

Perinatal risk factors in autistic spectrum disorder associated with EEG abnormalities

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Abstract

Background: Autism spectrum disorder (ASD) is a common complex neurodevelopmental disorder characterized by persistent deficits in social communication and interaction, restricted, repetition of behavior and interests. Furthermore, it was stated that children with ASD have high incidence of abnormal encephalography (EEG) findings even with no seizures.

Objectives: To assess the association between perinatal risk factors and autistic spectrum disorder associated with EEG abnormalities.

Methodology: ASD cases according to inclusion criteria. The study was held at the center of special needs children- Faculty of postgraduate childhood studies- Ain Shams University, over the period from beginning of April 2015 till December 2017, visiting the center of special needs twice per week, 3: 4 hours per visit. EEG abnormalities were recorded, Childhood Autism Rating Scale and Vineland Adaptive Behavior Scale were applied, it was available to meet 120 caregivers and their children to collect finally 50 cases.

Results: Regarding the incidence of ASD, there was a higher percentage of male than female, the ratio was 2.5: 1 respectively. Relation between prenatal insults and EEG changes of the patient group with autism, Left focal epileptiform activity which was found in half of the patients 68% of them with no prenatal insults and 32% with prenatal insults and this result is statistically significant $p = 0.034$.

Conclusion: There is a higher ratio of male than female presentations in ASD cases Epileptiform activities, abnormal background activities and slowing in different brain areas were observed and related to cases that exposed to perinatal insults.

Recommendations: More studies should be considered regarding pre and perinatal insults in more details and its effect on late EEG during childhood not only early infancy.

Keywords: Autism Spectrum Disorder (ASD), Electro Encephalo Graphy (EEG), Epileptiform activity (EA).

المخاطر الصحية في فترة ما حول الولادة عند المصابين بالذاتوية المصاحب له تغيرات في رسم المخ

الخلفية: اضطراب الذاتوية هو اضطراب النمو العصبي يتميز بالعجز في التفاعل الاجتماعي والتواصل ووجود سلوك مقيد ومتكرر. العديد من الاعتبارات تجعل البحوث على عوامل ما قبل ومحيط وحيثي الولادة تستحق أن تدرس. وقد كان واضحا أن رسم المخ يظهر في كثير من الأحيان بشكل مشوه في المراهقين والشباب البالغين المصابين بالذاتوية.

الأهداف: تقييم الارتباط بين عوامل الخطر في الفترة ما حول الحمل واضطراب الذاتوية المرتبط بتشوهات تخطيط كهربية الدماغ.

المنهجية: حالات الإصابة بالتوحد وفقا لمعايير الإدماج من مركز الأطفال ذوي الاحتياجات الخاصة، الدراسة تشمل 50 حالة حيث تم تسجيل تشوهات في تخطيط الدماغ، وتطبيق مقياس تصنيف التوحد في مرحلة الطفولة، وتطبيق مقياس السلوك التكيفي في فينلاندا.

النتائج: فيما يتعلق بنسبة الإصابة بالذاتوية كانت النسبة المئوية للذكور أعلى من نسبة الإناث، وكانت النسبة 2.5: 1 على التوالي. كما تم رصد علاقة بين المخاطر الصحية التي تعرضت لها الأم قبل الولادة وتغيرات تخطيط الدماغ من مجموعة المرضى المصابين بالذاتوية، وظهر اختلاف إحصائي دال فيما يتعلق بنشاط الصرع اليوري الأيسر، أيضا هناك فرق إحصائي كبير فيما يتعلق بعدم التماثل في النشاط الكهربائي خاصة ناحية اليمين في مجموعة المرضى الذين يعانون من الذاتوية ولديهم تاريخ مرضي تسبب في الحجز بالرعاية المركزة لحيثي الولادة.

الخلاصة: نسبة إصابة الذكور أعلى من الإناث في حالات الذاتوية، وقد لوحظت أنشطة بؤر صرعية، والأنشطة الخلفية غير الطبيعية والتباطؤ الكهربائي في مناطق الدماغ المختلفة، وكانت تتعلق بالحالات التي تتعرض للمخاطر الصحية قبل ومرحلة ما حول الولادة.

التوصيات: يوصى بإجراء مزيد من الدراسات التي تتعلق بالمخاطر الصحية في فترة ما حول الولادة وعلاقتها بالتخطيط الكهربائي لرسم المخ في حالات التوحد.

الكلمات المفتاحية: اضطراب طيف التوحد، تخطيط الدماغ الكهربائي، نشاط صرعي.

Introduction:

Autism Spectrum Disorder (ASD) is defined as a developmental disorder characterized by marked impairment in social interaction, communication and restrictive stereotypic patterns of behavior (American Psychiatric Association, 2000).

Numerous considerations surrounding ASD make research on pre-, peri- and neonatal factors deserve to be studied. For example, increasing evidence indicates that the prevalence of ASD has increased over the past 20 years at a rate not explained by improved detection of ASD in the population (Barbatesi et.al., 2005). This phenomenon raises the probability that environmental factors play a role (Parner et.al., 2008) and the proportion of children with a major gene defect is limited to a small proportion of ASD cases (Cohen et.al., 2005).

Studies of monozygotic twins showed that less than 70% of twin pairs are concordant for autism. This finding suggests the presence of nonheritable, prenatal, and perinatal risk factors for autism (Bristol et.al., 1996).

Aim Of The Study:

To assess the association between perinatal risk factors in autistic spectrum disorder with EEG abnormalities.

Design Of Study:

Cross sectional study which was conducted at regular working hours for ASD patients over the period from beginning of April 2015 till December 2017.

Subjects:

Patients: the study included 50 children aged from 18 months to 13 years old who were diagnosed as ASD cases according to DSM V, it was available to meet 120 caregivers and their children to collect finally 50 cases after exclusion of cases did not meet the inclusion criteria such as 12 patients with no EEG abnormalities, one child with congenital heart disease, 12 patients belonging to far governorates and it was difficult to continue follow up in Cairo governorate, 45 patients refused recent EEG performing for two main reasons: the first one that they have already conducted EEG but outside the unit of Faculty of postgraduate childhood studies which is not suitable for our study as we need special format matching the viewer of EEG recoding on computer, the second reason was refusing of sedation during EEG.

Place Of The Study:

This study was held at the center of special needs children Faculty of postgraduate childhood studies- Ain Shams University

1. Inclusion Criteria: Patients with ASD and EEG abnormalities both sex in age group from 18 months to 13 years, diagnosed according to DSM- 5
2. Exclusion Criteria:
 - a. ASD with no EEG abnormalities.
 - b. All double syndromes (Down syndrome with autism, Angleman syndrome with autism, Ehlers- Danlos syndrome with autism).
 - c. Patients with major cardiac problems.

- d. Patients with inborn errors of metabolism.

3. Ethical Aspects: Informed written consent was obtained from the care giver of the patients.

Methodology:

All patients underwent the following:

1. History taking: Full medical and psychiatric history, perinatal history and history of medications given to the patient.
2. Examination: Medical clinical examination, neurological and mental status examination
3. Vineland Adaptive Behavior Scales- Second Edition: Several studies have confirmed that the Vineland Adaptive Behavior Scales (Sparrow et.al., 2005), a well- standardized semi- structured caregiver report instrument for assessing adaptive behavior, can be used to document delays in adaptive development in individuals with autism spectrum disorders (Carter et.al., 1998) (Griffith et.al., 2010)
4. Childhood Autism Rating Scale (CARS): it is a 15 item behavioral rating scale developed to identify children with autism and to distinguish them from developed mentally handicapped children without autism so the CARS is considered a special powerful effective tool used for discrimination between autistic children and trainable mentally retarded children (Schopler et.al., 1986) (Morgan, 1988)
5. Investigations: All patients were subjected to: EEG examination where encephalographic abnormalities were detected.
6. Limitations of the study: refusal of the caregiver to perform the EEG.

Statistical Analysis:

The data were entered, coded and processed on computer using Statistical Packaged for Social Science (IBM SPSS version 22, 2013). The level $P \leq 0.05$ was considered the cut- off value for significance.

Results:

The current study was conducted on 50 patients with autistic spectrum disorder and EEG abnormalities recruited from Child psychiatry clinic of faculty of postgraduate childhood studies and center of children with special needs. In age group from 3 to 12 years with the mean of age± SD (6.0± 2.32). Gestational age less than 36 weeks and birth weight less than 2.5 kg represent only and twins were 8%. As regard the mode of delivery, NVD and CS were equal 50%, with a higher percentage of male than female (72%, 28% respectively), as shown in table (1)

Table (1) Descriptive data of the patient group with autism

	Range	Mean	±Sd
Age	3- 12	6.0	2.32
		no	%
Gestational Age	Less 36 Weeks	4	8
	More Than 36 Ws	46	92
Birth Weight	Less 2.5 Kg	4	8
	More Than 2.5Kg	46	92
Mode Of Delivery	NVD	25	50
	CS	25	50
One Of Twins		4	8
Sex	Male	36	72
	Female	14	28

Table (2) shows medical history of the patient group with autism. There were a low percentage of maternal hyperglycemia, maternal hypertension (HTN), maternal urinary tract infection (UTI) (2%, 6%, 6% respectively), however maternal thyroid and cardiac disease were 0%.

Table (2) Medical history of the patient group with autism

		Number	%
Hyperglycemia	No	49	98
	Yes	1	2
HTN	No	47	94
	Yes	3	6
UTI	No	47	94
	Yes	3	6
Thyroid Dis.	No	50	100
Cardiac Dis.	No	50	100

Table (3) shows prenatal and postnatal insults among the patient group with autism. There were a low percentage of only Prenatal, only postnatal, both prenatal and postnatal insults (20%, 16%, 14% respectively), it should be noticed that concept of insults in this study means maternal diabetes mellitus, maternal hypertension, maternal cardiac disease, maternal thyroid disease, maternal urinary tract infection, receiving treatment of chronic disease during pregnancy, vaginal bleeding, cord around the neck, premature rupture membrane, meconium aspiration syndrome, fetal distress, prematurity of the baby, low birth weight, low APGAR score, neonatal intensive care unit admission, hypoglycemia, neonatal sepsis, respiratory distress, neonatal jaundice, receiving treatment in the form of phototherapy or mechanical ventilation.

Table (3) Presence of Prenatal and postnatal concepts insult among the patient group with autism.

		no	%
Prenatal Only	No	40	80
	Yes	10	20
Postnatal Only	No	42	84
	Yes	8	16
Both Pre And Postnatal	No	43	86
	Yes	7	14

Table (4) shows relation between CARS result which represent severity of ASD and EEG changes of the patient group with autism, there was a statistical significant difference regarding the Right focal epileptiform activity, however there were no statistical significant difference regarding all other epileptiform activities.

Table (4) Relation between CARS and EEG changes of the patient group with autism

		CARS		χ^2	P Value
		Mild No (%)	Sever No (%)		
Rt Background Asymmetry	Absent	21(56.8)	16(43.2)	0.033	0.856
	Present	7(53.8)	6(46.2)		
Lt Background Asymmetry	Absent	21(53.8)	18(46.2)	0.334	0.563
	Present	7(63.6)	4(36.4)		
Right Frontal Slowing	Absent	24(57.1)	18(42.9)	0.193	0.709
	Present	4(50)	4(50)		
Left Frontal Slowing	Absent	24(55.8)	19(44.2)	0.004	0.948
	Present	4(57.1)	3(42.9)		
Right Central Slowing	Absent	27(57.4)	20(24.6)	0.665	0.415
	Present	1(33.3)	2(66.7)		

		CARS		χ^2	P Value
		Mild No (%)	Sever No (%)		
Left Central Slowing	Absent	27(56.2)	21(43.8)	0.030	0.861
	Present	1(50)	1(50)		
Right Temporal Slowing	Absent	13(61.9)	8(38.1)	0.512	0.474
	Present	15(51.7)	14(48.3)		
Left Temporal Slowing	Absent	12(50)	12(50)	0.674	0.412
	Present	16(61.5)	10(38.5)		
Right Focal Epileptiform	Absent	18(69.2)	8(30.8)	3.848	0.050*
	Present	10(41.7)	14(58.3)		
Left Focal Epileptiform	Absent	14(56)	11(44)	0.000	1.000
	Present	14(56)	11(44)		

Table (5) shows relation between prenatal insults and EEG changes of the patient group with autism, there was a statistical significant difference regarding the Left focal epileptiform activity however there were no statistical significant difference regarding all other epileptiform activities.

Table (5) Relation between prenatal insults and EEG changes of the patient group with autism.

		Prenatal Insults		χ^2	P Value
		No No (%)	Yes No(%)		
Rt Background Asymmetry	Absent	31(83.8)	6(16.2)	1.273	0.259
	Present	9(69.2)	4(30.8)		
Lt Background Asymmetry	Absent	33(84.6)	6(15.4)	2.360	0.124
	Present	7(63.6)	4(36.4)		
Right Frontal Slowing	Absent	33(78.6)	9(21.4)	0.335	0.563
	Present	7(87.5)	1(12.5)		
Left Frontal Slowing	Absent	34(79.1)	9(20.9)	0.166	0.684
	Present	6(85.7)	1(14.3)		
Right Central Slowing	Absent	37(78.7)	10(21.3)	0.798	0.372
	Present	3(100)	0		
Left Central Slowing	Absent	38(79.2)	10(20.8)	0.521	0.470
	Present	2(100)	0		
Right Temporal Slowing	Absent	17(81)	4(19)	0.021	0.886
	Present	23(79.3)	6(20.7)		
Left Temporal Slowing	Absent	20(83.3)	4(16.7)	0.321	0.571
	Present	20(76.9)	6(23.1)		
Right Focal Epileptiform	Absent	22(84.6)	4(15.4)	0.721	0.396
	Present	18(75)	6(25)		
Left Focal Epileptiform	Absent	23(92)	2(8)	4.500	0.034*
	Present	17(68)	8(32)		

Table (6) shows relation between NICU Admission and EEG changes of the patient group with autism, there was a statistical significant difference regarding the Rt Background asymmetry however there were no statistical significant difference regarding all other epileptiform activities.

Table (6) Relation between NICU Admission and EEG changes of the patient group with autism

		Nicu Admission		χ^2	P Value
		No No(%)	Yes No(%)		
Rt Background Asymmetry	Absent	32(86.5)	5(13.5)	5.973	0.015*
	Present	7(53.8)	6(46.2)		
Lt Background Asymmetry	Absent	32(82.1)	7(17.9)	1.696	0.193
	Present	7(63.6)	4(36.4)		
Right Frontal Slowing	Absent	32(76.2)	10(23.8)	0.501	0.479
	Present	7(87.5)	1(12.5)		
Left Frontal Slowing	Absent	33(76.7)	10(23.3)	0.282	0.595
	Present	6(85.7)	1(14.3)		
Right Central Slowing	Absent	37(78.7)	10(21.3)	0.239	0.625
	Present	2(66.7)	1(33.3)		

		Nicu Admission		χ^2	P Value
		No No(%)	Yes No(%)		
Left Central Slowing	Absent	38(79.2)	10(20.8)	0.952	0.329
	Present	1(50)	1(50)		
Right Temporal Slowing	Absent	18(85.7)	3(14.3)	1.256	0.262
	Present	21(72.4)	8(27.6)		
Left Temporal Slowing	Absent	18(75)	6(25)	0.242	0.623
	Present	21(80.8)	5(19.2)		
Right Focal Epileptiform	Absent	21(80.8)	5(19.2)	0.242	0.623
	Present	18(75)	6(25)		
Left Focal Epileptiform	Absent	19(76)	6(24)	0.117	0.733
	Present	20(80)	5(20)		

Discussion:

A meta- analysis conducted by Loomes et.al., 2017 fifty- four studies were analyzed and highlighted male: female ratio 3: 1 and this ratio clearly confirm the basic fact that boys are more vulnerable to ASD than girls. This result also confirms the value of research seeking for explanation of the greater male vulnerability

The study executed by Amira M Yousef et.al., 2017 which revealed that there was a significance between the EEG abnormalities and the severity of autism. Which is suggesting that the use of neurological investigation that means EEG should be considered during the evaluation of autistic subjects. In a similar way we found in our study of relation between CARS result which represent severity of ASD and EEG changes of the patient group with autism, there was a statistical significant difference regarding the right focal epileptiform activity.

In the current study, we found relation between prenatal insult and EEG changes of the patient group with ASD in the form of left focal epileptiform activity, similar result was obtained by Capal et.al., 2018 in a study was performed on 443 patients with ASD and showed that most of epileptiform discharges were focal (83%) and the majority commonly seen in the left temporal region and presence of the abnormal EEG results in the patient group of ASD suggests worse developmental and adaptive functioning, Behnam Heshmatian et.al., 2010 performed a study on 48 female mice in which pregnant mice were exposed to restraint stress twice a day for three days at the start of the last week of gestation and results of the study suggest that acute prenatal stress, which may mimic acute in human pregnancy, is a likely factor affecting seizure control in childhood temporal lobe epilepsy.

Both physical and socioemotional aspects may compromise infant neurodevelopment and Medical Trauma in the NICU could be define as the integrated and embedded cumulative early life experiences of stress, pain, and parental separation, this is why medical care that may affect short- and long- term developmental outcomes. Infants enter the NICU with their inherent and unique biologic endowment, genetic susceptibility, and experiences with the fetal environment. Genetic susceptibility alters the brain's response to stressors throughout the life span. These formative components are very important during the developing infant. While biologic and genetic features are not susceptible to modification, but the environment is a heavy influencer (D'Agata et.al., 2017). Several studies

highlighted NICU admission and its effect on CNS could be used as an explanation for the result showed in the current study about the statistical significant difference regarding the Rt Background asymmetry during studying relation between NICU Admission and EEG changes of the patient group with autism.

Conclusion:

There is a higher ratio of male than female presentations in ASD cases Epileptiform activities, abnormal background asymmetry in both right and left sides and slowing in different brain areas were observed and related to cases that exposed to pre and perinatal insults

Recommendations:

More studies should be considered regarding pre and perinatal insults in more details and its effect on late EEG during childhood not only early infancy in ASD cases

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