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Environmental influences that affect attention deficit/hyperactivity disorder

Study of a genetic isolate

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Abstract Three independent complex segregation analyses found that the cause of Attention Deficit/Hyperactivity Disorder (ADHD) was the presence of major genes interacting with environmental influences. In order to identify potential environmental risk factors for ADHD in the Paisa community—a very well described, genetically isolated group—we randomly selected a sample of 486 children between 6 and 11 years of age. This group included 200 children with ADHD (149 males and 51 females) and 286 healthy controls (135 males and 151 females). The ADHD DSM-IV diagnosis was obtained using the DICA and BASC evaluation instruments, and the children's mothers or grandmothers filled out a questionnaire on each child's exposure to prenatal, neonatal, and early childhood risk factors. The data were analyzed using cross tabulation and stepwise logistic multiple-regression analyses. Cross tabulation associated ADHD with a variety of factors, including miscarriage symptoms, premature delivery symptoms, maternal respiratory viral infection, moderate to severe physical illness in the mother during gestation, prenatal cigarette and alcohol exposure, neonatal seizures, asphyxia or anoxia, severe neonatal illness, mild speech retardation, moderate brain injury, and febrile seizures (odds ratio ≥ 2, $P < 0.05$). Stepwise logistic multiple-regression analysis also uncovered a block of variables, including male gender, maternal illnesses, prenatal alcohol exposure, mild speech retardation, febrile seizures, and moderate brain injury (odds ratio ≥ 2.0, $P < 0.05$). Future studies on the risk of developing ADHD must include these environmental factors as covariates.

Key words ADHD – hyperactivity – environmental risk factors – Colombia – genetics

Introduction

Attention Deficit/Hyperactivity Disorder (ADHD) (OMIM 143465) is the most common behavioral disorder of childhood [15]. Individuals with ADHD are at heightened risk for poor educational attainment, lower income, underemployment, legal difficulties, and impaired social relationships [13, 30, 65].

Several environmental factors that might increase the risk of developing ADHD have been proposed. Of all of them, prenatal exposure to nicotine and alcohol was found to increase the incidence of ADHD,

oppositional disorder (OD), and conduct disorder (CD) [11, 36, 37, 62, 63, 72]. Interestingly, ADHD has been reported as a risk factor for early alcohol and cigarette use and abuse [1, 35, 48].

Low birth weight (LBW) has also been evaluated as a potential risk factor for ADHD. A study found that ADHD children were three times more likely to have low birth weights, even after potential confounders such as exposure to alcohol and cigarettes were taken into account [46]. Season of birth is another postulated ADHD risk factor. Being born during September had an odds ratio (OR) of 5.4 for ADHD with learning disabilities and an OR of 4.5 for ADHD without psychiatric comorbidities. This suggests that a seasonal pattern of birth may exist for subtypes of ADHD, but it is also possible that this pattern is related to maternal respiratory infection (flu) during the first weeks of pregnancy [44], which is more common in winter.

ADHD has also been associated with medication exposure. There is clinical evidence that three-quarters of the children who receive Phenobarbital for febrile seizures or epilepsy develop hyperactivity symptoms, but it is not clear if this phenomenon is caused by the medication or the seizures [66].

It is clear that multiple environmental risk factors contribute significantly to the development of ADHD. Some of them may cause ADHD independently of genetic factors, but it is also possible that environmental influences interact with genetic vulnerabilities to exacerbate or complicate latent or already existing ADHD symptoms.

Over the past decade twin, adoption, family, and association studies have determined that genetic factors contribute to the etiology of ADHD. Phenotype sharing analyses in twins (monozygotic vs. dyzygotic), found that 91% of the variance in ADHD was due to genetic contributions, and only 8% to environmental contributions [2]. Adoption studies also confirmed that genetics, rather than shared environment, cause familial ADHD clustering [10, 20, 27]. In addition, family studies reported that a decrease in the kinship coefficient produced an increase in the relative risk of ADHD family recurrence when the ratio of the prevalence of ADHD in various kinds of relative pairs was compared to the prevalence of the disorder in the general population (λ statistic) [24].

In the same vein, two complex segregation analyses on families from ADHD probands demonstrated that the paradigm that best fit ADHD transmission variance was a sex-dependent Mendelian codominant model [21, 25, 39]. A third complex segregation analysis of nuclear families from a genetic isolate (the Paisa community in Colombia, South America) disclosed that dominant and codominant major gene models, and the non-multifactorial effects model, could not be rejected [38]. All the data from these three studies explain the predisposition to ADHD as the consequence of a dominant major gene (or genes interacting under an oligogenic frame), with a penetrance of ~50%, differential sex liability, and small environmental contributions.

This paper will address the environmental influences that increased the risk of developing ADHD in a sample of children from the genetically isolated Paisa community in Colombia, South America. Previous studies have shown that ADHD in this community is associated with a strong genetic component [2, 4–6, 31], but we think that identifying environmental risk factor covariates will contribute significantly to our understanding the genetic and epidemiological causes of ADHD.

Methods

Participants

A cohort of 200 children with ADHD and 286 healthy controls between the ages of 6 and 11 with Full Scale Intelligence Quotients (FSIQs) over 80 were selected for the study. Both groups were evaluated with psychiatric, neurological, and psychological interviews and examinations plus several validated rating scales adapted for the Colombian population [49, 52–54, 56, 58, 61]. Sample size was calculated for a non-matched, epidemiological, case–control design.

The prevalence of ADHD in the Colombian population was estimated at 9.5–17%. The prevalence of the DSM-IV-based ADHD subtypes was: combined type, 5–10%; predominantly inattentive type, 4–6%; and hyperactive-impulsive type, 0.5–1% [49, 55, 56]. Risk factor exposure for the control population ranged from 5% to 10% with a 95% confidence interval (CI) and a significant odds ratio (OR) greater than or equal to 2. For these parameters, the sample size should be between 160 and 400 participants in each group.

ADHD cases

Children with ADHD between the ages of 6 and 11 who had been referred to the Neurosciences Group or the Neuropsychology and Conduct Disorder Group for assessment and treatment were randomly selected from the clinical databases of both organizations. Only children with complete evaluations performed during the 2 years prior to the study were chosen. These evaluations used a combined approach that had been approved and validated for clinical, epidemiological, and genetic ADHD research [49, 55, 56].

The cases met all the ADHD DSM IV criteria [3], and all the children were being treated with methyl-

phenidate, to which they had responded well during at least the 3 months prior to the study. Children with depression, bipolar disorder, obsessive-compulsive disorder (OCD), or Tourette's syndrome were excluded, as were children with an FSIQ below 70 or children whose ADHD had been diagnosed in the previous 6 months.

There were 495 children in the original sample who met these criteria, and 200 were randomly chosen to participate in the study. Their DSM IV ADHD subtypes were 62.5% combined (n = 125), 22.5% inattentive (n = 45), and 15% hyperactive-impulsive (n = 30). All the cases were sorted by gender, age, school level, and socioeconomic status (SES).

Criteria for cases:

1. Psychiatrists and neurologists with extensive experience in ADHD diagnosis evaluated each child using the Diagnostic Interview for Children and Adolescents (DICA) [59] and the Behavior Assessment System for Children (BASC) [50, 51, 61] to ensure that they met all the DSM IV criteria for ADHD.
2. The parents of children who were chosen for the study responded yes to at least six of nine questions about the presence of DSM IV inattention symptoms and/or answered yes to at least six of nine questions about the presence of DSM IV hyperactivity and impulsivity symptoms presented in a questionnaire.
3. Children chosen for the study had a total score of 59 or more for inattention and hyperactivity-impulsivity on the ADHD checklist validated and standardized for Colombian children [49, 54].
4. Children chosen for the study scored 80 or higher on the Wechsler Abbreviated Scale of Intelligence (WASI)(Spanish version) [73].

Control children

In the year 2000, the total estimated Colombian population was 38,000,000, of whom 1,980,000 lived in the metropolitan area of Medellín (95% in the city itself). The control children were selected from the 458 approved elementary schools registered in the State of Antioquia and the city of Medellín. The schools were sorted by geographic distribution and socioeconomic status (SES). Generally, in Colombia, public schools enroll only children of low (1 and 2) and low-middle (3) SES. Children of middle and high SES (4 and 5) attend private schools. This segregation factor facilitates an SES-based design where schools are defined as the unit of selection.

A random sample of 80 schools was contacted and the researchers met with each school's principal and teachers to present the study. Seventy elementary schools agreed to participate. They gave the research team information on all their children between the ages of 6 and 11, which was placed in a database. Each child in grades 1 through 6 was assigned a random number. Only two to four children were selected for evaluation from each classroom so teachers would not have to fill out multiple rating scales, which might reduce evaluation accuracy.

An initial sample of 400 children was selected from the teacher-evaluated group and their families were contacted by phone. Three hundred of the children whose families agreed to let them participate were randomly chosen by a random numbers generator and were asked to take the DICA, BASC, and WASI. Only 14 of these children did not complete the entire evaluation, and they were excluded from the sample.

Criteria for controls:

1. Control children did not meet the DSM IV criteria for ADHD on either the DICA or BASC.
2. The parents of control children responded yes to no more than four out of nine questions about symptoms of inattention and/or to no more than four out of nine questions about symptoms of hyperactivity and impulsivity presented in an independent questionnaire.
3. Control children had a total score of 55 or less for inattention and hyperactivity-impulsivity on the ADHD checklist validated and standardized for Colombian children.
4. Control children had an FSIQ of 80 or more on the WASI.

Procedure

Cases

All psychiatric, medical, neurological, neuropsychological, and psychological records of the ADHD children were reviewed by neurologists and neuropsychologists. Parents provided information about the current clinical condition of their children and filled out the ADHD retrospective structured risk factor survey.

Controls

Parents of the selected students were contacted by phone and an appointment was arranged for signing the informed consent form, completing the ADHD retrospective structured risk factor survey, and filling out the rating scales. A neurological examination and a brief neuropsychological evaluation were performed on each child at the school. The children selected were in the upper half of their grade for academic achievement and the lower half for disciplinary history. Children with low academic achievement or disciplinary problems were excluded to guarantee that

none of the control children had ADHD. If the information was confused or incomplete, whoever had initially provided the data (parents, teachers, or children) was re-contacted and asked to confirm or to complete the data. If this was not possible, the child was excluded from the database.

Instruments

The DSM IV criteria for ADHD [3], using the psychiatric Diagnostic Interview for Children and Adolescents—parent revised Spanish version (DICA-PR) [59, 60]

The DICA-PR is a fully structured interview that supplements a clinical examination. It covers all of the major child/adolescent categories in the DSM-IV. It can be used to screen for and diagnose a broad range of behavioral problems, such as ADHD, oppositional defiant disorder (ODD), conduct disorder (CD), generalized anxiety disorder, phobias, OCD, depression, bipolar disorder, and psychotic symptoms. The test's reliability is estimated at 0.82–0.87 [59, 60].

DSM-IV-ADHD-symptoms questionnaire

This is a standardized questionnaire that evaluates the 18 DSM-IV ADHD criteria using yes/no queries. The child's parents were asked to fill it out twice, once with regard to their child's symptoms and once with regard to their own past behavior. This questionnaire has been used in clinical and epidemiological ADHD studies of the Antioquian population and has concurrent validity with the ADHD-DSM-IV-Checklist [48, 49, 54, 57].

Checklist for ADHD diagnosis

The checklist for ADHD diagnosis is an 18-item scale with questions that correspond directly to each of the nine DSM IV symptoms for inattention and the nine for hyperactivity-impulsivity. Each question is scored on a scale from 0 (never) to 3 (almost always). The maximum expected score for inattention or hyperactivity/impulsivity is 27. The scale can be used by both parents and teachers and has been standardized and validated with Colombian children [48, 49, 54, 57]. We used the checklist in a complementary fashion to assign participants to either the case or the control group. Children in the case group with total scores of 65 or over were excluded from the study.

Behavioral Assessment System for Children (BASC)

This multidimensional rating scale assesses internalizing and externalizing psychopathology in children and adolescents. The BASC includes questionnaires for parents and teachers and self-reports for children and adolescents [32, 33, 61]. It also has a standardized observation system and a structured interview for detecting medical and neurological disorders, plus a structured survey that retrospectively searches for potential environmental and other associated risk factors, including pregnancy problems, delivery difficulties, neonatal disorders, and neurological events that occurred between the ages of 1 and 5 [32, 33, 61]. The test has been standardized, evaluated using cluster analyses, and is used as a complementary diagnostic instrument for Colombian children and adolescents. A comparative cross-cultural study with Hispanic and African-American children has indicated that the factors do not vary cross-culturally [52, 53, 61].

Data analysis

All data were manually entered into a computer database. SPSS 10.0, EpiInfo 2000, and EPIDAT 2.1 were used to perform descriptive and inferential analyses. A standard χ^2 test compared categorical variables between cases and controls. After discarding deviations from the normal distribution using the Kolmogorov–Smirnov test, a standard ANOVA was used to test significant differences between cases and controls for each continuous variable. Bivariate analyses were independently applied to the grouping binary variables and the binary responses (yes or no) to the environmental risk factor questionnaires. In addition, a multivariate logistic regression procedure introduced gender and school achievement as covariates, along with other variables that showed significant differences in the univariate model between cases and controls (OR > 2 with CI 95% >1). Child age was excluded because it was highly correlated ($r^2 > 0.9$) with school grade. This exclusion eliminated a bias toward enhancing partial relative-risk size effects as consequence of collinear errors.

Results

Characteristics of the sample

Variable counts for cases and controls are summarized in Table 1. Although gender distribution was even in the school databases, statistically significant differences were observed between genders in the results. This is a consequence of the design because ADHD is more prevalent in boys than in girls. There were no differences between cases and controls in intelligence or SES, but control children had a relatively small (0.33) but significantly higher school achievement than ADHD children, which strongly

Table 1 Characteristics of the sample of 486 Colombian children, classified as 200 ADHD cases and 286 controls

Demographic variables	Controls (n = 286)	Cases (n = 200)	Statistic index	P value	Size effects
Categorical variables					
	Frequency (%)	Frequency (%)	χ^{2a}		
Males	135 (47.2%)	149 (74.5%)	36.03	0.000	
Females	151 (52.8%)	51 (25.5%)			
Socioeconomic strata			0.04	0.950	
1 (Very low)	3 (1.0%)	2 (1%)			
2 (Low)	97 (34%)	78 (39%)			
3 (Low middle)	147 (51.4%)	87 (43.5%)			
4 (High middle)	25 (8.7%)	18 (9%)			
5 (High)	14 (4.9%)	15 (7.5%)			
Quantitative variables					
	Mean (SD)	Mean (SD)	F*		
School achievement	2.9 (1.6)	2.4 (1.4)	3.60	0.000	0.33
Child's age	8.3 (1.6)	7.9 (1.5)	2.91	0.004	0.26
Age of the mother at pregnancy	26.9 (6.2)	26.1 (6.7)	1.10	0.269	0.12
Age of the father at child's birth	30.2 (6.8)	29.7 (7.2)	0.81	0.414	0.07
WISC-R					
Verbal IQ	107.8 (17.7)	104.8 (19.8)	1.93	0.16	0.16
Performance IQ	98.5 (16.3)	100.5 (17.7)	1.43	0.23	0.12
FSIQ	104.5 (15.7)	103.1 (16.8)	0.77	0.37	0.09

Values are means ± SD or number of participants
*Analysis of Variance (ANOVA). Significant level for comparisons $P < 0.05$
[a]Chi square (χ^2) for categorical variables comparisons, degree of freedom 7, significant level $P < 0.05$

suggests overlapping between the two groups. Child age also showed a similar trend, with a small size effect of 0.26. Only those demographic variables that demonstrated significant differences between groups (gender and school achievement) were used as covariates in the multivariate analysis.

Risk factors

Environmental risk factor distributions for cases and controls are summarized in Table 2. In general, ADHD children had a higher incidence of all prenatal, neonatal, and early childhood risk factors; but after adjusting OR > 2 with adjusted CI 95% >1, only 11 of 35 of the analyzed risk factors remained. The highest risks were observed for prenatal alcohol exposure (adjusted OR = 14.1, CI 95%: 1.7–114), moderate brain injury (adjusted OR = 12.5, CI 95%: 1.5–102.3), and high prenatal cigarette exposure (adjusted OR = 8.9, CI 95%: 1.0–78.4).

The multivariate logistic regression model determined that high school achievement is a protective associated covariate (OR = 0.8, CI 95%: 0.7–0.9), while male gender was a susceptibility covariate (OR = 3.4, CI 95%: 2.2–5.2). In the multivariate logistic regression model, the most significant environmental risk factor was high prenatal alcohol exposure (OR = 11.7, CI 95%: 1.5–94.1). Four additional variables (child's moderate brain injury before 5 years of age, maternal illness during pregnancy, child's mild speech retardation, and febrile seizures) were included in the model (see Table 3).

Discussion

This research found that 11 of 35 prenatal, neonatal, and early-childhood health variables studied as risk factors for ADHD were significant (OR > 2, CI 95% >1). As reported in other studies [7, 18, 29, 36], high maternal alcohol consumption (defined in our study as drunkenness at least once during the first 2 months of pregnancy) and prenatal cigarette exposure [37] should be considered the highest risk factors for developing ADHD during childhood. Since the multivariate logistic model excluded prenatal cigarette exposure when gender was added, prenatal cigarette exposure appears to be a male gender-specific vulnerability. Maternal high alcohol consumption had the highest OR (11.7). One recent study with 7-year old children found a fairly significant association between symptoms as a quantitative trait, using a 0–8 point scale, but in this study, also, boys had a higher risk than girls [68] (Table 4).

Unfortunately, in the current study the structured risk factor survey obtained from the BASC neurological interview, did not allow us to obtain information about the presence of fetal alcohol syndrome (FAS), which is characterized by physical malformations, generalized learning disabilities, and psychological impairment with an increased risk of developing ADHD and CD. The BASC interview does not inquire about the neonatal period or the presence of FAS signs and symptoms; but because all subjects were required to have a normal FSIQ, we are assum-

Table 2 Environmental Attention Deficit/Hyperactivity Disorder (ADHD) risk factors related to maternal exposure during pregnancy; problems during labor, delivery, and the neonatal period; early developmental problems; and neurological problems

Factors	Controls		Cases	
	Freq.[a]	%	Freq.[a]	%
Pregnancy problems				
Miscarriage symptoms (vaginal bleeding during the first 2 months)	23	8.2	31	15.7
Premature delivery symptoms (labor symptoms before 38 weeks)	19	6.8	33	16.7
Moderate to severe physical illness (hospitalizations for any type of health problem, including hyperemetic disorder, urinary infections, diabetes, intestinal parasites, arthritis, etc.)	7	2.5	19	9.6
Severe respiratory viral infection (flu)	14	5.0	29	14.6
Measles, Varicella, Rubella	0	0.0	2	1.0
Syphilis	0	0.0	1	0.5
Maternal toxoplasmosis	0	0.0	1	0.5
Drug abuse	4	1.4	2	1.0
Low cigarette exposure (1–3 cigarettes/day)	16	5.7	23	11.6
High cigarette exposure (4 or more cigarettes/day)	1	0.4	7	3.8
Alcohol exposure (drunkenness during the first 2 months)	1	0.4	10	5.0
Low alcohol exposure (under 10 drinks/week)	1	0.4	4	2.1
Toxemic disorder	25	8.9	18	9.1
Age of the mother >40 at pregnancy	3	1.1	7	3.5
Parental consanguinity	7	2.5	3	1.5
Labor, delivery, and neonatal problems				
Premature birth	24	8.5	19	9.6
Low birth weight	29	10.5	24	12.2
Asphyxia or anoxia	19	6.8	26	13.1
Need for an incubator	32	11.6	30	15.3
Minor malformations	7	2.5	9	4.5
Jaundice	16	5.7	18	9.1
Hypoglycemic disorder	10	3.6	9	4.6
Neonatal seizures	3	1.1	9	4.6
Blood transfusions	5	1.8	1	0.5
Severe neonatal illness (hospitalizations during the first month after birth)	22	7.8	29	14.6
Neonatal surgery	6	2.1	10	5.1
Developmental disorders and early neurological diseases				
Cephalic control retardation	8	2.9	3	1.5
Trunk control retardation	6	2.1	6	3.0
Walking retardation	9	3.2	8	4.0
Mild speech retardation	12	4.3	34	17.1
Meningitis	1	0.4	1	0.5
Epilepsy	0	0.0	3	1.5
Febrile seizures	17	6.1	33	16.7
Moderate brain injury	1	0.4	8	4.0
Cerebral palsy	0	0.0	0	0.0

[a]Frequency

ing that children with generalized learning disabilities or serious intellectual deficits caused by their mother's alcoholism were not included in the sample.

There are reports in the literature that cocaine and marijuana use during pregnancy are associated with child ADHD [47, 70, 71]. Our study found that drug abuse (frequent use during pregnancy of cocaine, marijuana, basic cocaine paste, and other strong drugs) was not a significant risk factor, and only 1.0% of the case mothers and 1.4% of the control mothers reported it. It may be a cultural trend in Colombia for young women to consume alcohol and smoke cigarettes rather than use strong drugs. It is also possible that the general Colombian population perceives alcohol and cigarettes as very soft drugs (or not drugs at all), and assumes they are not dangerous to fetal health. This assumption would explain the significant number of women that continued smoking and drinking during pregnancy.

Moderate and severe traumatic brain injuries have been reported as the cause of ADHD and other child and adolescent psychiatric disorders [14, 40–43]. In one study, approximately 48% of the children and adolescents who were followed after suffering a brain injury developed persistent ADHD symptoms [14]. A longitudinal study that used MRIs to measure the volume and spatial distribution of brain lesions in children and adolescents 3 months after they suffered a moderate or severe closed traumatic brain injury, found that 19.7% of the subjects developed severe

Table 3 Cross tabulation analyses for child Attention Deficit/Hyperactivity Disorder (ADHD) prenatal, neonatal, and early-childhood exposures. Logistic regression for adjusting OR by gender, child's age, and school grades. Significant risk factors

Factors	χ^{2a}	*P* value	OR	CI 95%	Adj. OR	Adj. CI 95%
Pregnancy						
Miscarriage symptoms	6.48	0.011	2.1	1.2–3.7	2.0	1.1–3.7
Premature delivery symptoms	11.78	0.0006	2.8	1.5–5.0	2.0	1.1–3.8
Moderate–severe maternal physical illness	11.38	0.0007	4.2	1.7–10.0	5.0	2.0–12.9
Severe maternal respiratory infection	13.16	0.0003	3.3	1.7–6.4	3.1	1.5–6.3
High cigarette exposure (4 or more cigarettes/day)	7.35	0.007	10.5	1.3–86.25	8.9	1.0–78.4
Alcohol exposure (drunkenness during the first 2 months)	11.29	0.0008	14.8	1.87–116.27	14.1	1.7–114.0
Neonatal period						
Neonatal seizures	5.79	0.016	4.4	1.2–16.6	5.6	1.4–22.5
Severe neonatal illness	5.67	0.017	2.0	1.1–3.6	2.0	1.1–3.6
Early childhood						
Mild speech delay	22.10	0.0000	4.6	2.3–9.2	3.8	1.9–7.8
Moderate brain injury	7.85	0.005	11.0	1.4–88.5	12.5	1.5–102.3
Febrile seizures	13.80	0.0002	3.08	1.7–5.71	2.86	1.49–5.48

OR = Odds ratio; CI = Confidence interval; Adj. = Adjusted
[a]Chi square (χ^2) Mantel–Haenszel correction for categorical variables comparisons, degree of freedom 7, significant level $P < 0.05$

Table 4 Final multifactor model of environmental ADHD risk factors. Multiple stepwise logistic regression

Factor	OR	CI 95%	*P* value
School achievement	0.8	0.7–0.9	0.002
Male gender	3.4	2.2–5.2	0.000
Maternal illness during pregnancy	4.5	1.7–11.9	0.003
High prenatal alcohol exposure	11.7	1.5–94.1	0.020
Mild speech retardation	3.5	1.6–7.5	0.001
Febrile seizures	2.0	1.0–4.0	0.048
Moderate brain injury	8.9	1.0–77.7	0.049

OR = Odds ratio; CI = Confidence interval

ADHD symptoms [26, 28]. Lesions in the right putamen were more frequent in those patients who developed secondary ADHD [26, 28].

A set of multiple logistic regression models found that the odds ratio of developing ADHD symptoms was 3.6 in children with thalamic lesions and 3.2 in those with basal ganglia damage [26]. Even when pre-injury learning problems and ADHD were controlled for in the analysis, high impairments in executive function, verbal phonological fluency, and inhibitory control were observed in children after severe or moderate closed head injury [19]. These cognitive changes are similar to those reported in children with ADHD [16, 74], and these findings agree with the results of the current study, which found a significantly high association between a history of moderate brain injury (defined as closed head injury with loss of consciousness for more than 1 h and less than 24 h) and ADHD diagnosis.

There are two important caveats about this risk factor: (1) there is probably event-related memory bias about brain injury in the case parent group that does not exist in the control parent group, and (2) it is common for people to associate neurological and psychiatric disorders of any type with head injuries. Unfortunately, medical records and neuroimaging studies were not analyzed to confirm the data obtained from the retrospective risk factor survey.

Early-childhood febrile seizures have also been associated with ADHD symptoms in school age children [16, 19, 67], and this phenomenon could be caused by the convulsions themselves or the anti-epileptic medications the child received. Phenobarbital causes severe hyperactivity in 76% of treated children, and the corresponding figure for other anti-epileptic medications is 31% [19]. Although a prospective study [16] of 4,340 children who were followed from birth to age six did not find behavioral disorders or disadvantages in school performance in the 103 children in the sample who suffered febrile seizures at age three, our retrospective study found that febrile seizures were a risk factor for developing ADHD (OR = 2.0).

As expected, male gender appeared to be a demographic risk factor (OR = 3.4). Several other studies confirm that boys develop severe and complicated form of ADHD more often than girls [9, 17, 22, 45]. Girls develop the inattentive form of the disease more often than boys and appear to have more intellectual and learning impairment, while the combined type linked to oppositional and conduct disorders affected boys mostly [3, 9].

An association between both ADHD and CD with low SES, social adversity, low parent income, low parent school achievement, poor familial structure, parent drug abuse, and familial psychopathology has been extensively reported [64]. These studies involved populations with low school performance, low FSIQ, and generalized learning disabilities. Our study did not link ADHD with SES differences, and these findings were similar to those obtained by several prevalence

studies, independently developed on the same isolated population, which found that low, middle, and high SES were not linked to the incidence of ADHD [55, 56]. One study of extended families that had several members who suffered from ADHD, ODD, and CD also found no significant SES differences between affected and unaffected family members [48].

In the same vein, one study of male offenders and CD adolescents in the Antioquian population, matched by age and SES with healthy non-offenders and non-CD adolescents, discovered a high association between ADHD symptoms, very low education level, low FSIQ, and familial adversity [53]. We interpret these findings to mean that risk factors related to SES and social adversity change when samples are recruited from ADHD or CD pools or if the members of the sample are only children, adolescents, or both. This is true whether or not the sample is controlled for FSIQ.

A complex matter that must be addressed in future studies is the fact that, in this population, a multigenerational linkage analysis of behavioral phenotypes in extended families found that ADHD is associated with disruptive behaviors, which was evidenced by highly significant pair-wise linkages among ADHD and ODD (LOD = 14.19), ADHD and CD (LOD = 5.34), ODD and CD (LOD = 6.68), and CD and alcohol abuse/dependence (LOD = 3.98) [6]. The highly significant LOD scores and the presence of linkage homogeneity through all the sets of families suggest the pleiotropic expression of specific vulnerability genes. The results of this study support the hypothesis that major genes underlie a broad behavioral phenotype in these families that can manifest as a range of symptoms, including ADHD, disruptive behaviors (ODD and CD), and alcohol abuse or dependence. In other words, different behavioral phenotypes comprise a nosological entity and the concept of comorbidity is inadequate [34]. In this context, we strongly suspect that the partial ADHD variance associated with alcohol and nicotine consumption might be the result of genetic cosegregation between these phenotypes and ADHD.

Although, a twin-based study found that maternal smoking was still a risk factor for ADHD development, even after controlling for genetic influences [68, 69], we think that recruiting large family samples and systematically examining them for environmental influences would uncover independent genetic and environmental risk factors for ADHD.

In summary, our data define environmental factors for ADHD in the genetically isolated Paisa community of Antioquia, Colombia, which has a high incidence of ADHD. These data are similar to those reported for multiple studies in developed countries. Our general findings support the theory of ADHD as a clinical and epidemiological problem caused by environmental factors interacting with genetic vulnerabilities [2, 8, 12, 23, 39]. Future investigations on the risk of developing ADHD should include the environmental factors we found to be significantly linked to ADHD as covariates that interact with susceptibility loci.

Limitations

Our results should be accepted with caution because:

1. Our samples came from very healthy school children with a fairly pure type of ADHD.
2. Since the ADHD risk factor survey is part of the BASC general neurological interview and does not evaluate behavior problems, it will probably not produce clinically significant associations.
3. The retrospective approach could have missed some important clinical information.
4. The sample sizes only allowed the detection of the most common risk factors.
5. Size effects could only be calculated for some demographic quantitative variables and not for risk factors, which were considered binary variables.
6. Comorbidities and the way they interact with ADHD and ADHD risk factors were not taken into account.
7. Detected risk factors could be overestimated because control children could belong to a supernormal healthy group.

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