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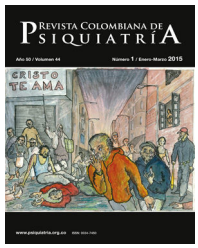

Artículo de revisión

The role of psychosocial adversity in the aetiology and course of attention deficit hyperactivity disorder

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ABSTRACT

Introduction: Attention deficit/hyperactivity disorder (ADHD) has genetic and environmental aetiological factors. There are few publications on the environmental factors. The objective of this review is to present the role of psychosocial adversity in the aetiology and course of ADHD.

Methods: A search was carried out in the following databases: PubMed, ScienceDirect, SciELO, ClinicalKey, EMBASE, Lilacs, OVID, APA and PsycNET. English and Spanish were selected without being limited by type of study or year of publication. Finally, a qualitative synthesis was conducted.

Results: ADHD development could be related to exposure to adverse factors in the family, school or social environment. It has been proposed as an explanatory mechanism that adversity interacts with genetic variants and leads to neurobiological changes. There may also be a gene-environment correlation whereby individual hereditary characteristics increase the risk of exposure to adversity, and indirectly increase the probability of developing ADHD. Research on psychosocial adversity represents a big challenge, not only due to the complexity of its construct, but also to the effect of subjective perception of a given event.

Conclusions: ADHD aetiology is complex and involves the interaction of both genetic and environmental factors, in which these factors correlate and cause the disorder. The study of the role of psychosocial adversity in ADHD is fundamental, but it remains a task that entails great difficulties.

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El Papel de la Adversidad Psicosocial en la Etiología y el Curso del Trastorno por Déficit de Atención con Hiperactividad

Palabras clave:
Trastorno por déficit de atención con hiperactividad
Etiología
Problemas sociales
Impacto psicosocial

R E S U M E N

Introducción: El trastorno por déficit de atención con hiperactividad (TDAH) tiene factores etiológicos genéticos y ambientales. Hay pocas publicaciones acerca de los factores ambientales. El objetivo de esta revisión es presentar el papel de la adversidad psicosocial en la etiología y el curso del TDAH.

Métodos: Se llevó a cabo una búsqueda en las siguientes bases de datos: PubMed, ScienceDirect, SciELO, ClinicalKey, EMBASE, Lilacs, OVID, APA y PsycNET. Se seleccionaron artículos en inglés y español sin limitar por tipo de estudio o año de publicación. Finalmente, se hizo una síntesis cualitativa.

Resultados: El desarrollo del TDAH podría estar relacionado con la exposición a factores adversos en el entorno familiar, escolar o social. Se ha propuesto como mecanismo explicativo que la adversidad interactúa con variantes genéticas y conduce a cambios neurobiológicos. También puede haber una correlación entre gen y ambiente, en la que las características hereditarias individuales aumentan el riesgo de exposición a la adversidad e indirectamente aumentan la probabilidad de sufrir TDAH. La investigación sobre la adversidad psicosocial representa un gran desafío no solo por la complejidad de su constructo, sino también por el efecto de la percepción subjetiva sobre un evento determinado.

Conclusiones: La etiología del TDAH es compleja y factores genéticos y ambientales presentan una interacción en la que estos factores se correlacionan y originan el trastorno. El estudio del papel de la adversidad psicosocial en el TDAH es fundamental, pero sigue siendo una tarea que conlleva grandes dificultades.

Introduction

Attention deficit/hyperactivity disorder (ADHD) has a worldwide prevalence of 5% in children under 18 years of age, and can persist in adulthood in up to 70% of cases.[1] It has been suggested that genetic factors are the main contributors in its etiology, as ADHD presents a heritability of up to 80%.[2] Family aggregation studies have found a 5-9 times greater risk of inheritance in first-degree relatives of ADHD patients compared to the general population; however, little is known about the precise estimation and the aggregation pattern, but it is clear that it varies according to the different degrees of relationship.

The greatest aggregation occurs in monozygotic and dizygotic twins and decreases in full siblings, middle siblings, and full cousins.[3] Molecular genetics studies have identified several loci and variants linked to ADHD. In genome-wide association studies, the loci that have been found most frequently have been 5p12, 10q26, 12q23, and 16p13. However, polymorphisms in the genes that encode dopamine receptors *(DRD4, DRD5)*, dopamine transporters *(DAT1, SLC6A3)*, synaptosome proteins *(SNAP-25)* and serotonin receptors *(HTR1B)* have also been described.[2]

This being said, the strength of the association between specific genetic variants and ADHD tends to be small and often not highly reproducible, so it is possible that there are multiple small-effect variations that are related to each other and to the environment.[4] In fact, in the variability analysis of these studies, the environment can explain about 16% of the variability observed between ADHD cases and their relatives.[3] In this way, genetics alone is not enough to explain the disorder, and the environment that surrounds the individual becomes relevant.

There are factors in the environment that can produce alterations in genetic functions without directly altering the DNA sequence through epigenetic mechanisms. This is mainly observed in periods of susceptibility of the different cells of the organism. Exogenous factors include physical and chemical agents that cause cellular, molecular, and genetic damage that trigger a cellular repair response, which can also be affected.[5] Various epidemiological studies have found an association between ADHD and risk factors such as cigarette and pesticide exposure during the prenatal period,[6,7] prematurity, low weight at birth, hypoxia at birth[8,9] and exposure to metals in early childhood.[10] It is possible that these events have neurodevelopment effects that result in the manifestations grouped under ADHD.[11]

Within this relationship between genes and the environment, it has been found that psychosocial factors can also influence critical periods of neurodevelopment. An association has been suggested between exposure to childhood adversity and the development of mental disorders in childhood and a high probability of presenting a mental disorder in adulthood. Adverse childhood experiences (ACE) can be found in almost a third of cases of psychiatric disorders in the course of life.[12] Among the disorders with the highest association are affective and anxiety disorders, behavioral disorders and the use of psychoactive substances.[13] For example, Green[14] reported that the probability of developing affective and anxiety disorders and for these to persist was higher in those

who reported maladaptive family functioning during childhood. For ADHD specifically, a higher frequency of exposure to adverse psychosocial events has also been reported.[15] Furthermore, in already diagnosed patients it has been seen that the social and family environment does influence the onset, course, comorbidity and severity of the disorder.[1,16] Thus, it has been suggested that, in subjects with ADHD, the form and circumstances of life may interact with genetically mediated biology. The objective of this review is to present the data on psychosocial adversity and its role in the etiology and course of ADHD, as well as to highlight some methodological considerations in its research.

Methods

A search of the PubMed, ScienceDirect, SciELO, ClinicalKey, EMBASE, Lilacs, OVID, APA, and PsycNET databases was performed. Articles in English and Spanish were selected without limiting by type of study, but research papers were privileged. The last 10 years of publication were considered for this review. Finally, a qualitative synthesis of the evidence was carried out for this narrative review.

Results

The search results are presented in 3 main categories: *a)* psychosocial adversity; *b)* family, school, social and community environment, and *c)* explanatory mechanisms.

Psychosocial adversity

Studies on the subject do not provide a concrete definition of adverse childhood experience and most of them focus on counting the total number of adversities experienced. It seems that adversity is difficult to define, but easy to identify when viewed, so there is no consistency regarding the definition and measurement of this construct. The proposal by McLaughlin[13] summarizes various approaches and defines childhood adversity as "exposure during childhood or adolescence to environmental circumstances that probably require significant psychological, social or neurobiological adaptation by the average child and that represent a deviation from the expected environment".

In general, ACE have been found to be common, with a frequency between 60% and 70% and these adversities may be interrelated. Some authors point out that up to 54.5% of adults and 66.7% of adolescents have experienced at least 1 adversity, and 55.2% of adults more than 1, with a mean of 2.8. The most frequently reported adversities have been medical illnesses or injuries of the parents (24%), economic difficulties (22%), family discord (18%) and paternal alcohol consumption (17%).[17,18]

Psychosocial adversity in ADHD

Child psychiatrist Michael Rutter was one of the first to suggest the role of psychosocial adversity in the etiology of mental disorders. He revealed that the development of psychopathology was associated with a set of adversity factors rather than the presence of a single factor.[1] From these studies, Rutter's Indicators of Adversity (RIA)[15] were constructed and included 6 family and environmental indicators that correlated with childhood mental disorders, particularly ADHD. These indicators have been used in some researches and are defined as shown in table 1.

Rutter's work showed that a single indicator did not significantly increase the risk; however, the presence of 2 indicators increased the probability of mental disorders 4 times, and the presence of 4 indicators resulted in a 10-fold increase in the risk for the child.[19] Some follow-up studies have found that family rates of psychosocial adversity assessed by exposure to parental psychopathology, conflict and poor family cohesion, would be the most important predicting factors to determine the severity and persistence of ADHD. Poverty is a determining factor in subjects with inattention, not only for the presence and persistence over time, but it has also been linked to lower future income in adulthood.[20]

Family, school, social and community environment

Family environment

It refers to multiple closely related concepts, including conflict, cohesion, family adaptability, and generally where members support each other within an enriching environment.[21]

In the Biederman[19] study it was found that all the indicators of psychosocial adversity, except for large family size, had a significant association with the presence of ADHD. Also, greater family cohesion has been associated with fewer externalizing and internalizing problems and inattention symptoms at 6 and 11 years while greater family conflict was associated with larger inattention, internalizing and externalizing problems. Other studies have found an association between ADHD and conflict between parents, poor family cohesion and psychopathology in parents, especially the amount of years that the child has been exposed to maternal psychopathology. In this regard, several authors during recent years have highlighted that the presence of ADHD or depression in parents is related to more comorbid and severe ADHD in children.[22–25]

On the other hand, there is an alternative possibility that implies a change in the direction of association. This proposes that in the presence of a child with ADHD, the family dynamics change, leading to disruptions in family and marital functioning, poor relationships between parents and children, reduced self-efficacy and increased parental stress levels.[26,27]

School environment

Few studies have investigated factors associated in the school context with the development of the disorder. However, there is a wide range of evidence that students with ADHD experience relationship difficulties with peers and teachers, such as rejection even after brief interactions.[28,29] On the other hand, there is evidence of significant academic difficulties such as non-compliance with school work, suspensions/expulsions[30] and lower scores on tests of cognitive domains. This leads to a higher level of stress in the teaching process.[29,31]

Considering that ADHD symptoms are more noticeable in the school environment and are frequently identified for the first time in this context,[32] some studies have shown

Table 1 – Rutter's indicators of adversity.

#	Indicator	Definition
1	Low social class	Defined as a classification for both parents with a lower score in at least one of the following variables: education (having completed or not completing basic schooling), occupation (receiving a disability pension, which in most of the cases is due to mental or physical illness) or low income (an income one fifth lower than the general population for each sex and calendar year)
2	Serious marital discord	Measures family conflict derived from the Moos Family Environment Scale, which assesses the quality of interpersonal relationships between family members in three dimensions: cohesion (degree of commitment, help and support between members of the family); expressiveness (open acting and expression of feelings) and conflict (presence of anger, aggression and openly expressed conflict)
3	Large family size	A household with 4 or more children (including the index case)
4	Paternal criminality	If the father of the index case has ever received a custodial sentence or a suspended sentence for some criminal act (violence, theft, arson, murder, sexual abuse, fraud and extortion)
5	Maternal mental disorder	If the mother of the index case has presented a psychiatric disorder
6	Institutionalization	If the index case has ever been in a foster home, childcare institution or orphanage, with or without parental consent

Adapted from Østergaard et al.[15] and Biederman et al.[19].

that a younger age when entering school increases the probability of having related symptoms with ADHD or other psychopathology.[33] Children who entered school before age 6 have been shown to have higher scores on the SNAP IV (Swanson, Nolan, and Pelham Version-IV ADHD Rating Scale).[32] However, it is not clear if there is any trigger for ADHD when entering school earlier, or if entering without full brain development produces symptoms that would later be diagnosed as ADHD.

Social and community environment

Some authors suggested that relational trauma, particularly abuse in the early years can cause ADHD.[34,35] Children with ADHD have been found to experience greater stress and adversity in early life than their peers, and both abuse and neglect are associated with the presence of symptoms.[36,37] The consequences of abuse and ADHD symptoms share some characteristics such as aggressiveness, hostility, poor anger management, impulsiveness, depressive symptoms, cognitive difficulties, discipline problems at school, social isolation and poor social skills, among others. This overlap has aroused debates about the possible association between ADHD and child abuse, as post-traumatic responses related to abuse could be misinterpreted as ADHD.[38]

Specifically, physical abuse has been more strongly associated with aggressiveness and externalizing problems, whereas sexual abuse has been related directly with symptoms of post-traumatic stress disorder (PTSD) and later with internalizing symptoms.[38] Ford et al.[39] followed a cohort of children between the ages of 6 and 17 with a diagnosis of ADHD, and they found that 25% of the sample had been exposed to physical abuse and 11% to sexual abuse. It seems that the association with child mistreatment could be different depending on the ADHD subtypes. The inattentive subtype has been associated with poor supervision (odds ratio [OR] = 1.63; 95%CI, 1.21-2.20), physical neglect (OR = 2.07; 95%CI, 1.37-3.11), physical abuse (OR = 1.59; 95%CI, 1.13-2.25), and sexual abuse (OR = 2.61; 95%CI, 1.52-4.48). The hyperactive/impulsive subtype was not as related with poor supervision and physical abuse but was highly related with physical neglect (OR = 2.65; 95%CI, 1.86-3.78) and sexual abuse (OR = 2.90; 95%CI, 1.69-4.95).[40] To the contrary, other studies did not find a clear association between the history of trauma and the presence of ADHD.

Recently, social deprivation has been an issue gaining relevance. Subjects who experience it in adoption institutions receive little social and cognitive stimulation. Cohort studies of adopted children have found that symptoms of inattention and hyperactivity are more frequent in late adopters and their intensity was greater according to the duration of the deprivation experienced in the institution.[41] Moreover, having been deprived produces a greater severity of ADHD symptoms,[41] and is related to its persistence until adolescence and adulthood.[42] In a longitudinal study by Rutter,[43] 2 groups of adopted children were compared: one group who lived in institutions while the other group had not, it was found that at the age of 6 and 11 the first group presented a higher frequency of inattention and hyperactivity. This finding was more noticeable in those subjects adopted after 6 months of age. A recent study showed the protective role of a shorter duration of out home placement, especially at the cognitive and emotional level in at risks for ADHD.[44]

It should also be noted that a significant proportion of children after exposure to traumatic experiences such as natural disasters (earthquakes, hurricanes, floods), traffic accidents or terrorist acts (bombings), show psychological reactions that significantly interfere with their lives. Sometimes the reactions occur with symptoms such as increased psychomotor activity or decreased concentration, making it difficult to differentiate between PTSD and ADHD. Although it is an important field, its study is complex because there is interference in the measurement of its outcomes.[45,46]

Explanatory mechanisms

Gene-environment interaction

Genes and environmental influences can interact to give rise to ADHD and other mental disorders.[34] This gene-environment interaction (GxE) describes any phenotypic event that is due to changes in the effect of the gene by the

environment or, conversely, by genetics of the environment. Depending on the stage of neurodevelopment, the psychosocial environment can mediate gene expression, particularly in the first years of life.[34] In this way, gene expression occurs only in a subgroup of individuals exposed to the environmental factor, which explains why not everyone who carries the gene expresses the disorder. Empirical evidence of the role of GxE in ADHD cases so far has found statistical significance of the interaction between dopamine transporter gene *(DAT1)* polymorphisms with prenatal cigarette exposure[47] and fetal growth,[48] along with dopamine receptor gene *(DRD4)* polymorphisms and exposure to pesticides.[49]

The evidence regarding the psychosocial environment is still incipient. A cross-sectional study based on a cohort of German-born infants assessed whether the psychosocial environment moderated the effect of variations in the *DAT1* gene.[50] A structured interview was applied to 305 adolescents to establish the diagnosis of ADHD, the *DAT1* variants were genotyped and the presence of psychosocial adversity was determined from a modification of the RIA. In a first analysis, no effect of *DAT1* variants on ADHD symptoms was found. However, taking into account the psychosocial environment in those individuals with some variants (haplotype 6R-10R/6R-10R) in the presence of high adversity, they presented symptoms of inattention and hyperactivity / impulsivity more frequently, with statistical significance of the interaction (p value between .013 and .017) even after adjusting for the history of parental psychiatric disorder and obstetric complications in childbirth. The association of this same haplotype and ADHD symptoms has also been found when there is social deprivation. This would indicate that variants of *DAT1* would have an effect according to the psychosocial environment and its effects would only occur in those who have presented high adversity or deprivation.

A possible explanation for this is that dopaminergic dysfunction in this case only occurs in stressful situations. For example, elevated levels of dopaminergic markers have been found after sexual abuse or increased striatal dopaminergic transmission related to physical abuse and family disputes, which may have been caused by the stimulation of cortisol in the release of this neurotransmitter. Thus, it is possible that *DAT1* variants produce changes in the dopamine transporter, the main regulator of the reuptake of this neurotransmitter in the presynaptic neuron and contributing to this dopaminergic dysfunction. In this way, haplotypes could explain that individuals respond differently to negative and positive environmental experiences, meaning we would not only have to consider these to be plasticity genes.[51]

Gene-environment correlation

There is also a relationship in which genetic and environmental risk factors coexist non-randomly, such that certain hereditary characteristics of the individual create a risk of exposure to certain environmental risk factors that indirectly increase the probability of presenting ADHD, known as gene-environment correlation (rGxE).[52] In other words, there would be a genetic vulnerability not only to ADHD but to psychosocial adversity. We would not be studying only the modification that the environment makes of the genetic effect in producing ADHD, but that genetics act in such a way in the environment that it finally leads to adversity. The correlation between genes and the environment in human behavior can occur in 3 ways: genetic variants present in parents that produce the psychosocial environment in which the child is raised (passive rGxE), genes that originate some traits that create psychosocial adversity (evocative or reactive rGxE), or children create their psychosocial environment from their lessons and behaviors which respond to inherited dispositions (active rGxE).[53]

The few studies that have directly evaluated rGxE in the development of childhood psychopathology have focused on other externalizing symptoms such as antisocial behavior. In general, genetic factors that create a risk for behavior problems are empirically examined. Children who were adopted and who had a genetic risk of antisocial behavior (antisocial parent) were compared in a cohort study with those who had no such history. Adoptive families were found to report more frequently over time negative or coercive parenting styles in response to child behaviors, which might suggest evocative rGxE.[54] Another study found a rGxE between the candidate gene *MAO-A* and maltreatment in a genetic variant associated with antisocial behavior and ADHD.[55] This topic is relevant when considering the high comorbidity of ADHD with this disorder.

Psychosocial determinants

In addition to biological mechanisms, it is worth mentioning the effect of adversity from other theoretical models. Although a neurobiology mechanism is observed which is affected by genetic and environmental factors, there are other "significant structures" such as the cognitive ones. These develop over time and constitute the continuous interpretation of the world that a person makes, which is also known as a schema. In ADHD, some psychologists have proposed that maladaptive schemes such as emotional deprivation develop from childhood. This is the belief that their own emotional needs will not be met by others and that it may be due to poor interaction with parents and/or companions in their childhood. Subjugation is another example, where the individual believes that he should submit to the control of others to avoid rejection by peers at school.[56] Likewise, the representations and meanings that a child attributes to each situation that he lives can be different. In an analysis of the narratives of preschool-age children from a community sample, he found that negative representations about parents were related to the presence of ADHD symptoms, without a correlation with what parents reported about the family environment.[57]

In the same way, coping mechanisms have been conceptualized, which are the cognitive efforts of each person to handle the demands that adversity implies. Various descriptive studies have identified that these mechanisms are different for each person, depending on age and the environment in which adversity occurs. These studies propose that those subjects who focus on managing emotion rather than the problem generated by adversity are those with more externalizing symptoms. On the other hand, the influence of culture has been described on the type and number of adverse events, the capacity and resources to respond to them, as well as the definition of ADHD and its complex association with psychosocial adversity.[58]

Discussion

The evidence on the genetic component of ADHD is strong and comes from large studies of adoptions, twins and relatives. It shows that ADHD has a familiar component and an inheritable one with many genes involved.[59] However, due to the great variability in the results, it is possible that its effects depend on the influence of environmental factors. Also, the fact that the onset, course and severity of ADHD can be influenced by environmental factors, would indicate the importance of the environment in this disorder.[14] Human and animal studies show that stressful experiences can increase or decrease the susceptibility stress that can be identified as ADHD, although the exact mechanisms for this are not yet clear.[60] There is no single factor or mechanism that is necessary or sufficient to cause ADHD, so we would be facing a complex multifactorial etiology.[59]

Given this etiological complexity, it is essential to study the role of adversity in ADHD. However, this task represents great difficulties. On one hand, there is no unified definition of psychosocial adversity and the few that are available fail to cover the complexity of the construct. For example, an event that occurs in an individual's life can be considered stressful considering criteria such as RIAs but the individual's perception may be different and may be a source of variation of the influence that adversity has in the course of their symptoms. This all relates to meanings and personal valuations that could be approached with qualitative research to try to understand them and formulate a theory about it.

Likewise, the temporal relationship between the adverse event and the appearance of psychopathology must be considered. In some cases, it can be proximal (a recent event) and in others distal (a past event). It will also depend on the number of events a subject experience; some theorists consider that an event can produce a change in the neurobiology of an individual and modify their behavior, while for others it is the number of events that can cause such change, that is, an accumulation of various events or chronic adversities.[18] In this regard, some studies show that the greater the number of adversities, the greater the probability of presenting ADHD symptoms, regardless of the age of the presentation of events and gender.[36]

On the other hand, there are difficulties in defining the outcome. In the different studies the categorical diagnosis of ADHD is taken, while in others the symptoms of the disorder are mentioned. Furthermore, the symptoms that make up the subtypes of the disorder are likely to be due to substantial differences, which implies a high heterogeneity in the phenotype.[61] In the longitudinal follow-up of twin pairs, it has been seen that those with an overactive and impulsive predominance tend to decrease the symptoms presented towards adolescence, while the course of the inattentional predominance is more stable. In the cases that persist, genetic factors explain this behavior to a great extent.[53] In other words, the cases that persist in adolescence and adulthood are highly familiar,[59] so the environmental influence may be less, or at least different, from that of the cases that improve with time.

Addressing these difficulties can be quite a methodological challenge. Studies evaluating the etiology and course of ADHD should be longitudinal, population-based, with early recruitment of healthy children and careful assessment of the environment from an early age. Periodic evaluations should monitor the onset and course of symptoms, without focusing so much on the diagnostic category, but rather on the symptomatic dimensions as recommended by Rutter.[60] Within the measurement of exposure to adversity the time of the stressor: the perception of it, the duration and its relationship and summation with other stressors in the different scenarios (family, school, neighborhood, etc.) should be considered. It is also necessary to evaluate interactions cautiously, since in most cases the multiplication of 2 terms and their statistical significance are taken. It would be important to carry out more complex equations that obey a theoretical support defined *a priori*. Another possible solution is to carry out controlled clinical trials, where allocation to multimodal interventions specifically aimed at psychosocial adversity is made and it is analyzed how this impact on different genetic circumstances. This would expose the criterion of causality demonstrated by relating improvement in the outcome as the exposure is reduced. It is important that this type of research would allow a more comprehensive approach to subjects with the disorder, allowing therapeutic and possibly preventive interventions to be effective.

Conclusions

ADHD has a complex multifactorial etiology in which the gene-environment interaction is evident. Several studies illustrate the effect of these components in a bidirectional way. The environment plays a role by interacting and influencing the expression of genes, and gene expression can explain changes in the environment. Psychosocial adversity is one of the factors that plays a role in the expression of ADHD. It has been suggested that when adversity occurs cumulatively from multiple events and/or chronically it is associated with the development and course of ADHD symptoms. Studying psychosocial adversity in ADHD is essential, but it is still a task that represents great difficulties.

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Author contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Sujey Gomez-Cano, Juan Pablo Zapata-Ospina, Mauricio Arcos-Burgos and Juan David Palacio-Ortiz. The first draft of the manuscript was written by Sujey Gomez-Cano and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conflict of interests

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