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How Do Parental Factors Increase the Probability for Autism and Attention Deficit Hyperactivity Disorder?

Shumoos Riadh M.Shafeea[*,1],Zinah M. Anwer[1] and Zainab Ali Saleem[2]

[1]Department of Clinical Pharmacy, College of Pharmacy, University of Baghdad, Baghdad, Iraq.
[2]College of Medicine, University of Baghdad, Baghdad, Iraq.

Abstract

Two prevalent neurodevelopment disorders in children are attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). The fifth version of the Diagnostic and Statistical Manual of Mental Disorders describes autism as a condition marked by limitations in social communication as well as restricted, repetitive behavior patterns. While impulsivity, hyperactivity, and lack of concentration are signs of attention deficit hyperactivity disorder. Boys experience it more frequently than girls do. This study sought for possible factors that put children at risk for autism and attention deficit hyperactivity disorder, and it investigated the association between neurodevelopment disorders in children and parental risk factor in Iraqi population. This was a cross sectional, comparative study applied in The National Center for Autism/Medical City Complex from January to April 2022.In which120 child withneuro development disorders and 120 controls participated. The data collected from the questionnaires was analyzed using SPSS 25. Independent T-test and Chi-Square test were carried out for the bivariate analysis of the data**.** Among the tested variables four parent-related factors were significantly (*P*-value < 0.05) associated with neurodevelopment disorders in children: Family history of psychiatric illness, smoking of any parent, pregnancy and labor complications, used progesterone during pregnancy. In addition to these significant parent-related risk factors, paternal age at conception time were significantly (*P*-value < 0.05) associated with neurodevelopment disorders of children. Based on this case control study, mothers with pregnancy & labor complications, paternal age at conception, smoking of any parent,mothers used progesterone during pregnancy and family history of psychiatric illness, had higher risk of neurodevelopment disorders.

Keywords: Autism Spectrum Disorder, Attention Deficit Hyperactivity Disorder, Neurodevelopment Disorders, Risk factors.

كيف تزيد عوامل الوالدين من احتمالية التوحد واضطراب فرط الحركة وتشتت الانتباه؟

شموس رياض محمد شفيع *[،١]، زينة مظفر أنور[١] و زينب علي سليم[٢]

[١] فرع الصيدلة السريرية ،كلية الصيدلة،جامعة بغداد ،العراق
[٢]كلية الطب ،جامعة بغداد ،العراق

الخلاصة

يوجد اثنان من اضطرابات النمو العصبي السائدة عند الأطفال هما اضطراب نقص الانتباه وفرط النشاط واضطراب طيف التوحد. يصف الإصدار الخامس من الدليل التشخيصي والإحصائي للاضطرابات العقلية التوحد بأنه حالة تتميز بالقيود في التواصل الاجتماعي بالإضافة إلى أنماط السلوك المقيدة والمتكررة. في حين أن الاندفاع وفرط النشاط وقلة التركيز علامات على اضطراب نقص الانتباه وفرط الحركة. يعاني الأولاد من ذلك بشكل متكرر أكثر من الفتيات.الهدف: بحثت هذه االدراسة عن العوامل المحتملة التي تعرض الأطفال لخطر التوحد واضطراب نقص الانتباه وفرط الحركةكما بحثنا في العلاقة بين اضطرابات النمو العصبي لدى الأطفال وعامل الخطر الأبوي لدى السكان العراقيين. هذه دراسة مقطعية ومقارنة مطبقة في المركز الوطني للتوحد / مجمع المدينة الطبية. تم إجراؤها على مدى أربعة أشهر من يناير إلى أبريل ٢٠٢٢ ، وشارك فيه ١٢٠ طفلاً يعانون من اضطرابات النمو العصبي و ١٢٠ شخصًا من المجموعة الضابطة. تم تحليل البيانات التي تم جمعها من الاستبيانات باستخدام SPSS 25. تم إجراء اختبار T المستقل واختبار Chi-Square للتحليل ثنائي المتغير للبيانات.من بين المتغيرات التي تم اختبارها ، كانت هناك أربعة عوامل مرتبطة بالوالدين بشكل كبير (قيمة P<٠,٠٥) مرتبطة باضطرابات النمو العصبي لدى الأطفال: التاريخ العائلي للأمراض النفسية ، والتدخين من أي من اي منالوالدين، ومضاعفات الحمل والولادة ، واستخدام البروجسترون أثناء الحمل. بالإضافة إلى عوامل الخطر هذه المرتبطة بالوالدين ، كان عمر الأب في وقت الحمل مرتبطًا بشكل كبير (قيمة P<٠,٠٥) باضطرابات النمو العصبي للأطفال.بناءً على هذهالدراسة ، فإن الأمهات اللواتي يعانين من مضاعفات الحمل والولادة ، وعمر الأب عند الحمل ، وتدخين أي نت الوالدين ، والأمهات اللائي يستخدمن البروجسترون أثناء الحمل وتاريخ العائلة من الأمراض النفسية ، كان لديهن مخاطر أعلى للإصابة باضطرابات النمو العصبي.

الكلمات المفتاحية:اضطراب طيف التوحد ، اضطراب فرط الحركة ونقص الانتباه ، اضطرابات النمو العصبي ، عوامل الخطر.

Introduction

The two neuropsychiatric conditions in children with the highest prevalence rates are Attention Deficit Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD). In the Diagnostic and Statistical Manual of Mental Disorders (DSM - 5) published by

*Corresponding author E-mail: sunsriadh@gmail.com
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fragile X syndrome, tuberous sclerosis, Down syndrome,).

The exclusion criteria were the same for the control group.

Scores

- Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, DSM-5 diagnostic criteria for ASD

Childhood disintegrative disorder, Asperger's disorder, autistic disorder (autism), and pervasive developmental disorder not otherwise specified are all included in the DSM-5 category known as ASD.

- Childhood Autism Rating Scale, Second Edition (CARS-2)

Is a popular behavior-observation instrument that was developed more than 34 years ago and has since been adopted in a wide variety of contexts for assessing the presence and severity of autism symptomatology in both children and adolescents. It provides a score between 1 and 4 to determine the severity of autistic behaviors in 14 functional areas. In order to divide patients into 3 stages, the grades are added to get an overall score:

- Severe autism score between (37 and 60).
- Mild to moderate autism score between (30 and 36.5).
- Absences of ASD score (less than 30).

Methods

Study design

A cross sectional and comparative study applied in The National Center for Autism/Medical City Complex during four months from the first of January until the 30thof April 2022.

The local Research Ethics Committee gave its approval to all study methods. After the nature of the procedures had been clearly described, participants' parents verbally gave their approval. The interview with the parents was face to face, with the help of a specialist physician to diagnose the disease correctly. Parents answered a variety of closed- and open-ended questions about their medical history, including ones about difficulties during and after pregnancy, labor, and delivery.

Statistical analyses

The data was analyzed using Statistical Package for the Social Sciences (SPSS) software version 25. Descriptive statistics (means, standard deviation, frequencies and percentages) were conducted for all study items. Pearson Chi-Square or Fisher's Exact Tests were used to measure the associations between the potential risk factors (parent-related) and NDDs (ASD/ ADHD). Independent T-test was used to measure the difference in the

the American Psychiatric Association, these these disorders are classified as Neurodevelopment Disorders (NDDs). Autism spectrum disorder is a complicated neurodevelopment disorder that is characterized by behavioral and psychological problems in children. These children' limited capacity for adaptation causes them to feel upset when their environment changes. Early childhood is characterized by the symptoms, which impair daily functioning. Language difficulties, intellectual deficits, and seizures founder more commonly in individuals with ASD than those in the general population[(1)].ASD affects more than 5 million people in the US, with a prevalent incidence of 1.7% in children.

Attention Deficit Hyperactivity Disorder is a common neurodevelopment disorder that is characterized by a pattern of impaired sustained attention and increased impulsivity or hyperactivity[(2)]. Additional symptoms include disorganization, emotional control issues, a hot temper, and emotional liability. There are also a few cognitive function problems[(3)]. The frequency of ADHD in children is estimated to be 5% worldwide [(4)].

Autism's cause is not well understood. ASD is a complex disorder, and its occurrence is thought to be influenced by both genetic and environmental factors. According to a recent study, genetic variables could account for between 35% and 40 % of autism cases[(5)].Other factors, such as environmental elements that affect a baby before, during, and after birthare likely to account for the remaining 60% to 65%[(6)].

The study aims to identify parental risk factors and associated with neurodevelopment disorders (ASD and ADHD) in Iraqi children.

The sample composed of 240 child and adolescents who were divided into two groups as follows:

1. There were 120 child and adolescents in the initial group already diagnosed with ASD or ADHD according to the DSM-5 diagnostic criteria and Childhood Autism Rating Scale (CARS) for ASD, in The National Center for Autism/Medical City Complex.
2. The second group (control) was made of 120 child and adolescents.

Inclusion criteria

Children who both fulfilled the DSM-5 criteria for ASD and had a CARS score below 30 were enrolled in the study's initial group.

The healthy children were the controls in the second group.

Exclusion criteria

Exclusion criteria: recognized neurogenetic conditions (*e.g.:*

education and more than three-quarters of them were housewives. More than 67.5% of fathers had secondary education and more than 60% were self-employed. The average age of all participants' mothers at conception was 29 (±6.3) years and the average age of their fathers at conception was 35 (±6.4) years (Table 1).

provenance of child behavioral disorders according to parent age at conception. P-value of less than 0.05 was considered statistically significant.

Results

Approximately three-quarters of children's mothers had primary or secondary

Table 1. The socio-demographic characteristics of both patient and control groups and their parents

Characteristics	Subcategories	Patient group		Control group	
		N	%	N	%
Education level of child mothers	Illiterate	9	7.5	7	5.8
	Primary	21	17.5	15	12.5
	Secondary	72	60.0	74	61.7
	College	18	15.0	24	20
Education level of child fathers	Illiterate	2	1.7	5	4.2
	Primary	13	10.8	5	4.2
	Secondary	81	67.5	62	51.7
	College	24	20.0	48	40
Child mother occupations	Governmental employee	23	19.2	9	7.5
	Housewife	89	74.2	104	86.7
	Self-employed	8	6.7	7	5.8
Child father occupations	Governmental employee	47	39.2	42	35.0
	Retired	1	.8		
	Self-employed	72	60	78	65.0
Residence location	Urban	115	95.8	115	95.8
	Rural	5	4.2	5	4.2
Parent age at conception (years)	N	Minimum	Maximum	Mean	Std. Deviation
Mother age	240	18.00	50.00	29.05	6.26
Father age	240	19.00	51.00	35.13	6.36

Approximately 40% of patient group had family history of psychiatric illness and 28.3% of their parents were smokers (Table 2).

More than two-thirds (68%) of the mothers of children with NDDs have used progesterone during pregnancy and 36.7% of them had pregnancy or labor complications.

Table2. The potential risk factors for Autism Spectrum and Attention Deficit Hyperactivity Disorders for patient group

Parent-related Risk factor	N	%
Mother used Progesterone during pregnancy	81	68.1
Mom had pregnancy or labor complications	44	36.7
Family history of Psychiatric illness	49	40.8
Any smoking parent	34	28.3
Mom had bleeding during pregnancy	16	13.3
Parents are relatives	11	9.1
Father's Psychiatric Illness	7	5.8
Mother's Psychiatric Illness	6	5.0

Only small percentages of patient mothers had chronic disease(s) and were taking chronic medication(s) during pregnancy. The majority of patient mothers (89.2%) were between 20 and 40 years at the time of conception while 63.3% of patient fathers where between 30 and 40 years at the time of conception (Table 3).

Table 3. Parent characteristics at conception or during pregnancy

	Subcategories	N	%
Used medications	Paracetamol	9	7.5
	SSRI	2	1.7
	Depakine (valproic acid)	2	1.7
	Insulin	4	3.3
	Antihypertensive	7	5.8
	Thyroxine	2	1.7
Mother's chronic diseases	Hypertension	3	2.5
	Polycystic ovary syndrome	5	4.2
	Diabetes mellitus (DM)	1	.8
	Hypothyroidism	1	.8
Father's age at conception (years)	<30	22	18.3
	30-40	76	63.3
	40-50	17	14.2
	>50	5	4.2
Mother's age at conception (years)	<20	6	5.0
	20-30	56	46.7
	30-40	51	42.5
	40-50	7	5.8

SSRI=selective serotonin reuptake inhibitor. *

According to the Pearson Chi-Square/ Fisher's Exact Tests, four parent-related factors were significantly (*P*-value < 0.05) associated with NDDs: Family history of psychiatric illness, smoking of any parent, pregnancy and labor complications, used Progesterone during pregnancy.

In other words, children with NDDs had higher percentage in these factors (family history of psychiatric illness, smoking of any parent, mothers with pregnancy and labor complications, those who used Progesterone during pregnancy) compared to control children (Table 4).

Table 4. The associations between the potential parent-related risk factors and child neurodevelopment disorders (ASD/ADHD)

Risk factors			Groups		*P-value*
			Patient	Control	
Father's Psychiatric Illness	No	Count	113	119	.066
		%	48.7%	51.3%	
	Yes	Count	7	1	
		%	87.5%	12.5%	
Mother's Psychiatric Illness	No	Count	114	118	.281
		%	49.1%	50.9%	
	Yes	Count	6	2	
		%	75.0%	25.0%	
Family History of Psychiatric Illness	No	Count	71	117	.000*
		%	37.8%	62.2%	
	Yes	Count	49	3	
		%	94.2%	5.8%	
Smoking of any Parent	No	Count	86	104	.004*
		%	45.3%	54.7%	
	Yes	Count	34	16	
		%	68.0%	32.0%	
		%	51.2%	48.8%	

*Significant according to Pearson Chi-Square or Fisher's Exact Test.

Continued table 4 .

Risk factors			Groups		*P-value*
			Patient	**Control**	
Mothers with Pregnancy & Labor Complications	No	Count	76	117	.000*
		%	39.4%	60.6%	
	Yes	Count	44	3	
		%	93.6%	6.4%	
Mothers used Progesterone during Pregnancy	No	Count	39	113	000*
		%	25.7%	74.3%	
	Yes	Count	81	7	
		%	92.0%	8.0%	

*Significant according to Pearson Chi-Square or Fisher's Exact Test.

In addition to the above significant parent-related risk factors, the age of child parents at conception (fertilization) time were significantly (*P*-value < 0.05) associated with NDDs of children (according to Independent T-test). In other words, elder age of parents was significantly associated with child NDDs (ASD and ADHD) (Table 5).

Table 5. The difference in the provenance of child behavioral disorders according to parent age at conception

Parent age at conception	Groups	N	Mean	Std. Deviation	*P-value*
Mother age at conception	Patient	120	29.82	6.56	.056
	Control	120	28.28	5.89	
Father age at conception	Patient	120	36.19	6.63	.009*
	Control	120	34.06	5.91	

*Significant (P-value < 0.05) according to Independent T-test

Discussion

This case control study was conducted to determine the prenatal and familial factors related to ASD and ADHD in Iraqi individuals.

The results of the current investigation support earlier findings about the paternal age at delivery. It is essentially impossible in a research of this size to fully control for mother and paternal age at birth due to their strong correlation; only extremely large studies can achieve this[7].

When it comes to reproductive issues, paternal age has an impact on the health and development of the kid and is just as important as mother age [8].

It is uncertain what biological processes underlie this association. According to Reichenberg al[9] , the association between paternal age and autism may result from imprinted genes, spontaneous de novo mutations that increase with spermatagonia age, or confounding by sociocultural environmental factors[9].

The ages of the mother and father at birth are definitely related[10]and many of the studies included did not take into account the mother's age or the father's age. The vulnerability to autism may be influenced by the advanced ages of both parents, or perhaps only the maternal or paternal ages are etiologically significant. There is proof that father age may be more significant. Three studies found only a significant association for paternal age at birth [19,11,12], and one study found only a significant association for maternal age in the four studies that adjusted for the age of the co-parent. In the current sample did not reveal any potential effects of maternal age variables on the prevalence of NDDs.

Risk factor of autism in this study other drugs in this study did not show potential effects on NDDs. However , In the study conducted by[13,14], they found that exposure to valproic acid (VPA) during pregnancy was associated with an increased risk of NDDs. Also there is relationship between pregnant women taking antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and the onset of ASD has been suggested. Serotonin plays a role in fetal and postnatal brain development [15].

Exposure to cigarette smoking was not considered an increased risk factor of autism in this study.

Valproic acid (VPA) and selective serotonin reuptake inhibitors (SSRIs) did not reveal any possible effects on NDDs in this investigation. However, they discovered that valproic acid consumption during pregnancy was linked to a higher incidence of NDDs in the study done by[13,14] . Additionally, a link between the start of ASD and pregnant women taking antidepressants like SSRIs has been hypothesized. The development of the embryonic and postnatal brain is influenced by serotonin [15].

Exposure to tobacco use (passive smoking) was reported in 28.3% of the prenatal variables noted in this research. Retrospective epidemiological research have found that a disproportionately high number of mothers of children with ASD were exposed to smoke during pregnancy. As a result, other toxic chemicals and maternal smoking were both taken into account as potential maternal confounding factors [6]. According to some researchers, mother smoking during pregnancy may have potential effects on the reproductive cells' lineage, in addition to being connected to an increased risk of spontaneous abortions, premature birth, and low birth weight. The conclusions on its relationship to ASD are still debatable[16].

In their investigation, Zhang et al. discovered a link between maternal second-hand smoking during pregnancy and a higher incidence of autism. The authors argued that a number of substances, including metals and polycyclic aromatic hydrocarbons, which could cause fetal hypoxia and affect brain development, were present in second-hand smoke and had negative health impacts[16][17].

The current study shows a significant relationship between the use of progesterone and NDD, prenatal progestin exposure is a strong risk factor for autism-like behavior[18]Epidemiological studies have demonstrated that sex hormones may contribute to the development of autism and that hormone imbalances in pregnant women are a substantial potential risk factor for autism in their kids. This includes eating seafood contaminated with progesterone, taking progesterone pills, and using progesterone to prevent abortion[17].Progesterone has been shown to modify neurogenic responses and impair the development of cognitive responses by down-regulating the expression of estrogen receptor beta ERβ. It has been discovered that the expressions of ERβ and the estrogen receptor co-factors were significantly suppressed in the brains of autistic patients[19]. As a result, it is hypothesized that prenatal exposure to synthetic progesterone can cause autism-like behaviors in kids by suppressing ERβ. Levonorgestrel exposure during pregnancy caused autistic symptoms in offspring and suppressed ERβ expression in the brain, according to an in vivo rat model exposed to progesterone. Additionally, some in vivo studies demonstrated that ERβ deletion mice manifested clear signs of anxiety, cognitive impairments, and depressive behavior[20]. Since it has been discovered that ERβ suppression causes autistic behavior, estrogen receptor agonists and/or ERβ overexpression may aid to ameliorate autistic behavior. Resveratrol, a substance that activates the ERβ, was found to be effective in treating autism-like behaviors carried on by prenatal progesterone exposure[18] . Pre-term birth and a mother's history of abortion are typically linked to the use of progestin to prevent threatened abortions [21][22], and birth asphyxia is typically directly linked to brain damage from the hypoxic condition[23].

But it is important to be aware of some limitations. Birth history risk factors and associated outcomes can be significantly impacted by differences in the quality of treatment offered by hospitals, obstetricians, and mothers' lifestyles, as well as by the existence of multiple risk factors. We were unable to investigate some unusual conditions due to the small sample size. Future research is required to better understand the causes of autism and ADHD in Iraq utilizing standardized diagnostic criteria, genetics and how they interact with environmental variables, and global comparisons of risk factors.

Conclusion

Based on this case control study, mothers with pregnancy & labor complications, paternal age at conception, smoking of any parent, mothers used progesterone during pregnancy and family history of psychiatric illness, had higher risk of NDDs, suggesting that the individual and social harmful effects of these disorders can be prevented by controlling the associated factors before or immediately after birth.

In summary, further rigorous research, taking into consideration these factors, is needed to assist in early detection, prevention and subsequent intervention targeting ASD and ADHD.

Conflict of interest

The authors declare no conflict of interest.

Funding

No funding was received for conducting this study.

Ethics Statements

Official administrative approvals were obtained from The National Center for Autism/Medical City Complex (who were provided with detailed information regarding the study aim and methodology) and the Children Welfare Teaching Hospital/ Medical City complex prior to start of the study. All participants enrolled in this study received an adequate explanation of the purpose of the current study, and their verbal informed consent was obtained after explaining and clarifying the objective of the study.

Author Contribution

Shumoos Riadh M. Shafeea participated in collecting the sample, interviewing with parents, analyzing data, writing and reviewing the manuscript. Zinah M. Anwer participated in the study designing, selecting the scale used in the study, and reviewing the manuscript. Both authors have read and approved the final version of the manuscript.

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