood of having negative results and risks at a mental health level, the clinical study of siblings of probands with ADHD - a high-risk population - is necessary due to the various implications they have at the level of prevention, timely treatment, and improved prognosis of these subjects. Mental health care of first-degree family members is doubtless a factor that must not be underestimated, given that otherwise it can negatively affect the likelihood of response to any proposed treatment.

More studies are required which approach the risk and protection factors for family members of subjects affected by ADHD for various outcomes such as ADHD.

As well as the genetic aspects, subsequent studies should assess the cognitive, emotional, and individual per-

ception variables of the environment in these populations. This will assist understanding of phenomena such as vulnerability or resilience to one or more psychiatric disorders.

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