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Neonatal Risk Factors for ASD and ADHD and Therapeutic Regimens for their Management in Children and Adolescents

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Abstract:

Background: Attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders (ASD) are both neurodevelopmental disorders that affect children early in life. Both conditions have a complicated origin.

Objectives: The aim of this study is to evaluate the neonatal complications linked with ASD and ADHD and to outline the utilization of psychotropic medications in the management of children and adolescents with ASD.

Methods: This study was conducted from January to April 2022 in the National Center for Autism/Medical City Complex in Baghdad. It involved 120 children with neurodevelopmental disorders and 120 controls participants. A questionnaire was used to collect the data, which was then analyzed using SPSS 25.

Results: There are five perinatal factors that have significant associations with child behavioral disorders, as indicated by a P-value of less than of 0.05. These factors are: Low birth weight (LBW), newborn complications, preterm-birth, being the last child and children delivered via a caesarean section. Additionally, the types of behavioral disorders have significant associations with the use of psychotropic medications. Around 50% of children with both ASD and ADHD, as well as children with ADHD alone, have used psychotropic medications. By comparison, only about 27% of children with ASD have used these medications.

Conclusions: Neonatal risk factors may be linked to neurodevelopmental disorders. Medications are used to manage ASD and ADHD in children and youth.

Key words: Autism Spectrum Disorder; Attention Deficit Hyperactivity Disorder; Neurodevelopment Disorders; Risk factors; psychotropic medications.

Introduction:

Two neurodevelopmental disorders (NDDs) with a high prevalence and severity are attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). Deficits in social interaction and communication, as well as stereotyped, repetitive, and constrained patterns of behavior, interests, and activities, are characteristics of ASD. Inattention and hyperactive/impulsive symptoms are hallmarks of ADHD (1).

ASD and ADHD were for a while evaluated separately since the DSM-IV-TR diagnostic criteria did not permit the diagnosis of ASD and ADHD in the same instance. Recent research has shown that autistic symptoms frequently co-occur with ADHD symptoms, and that there are clinical, genetic, and neuropsychological overlaps between autism and ADHD. Due to the elimination of autism from the diagnosis of ADHD, ASD and ADHD were both defined under the section of Neurodevelopmental Disorders in DSM- 5(2).

There is no known cause or mechanism for ASD. Environmental factors may combine with genetic factors to increase risk. It is thought that the mechanism underlying the etiology of ASD is most likely polygenic and potentially epistatic(3).

In addition to various non-pharmacological approaches, the treatment for ASD is frequently multimodal and may involve early intensive behavior therapy (applied behavior analysis), speech therapy, occupational and physical therapy, social skills training, special education, and vocational training(4).

There are currently no drugs licensed for the care of ASD's core symptoms. Risperidone and aripiprazole were approved by the US Food and Drug Administration (FDA) for use in patients with ASD in 2006 and 2009, respectively. Both medicines are used to treat irritation and aggression. Other off-label drugs have been investigated for their use in

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treating symptoms and co-occurring problems like abnormal social behavior, hyperactivity, repetitive behaviors, cognition, and insomnia that are typical in people with ASD(5).

Cases and Methods

Study design

A case-control study conducted in The National Center for Autism/ Medical City Complex, Baghdad over a period of four months: First of January to 30th of April 2022. All study procedures were approved by the local Research Ethics Committee. Verbal consent from parents or legal guardians of participants was obtained after the nature of the procedures had been fully explained. Parents completed a medical history questionnaire with a combination of closed and open-ended questions about the type of delivery, neonatal complication, and the type of treatment the patients received.

The study included 240 children and adolescents who were classified into two Groups:

Group 1 (cases): 120 children and adolescents who were already diagnosed with ASD or ADHD according to the DSM-5 diagnostic criteria and childhood autism rating scale (CARS) for ASD, while the diagnosis of ADHD depends on the physician's diagnosis according to the symptoms. This group was recruited from the National Center for Autism in the Medical City Complex. Baghdad. This group was subdivided into three subgroups, those with ASD (52), ADHD (28), and those with both ASD and ADHD (40).

Group 2 (controls): 120 children and adolescents, who were visiting the out-patient clinics of the Children's Welfare Teaching Hospital/ Medical City complex and were selected randomly for this group.

Inclusion criteria

- Children who fulfilled the DSM-5 criteria for ASD and whose CARS score was below 30 were enrolled in group 1.

-Children in the second (control) group had normal intelligence, normal development, and no mental illnesses.

The children in both groups were at least two years old. This was based on the observation that ASD is very certain to be present by the age of three years. For both groups, the age range was 2 to 17 years.

Exclusion criteria: Patients who had other already diagnosed neurogenetic conditions (e.g. epilepsy, brain tumor, or Down's syndrome).

Scores

DSM-5 diagnostic criteria for ASD

The American Psychiatric Association developed a list of mental disorders along with their appropriate diagnostic criteria. Because a comprehensive description of the underlying pathological processes for the majority of mental disorders is not possible, it is important to emphasize that the current diagnostic criteria are the best available description of how mental disorders are expressed and can be recognized by trained clinicians. The new DSM-V in 2013 incorporated childhood disintegrative disorders, Asperger syndrome, pervasive developmental disorders (PDD), and autism under the umbrella term "ASD" and provided new diagnostic criteria for ASD(6).

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

It is a well-known behavior-observation tool that was created more than 34 years ago and has since been implemented in a wide range of contexts for determining whether autistic symptomatology is present and how severe it is in both children and adolescents. Each of the 15 items is rated on a seven-point scale (1, 1.5, 2...4) and a total score is determined by summing the ratings on all 15 items. CARS total scores range from 30-60(this range means that child diagnosis with ASD) so children are divided into:

- Severely autistic, score is between (37 and 60),
- Mildly to moderately autistic, score is between (30 and 36.5),
- Absences of ASD, score (less than 30).(7)

Ethical consideration

This study was approved by the Scientific Committee of the College of Pharmacy/ University of Baghdad.

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) prior to commencement of the study. All participants' caregivers enrolled in this study received and adequate explanation of the purpose of the current study and their verbal informed consents were obtained after explaining and clarifying the objective of the study.

Statistical analyses

Data was analyzed using the Statistical Package for the Social Sciences (SPSS) software version 25. Descriptive statistics (means, standard deviations, frequencies and percentages) were conducted for all study variables. The Pearson Chi-Square or Fisher's Exact Tests were used to measure the associations between the potential risk factors and NDDs (ASD/ ADHD). P-value of less than 0.05 was considered statistically significant. GraphPad Prism 7 was used to create figures to describe the categories of patients with behavioral disorders and the severity of ASD, ADHD and their combination.

Results

More than three-quarters of the participating children were between three and 12 years old. The majority of the participants were males. Seventy percent of the cases and 40% of the controls were delivered through cesarean section (Table 1).

Table 1: Distribution of the cases and controls by age, gender and mode of delivery

		Cases		Controls	
Variables	Categories	N	%	N	%
Age group (years)	< 3	20	16.7	10	8.3
	3-5.9	51	42.5	42	35.0
	6-11.9	41	34.2	64	53.3
	12-17.9	8	6.7	4	3.3
Gender	Male	98	81.7	64	53.3
	Female	22	18.3	56	46.7
Mode of delivery	Normal vaginal	36	30.0	72	60.0
	Caesarian section	84	70.0	48	40.0
Total		120	100.0	120	100.0

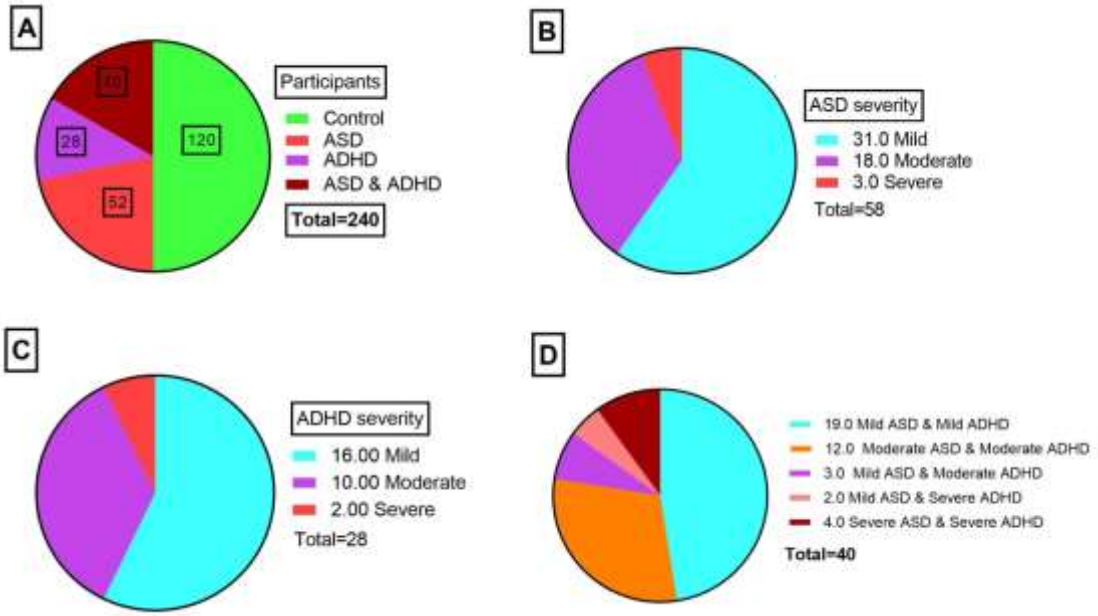

Figure 1: The categories of patients with behavioral disorders and the severity of ASD, ADHD and their combination
A: classification of all participants (control and patient groups).
B: The classification of children with ASD according to the disorder severity.
C: The classification of children with ADHD according to the disorder severity.
D: The classification of children with both ASD and ADHD according to severity of each disorder.

The cases had also experienced neonatal problems including pre- or post-term births (13.3%), LBW (10.8%) and other complications (11.3%). Approximately 42% of the cases had both communication and behavioral problems (Table 2)

Table 2: Neonatal risk factors for ASD and ADHA

Neonatal risk factors		No.	%
Pre- or post-term births		32	13.3
Low birth weight		26	10.8
Neonatal complications***		27	11.3
Head trauma		6	5.0
Birth order	First	28	23.3
	Between first and last	47	39.2
	Last	45	37.5
Symptom	Communication Problem	37	30.8
	Behavioral Problem	28	23.3
	Both	50	41.7
	School problems*	5	4.2

* School problems: Phobia, learning problem, excessive worry, difficulty with social interaction.
** One patient might have more than one risk factor.
***Neonatal complications (asphyxia, severe jaundice, severe infection, meconium aspiration).

Five perinatal complications/factors were significantly associated with child behavioral disorders: LBW, neonatal complications, preterm-birth, being the last child and children delivered via caesarean section (P-value < 0.05) (Table 3).

Table 3: The associations between the neonatal-related complications/factors and NDDs (ASD/ADHD)

Neonatal complications	Groups		P-value	
	Cases	Controls		
	No. (%)	No. (%)		
Low birth weight (2.5kg)	No	99 (82.5)	115 (95.8)	0.002*
	Yes	21 (17.5)	5 (4.2)	
Neonatal complications (asphyxia, severe jaundice, severe infection, meconium aspiration)	No	101 (84.2)	112 (93.3)	0.041*
	Yes	19 (15.8)	8 (6.7)	
Preterm-birth	No	103 (85.8)	114 (95.0)	0.028*
	Yes	17 (14.2)	6 (5.0)	
Post-term birth	No	115 (95.8)	116 (96.7)	0.734
	Yes	5 (4.2)	4 (3.3)	
Birth order	First child	28 (23.3)	29 (24.2)	0.028*
	In between	47 (39.2)	64 (53.3)	
	Last child	45 (37.5)	27 (22.5)	
Type of Delivery	Normal	36 (30.0)	72 (60.0)	0.000*
	C/S	84 (70.0)	48 (40.0)	

The cases received five main categories of therapeutic regimens: Behavioral and tonic treatments (54.2%), behavioral and psychotropic medication(s) (24.2%), behavioral and clonidine (13.3%), behavioral treatment only (13.3%) or a combination of behavioral, psychotropic and clonidine (2.5%). Forty percent of the cases received one or more psychotropic medications (Table 4).

Table 4: The treatments received by the children with behavioral disorder(s) (ASD/ADHD)

Received Treatment		N	%
Behavioral + Tonic Treatments		65	54.2
Behavioral and psychotropic	Behavioral treatment + Risperidone	16	13.3
	Behavioral + Methylphenidate	6	5.0
	Behavioral + Aripiprazole	2	1.7
	Behavioral + Aripiprazole + Methylphenidate	2	1.7
	Behavioral + Respiridone + Methylphenidate	1	0.8
	Behavioral + Atmoxetin	1	0.8
	Behavioral + Fluoxetine	1	0.8
Behavioral treatment + Clonidine		16	13.3
Behavioral Treatment only		7	6.7
Combination Therapy	Behavioral + Risperidone + Clonidine	2	1.7
	Behavioral + Aripiprazole + Clonidine	1	0.8
Number of used psychotropic medications			
0		72	60.0
1		42	35.0
2		6	5.0
	Total	120	100.0

The types of behavioral disorder had a significant association with the use of psychotropic medications (P-value < 0.05). Half of the children with ADHD or with both ASD and ADHD had used psychotropic medications compared to about 27% of the children with ASD only who used psychotropic medications (Table 5).

Table 5: The association between the types of behavioral disorder and use of psychotropic medications

Type of Disorder	Psychotropic medications		P-value
	No	Yes	
	No. (%)	No. (%)	
ASD	38 (73.1)	14 (26.9)	0.038*
ADHD	14 (50.0)	14 (50.0)	
Both ASD & ADHD	20 (50.0)	20 (50.0)	

Discussion

The male predominance in the current study is consistent with epidemiological findings in other Asian countries(8). Gender is one of the strongest risk factors for developing ASD with a male prevalence of 3 to 4 folds higher than females. In the absence of intellectual disability, this ratio increases further to 7:1(9). Baron-Cohen et al(10) has proposed the "extreme male brain" theory to explain the significant gender differential in ASD incidence. This theory suggests that excess prenatal androgen exposure contributes to the development of autistic traits in offspring by amplifying traits thought to be more typical of males, such as systemization, while diminishing traits being commonly associated with the femininity, such as empathy(9). Steroid hormones have long been thought to exert profound effects on the sexual dimorphism of the brain; however, the exact mechanism has yet to be fully understood(11).

The World Health Organization (WHO) defines low birth weight as a weight at birth being less than 2500 g (5.5 lb). The finding of the current study of a significant association of LBW with NDDs is

consistent with the results of a Swedish study which showed that the most prevalent disorders among premature/LBW children were ADHD, learning disability, developmental delay, and anxiety(12). It also showed that LBW was a significant ASD risk factor(12).

As for neonatal complications, severe neonatal jaundice when untreated is a risk factor for developing ADHD or ASD during childhood. Some studies had also reported a significant association between ASD and jaundice (13).

It has been postulated that perinatal viral infections may lead to ASD through direct infection of the CNS, infection elsewhere in the body that could trigger diseases in the CNS, or through the alteration of maternal or offspring immune response(14).

In addition, perinatal period is associated with a greater risk of brain injury due to causes such as intrapartum hypoxic ischemia, and brain injury during assisted modes of delivery. Rennie et al (16) found an association between intrapartum hypoxic ischemia and a range of childhood disabilities, including cognitive deficit.

A study conducted by Kroll et al has shown that individuals who were born very preterm had higher rates of psychiatric diagnoses compared to term-born controls(17), which was also found by the current study. Preterm births plays a vital part in the prevalence of LBW, which has been previously reported by Nawaz et al. (18). This is supported by the finding of a high prevalence of neurodevelopmental disorders and preterm births seen reported by Rennie JM et al (16) .

As for the association of birth order (last child) with a higher risk of ASD than the first child, the available yields contradictory findings. Ugur et al (19) found a significant association of the ASD group and being the first-born child in their case-control study in Turkey. A meta-analysis by Gardener et al also (20) revealed an association between autism risk and being a first-born child.

The results of the current study concur with those of a study in which later-born siblings of children with ASD or ADHD appear to be at elevated risk for the same disorder but also of being diagnosed with the other disorders. Parents' concern about having another affected child after having an autistic first child can be one explanation for this pattern. "Stoppage rule" is the term used to describe this phenomenon(19).

The finding of the current study on the association of cesarean delivery with NDDs is consistent with a previous study conducted by Zhang et al, in which cesarean births were associated with an increased risk of ASD and ADHD, irrespective of cesarean delivery modality, compared with vaginal delivery(21).There have been several explanations for this association, including oxytocin dysregulation, reduced stress during delivery, and anesthesia-induced neurotoxicity. During labor, the mother's pituitary gland secretes oxytocin, a peptide that travels through the bloodstream to the fetus. According to research by Gialloreti et al, oxytocin levels during labor have an impact on how a child develops in terms of social behavior, social interaction, and sexual behavior(22). A cesarean delivery stops the natural oxytocin production by the mother. The plasma levels of oxytocin in children born via cesarean section are known to be much lower than those born vaginally (Husarova et al)(23).

The cesarean sections disturbance of the oxytocinergic system may have an impact on the baby's brain development, which may contribute to the onset of autism. The rate of cesarean section in Iraq is substantially greater than accepted. The rates are higher in the Kurdistan Region, while the whole country has witnessed a remarkable increasing trend from 2011 to 2018. Women with higher socioeconomic status have higher cesarean section rates, while women with lower socioeconomic status have a rising trend(24).

The goal of treatment of children with ASD is to reduce symptoms that interfere with everyday activities and quality of life. Because ASD has a distinct impact on each individual, each person with ASD has different strengths, problems, and treatment needs (25).

All patients in the current study received behavioral treatment, which is consistent with results of previous studies in which behavioral therapy was the most commonly used intervention, followed by drug therapy and dietary intervention(26). Behavioral therapy is the most frequently used intervention among ASD children and is applied to almost all of them. Previous research suggests that evidence-based interventions, especially if initiated early, can alleviate problem behaviors and promote improvement in core symptoms common to children with ASD(27).

Although there is currently no cure for ASD, symptoms can improve over time with appropriate treatment and, in a small minority, be minimized to the extent that they lose their diagnosis of ASD. This study shows that in less than a quarter of the patients receiving psychotropic medications.

Psychotropic medications (aripiprazole and risperidone) are the only two FDA-approved drugs for treating autism. In the current study, risperidone was the drug most frequently used 13.3% among other medications; it is however, limited by the small number of cases. This is consistent with increasing evidence that early intervention is critical for improving long-term outcomes for patients with ASD(28). There are several studies investigating the efficacy of risperidone, which constitute a considerable body of evidence to determine its effectiveness in ASD. However, many of these studies are contradictory or inconclusive, especially regarding their efficacy in the treatment of inadequate speech and lethargy(29).

Aripiprazole appears effective for the short-term medication intervention of children and adolescents with ASD(30). In the current study, the use of aripiprazole was less than that of risperidone because it is not available in hospitals and because it is more expensive.

Clonidine was used by a similar percentage of patients who used risperidone (13.3%). Clonidine may be an effective and low-cost pharmacological option for individuals with ASD and behavioral disturbances. Two small double-blind, placebo-controlled studies and one retrospective open-label study have examined clonidine for the treatment of hyperactivity and impulsivity in children and adolescents with ASD; both studies found clonidine to be at least modestly effective for symptoms of hyperactivity (31,32). Some of the studies found it to be helpful for other symptoms as well, such as social relationships, sensory responses, irritability, sleep, and aggression.

Despite not being approved by the FDA, clinicians use a variety of off-label treatments to treat ASD-related conditions, including antidepressants, antipsychotics, methylphenidate, and atomoxetine(33).

In the current study, psychotropic medication prevalence was compared across individuals with ASD, ADHD, and ASD with co-morbid ADHD (ASD+ADHD). It showed that both the ADHD group and children with ASD and ADHD have usually used a high number of psychotropic medications, which is consistent with the results of another study reporting that children and adolescents with ASD and ADHD use a high number of psychotropic drugs(34).

For ADHD specifically, physicians may prescribe medications to help with managing symptoms like hyperactivity, agitation, inattentiveness, etc. Medications may consist of stimulants, antidepressants, or other pharmaceuticals suited to enhancing cognition(35).

In the current study, the ASD group was the least group using psychotropic drugs. In their investigation, Rasmussen et al found that psychotropic medications use in children with ASD in Denmark seemed to follow the comorbidity such as irritability, ADHD and obsessive-compulsive disorder (OCD) and not targeting ASD itself (36). This is reassuring, considering that there is no effective treatment for ASD core symptoms and the fact that the majority of children with ASD have a comorbid psychiatric disorder. In contrast, one study showed noticeable drug use in children with ASD and no comorbid disorder, potentially indicating that medication is used to treat ASD(37).

Despite the recent advances in the pharmacotherapy of ASD, current evidence-based options for treatment remain limited. There is no evidence that any of the reviewed medications have a significant impact on social withdrawal, which is one of the characteristic symptoms of this developmental disorder.

Conclusions

A number of neonatal risk factors (LBW, newborn complications, preterm-birth, being the last child and children who were delivered via caesarean section) appear to be associated with neurodevelopmental disorders. Medications are being used for the management of children and youth with ASD and ADHD.

Author's′ declaration:

Conflicts of Interest: None.

We hereby confirm that all the Figures and Tables in the manuscript are ours.

-Authors sign on ethical consideration′s approval-Ethical Clearance: The project was approved by the local ethical committee in the University of Baghdad College of Pharmacy. According to the code number (2566.22-3-2022).

Author Contributions

Study conception & design: (Zinah M. Anwer, Zainab A. Saleem). Literature search: (Shumoos R. Mohammad). Data acquisition: (Shumoos R. Mohammad). Data analysis & interpretation: (Shumoos R. Mohammad). Manuscript preparation: (Shumoos R. Mohammad). Manuscript editing & review: (Zinah M. Anwer, Zainab A. Saleem).

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عوامل الخطر لدى حديثي الولادة لاضطراب طيف التوحد واضطراب فرط الحركة ونقص الانتباه والأنظمة العلاجية المستخدمة لتدبيرهما بين الأطفال واليافعين

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الخلاصة

خلفية البحث: يعد اضطراب نقص الانتباه وفرط النشاط (ADHD) واضطرابات طيف التوحد (ASD) من اضطرابات النمو العصبي التي تؤثر على الأطفال في وقت مبكر من الحياة. كلا الشرطين لهما أصل معقد.

الأهداف: الهدف من هذه الدراسة هو تقييم المضاعفات الوليدية المرتبطة باضطراب طيف التوحد واضطراب فرط الحركة ونقص الانتباه وتحديد الخطوط العريضة لاستخدام الأدوية ذات المؤثرات العقلية في إدارة الأطفال والمراهقين المصابين باضطراب طيف التوحد.

المرضى والمنهجية: أجريت هذه الدراسة في الفترة من كانون الثاني/يناير إلى نيسان/أبريل 2022 في المركز الوطني للتوحد/مجمع المدينة الطبية في بغداد. شارك فيها 120 طفلاً يعانون من اضطرابات النمو العصبي و120 مشاركًا من مجموعة المراقبة. وتم استخدام استبانة لجمع البيانات، ثم تم تحليلها باستخدام برنامج SPSS 25.

النتائج: هناك خمسة عوامل في الفترة المحيطة بالولادة لها ارتباطات كبيرة بالاضطرابات السلوكية لدى الطفل، كما يتضح من قيمة P أقل من 0.05. هذه العوامل هي: انخفاض الوزن عند الولادة (LBW)، ومضاعفات حديثي الولادة، والولادة المبكرة، وكون الطفل الأخير والأطفال الذين يتم ولادتهم عن طريق عملية قيصرية. بالإضافة إلى ذلك، فإن أنواع الاضطرابات السلوكية لها ارتباطات كبيرة باستخدام الأدوية النفسية. حوالي 50% من الأطفال المصابين باضطراب طيف التوحد ASD واضطراب فرط الحركة ونقص الانتباهADHD، وكذلك الأطفال الذين يعانون من اضطراب فرط الحركة ونقص الانتباه ADHDوحدهم، استخدموا أدوية نفسية. وبالمقارنة، فإن حوالي 27% فقط من الأطفال المصابين باضطراب طيف التوحدASD استخدموا هذه الأدوية.

الإستنتاجات: قد تكون عوامل الخطر عند الأطفال حديثي الولادة مرتبطة باضطرابات النمو العصبي. تُستخدم الأدوية لإدارة اضطراب طيف التوحد واضطراب فرط الحركة ونقص الانتباه لدى الأطفال والشباب.

الكلمات المفتاحية: إضطراب طيف التوحد، إضطراب فرط الحركة ونقص الإنتباه، إضطرابات النمو العصبي، عوامل الخطر، الأدوية النفسية.