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RESEARCH ARTICLE

STUDY OF SOME PERINATAL AND NEONATAL RISK FACTORS FOR AUTISM.

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Abstract

Background: Autism is one of the most prevalent neurodevelopmental disorders among children with unknown cause.
Aim: This study has been conducted to determine the possible perinatal and neonatal risk factors of autism.
Method: The present study is a case control study, 50 children with autismall of them fulfilling the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM–IV-TR) recruited from the Psychiatric Clinic, Institute of Postgraduate Childhood Studies, Ain Shams University and 50 apparently healthy children of matchingage& sex recruited from different outpatient clinics as control group.
Detailed history to all children including all the suspected risk factors through well-designed questionnaire and general examination with laying stress on neurological examination were done to all children enrolled in the study. Assessment of severity of autistic symptoms was done to cases.
Results:
High paternal and maternal age≥ 35 years at child birth, breech and other abnormal presentation, caesarean delivery, Preterm baby< 37 weeks of gestation, low birth weight < 2500 gm., 1st baby in the family and neonatal hyperbilirubinemia were identified as significant risk factors of autism.
Conclusion:
Our findings support several perinatal, neonatal and paternal risk factors of autism. However, some have been associated with autism in several studies and should be considered as potential risk factors that provide small contributions to the etiology or causal pathway of autism.

Introduction:-

Autism spectrum disorder is defined by the Diagnostic Statistical Manual of Mental Disorders 5 (DSM 5) as a neurobehavioral disorder manifested by persistent deficits in social and communication interaction, deficits in developing, understanding and maintaining relationships, as well as abnormal and fixed interests and repetitive behavior **(American Psychiatric Association; 2013)**.

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Symptoms must be present at early childhood and interfere with daily function. Autism is 4–5 times more prevalent in males than in females. It is now one of the most common childhood morbidities presenting in various degrees of severity **(Tchacanas and Adesman, 2013).**

For 2012, the combined estimated prevalence of ASD among the 11 ADDM (Autism and Developmental Disabilities Monitoring) Network sites was 14.6 per 1,000 (one in 68) children aged 8 years. Estimated prevalence was significantly higher among boys aged 8 years (23.6 per 1,000) than among girls aged 8 years (5.3 per 1,000) **(Christensen, 2016).**

The prevalence of ASD among children with developmental disorders in Egypt was documented as 33.6 %**(SeifEldin et al., 2008)** and there is one child every 870 Egyptian children has autism **(Haffiz, 2007).**

Increased prevalence would suggest directing more attention towards changing environmental factors instead of continuing to focus on genetics **(Arndt et al., 2005).**

Although the etiology is unknown, the etiology is now largely considered to be multi-factorial in which the interactions of genetic, epigenetic and environmental influences play a causal role**(Landrigan, 2010).**

Studies based on concordance rates among monozygotic twins and families suggest a possible role of both genetic and environmental factors in the etiology of ASD **(Mamidala et al., 2013).**

A recent study suggests that genetic factors account for only 35–40% of the contributing elements, the remaining 60–65% are likely due to other factors, such as prenatal, perinatal, and postnatal environmental factors. Since ASDs are neurodevelopmental disorders, neonatally observed complications that are markers of events or processes that emerge early during the perinatal period may be particularly important to consider **(Froehlich-Santino et al., 2014).**

Aim of the work:-

The aim of the study is to identify parental, perinatal and neonatal risk factors that may contribute to development of autism.

Patient and method:-

This study carried out as case control study .there was 100 children enrolled in this study in the period from January 2014 to January 2015, the children were divided in two groups.

Group **A** (Cases group):consisted of fifty autistic children recruited from the Psychiatric Clinic, Institute of Postgraduate Childhood Studies, Ain Shams University.

Inclusion criteria:-

1. Children of both sex aged from 3 to 12 years.
2. Autistic disorder diagnosed according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM IV TR) criteria.

Exclusion criteria:-

1. Patients refused participating in the study.
2. Neurologic syndromes associated with autistic behavior.
3. Other pervasive developmental disorders.

Group B (control group):-

Fifty healthy children of matching age and sex from the general population recruited from different outpatient clinics as control group.

Methods:-

For inclusion in the study, an informed consent was obtained from the parents.

The children were subjected to the following:-

1. Clarification aim of the study to all parents after that a written informed consent obtained.
2. Detailed history taking including all the suspected risk factors through well-designed questionnaires
3. General examination to all children with laying stress on neurological examination.

4. Verification of diagnosis using DSM-IV-TR criteria of autism for cases. DSM-IV-TR is the diagnostic criterion for the five Pervasive Developmental Disorders (PDDs) i.e. impairment of language, social skills, and restricted stereotyped interest or activity **(American Psychiatric Association, 2000).**
5. Assessment of severity of autistic symptoms for cases using Childhood Autism Rating Scale (CARS), which rates the child on a scale from one to four in each of fifteen areas (relating to people, emotional response, imitation, body use, object use, listening response, fear or nervousness, verbal communication, non-verbal communication, activity level, and consistency of intellectual response, adaptation to change, visual response, taste, smell, touch response and general impression). Its total scores range between15-60. The severity of autistic symptoms was categorized according child's total score to mild (30 - < 33), moderate (33 - < 37) and severe (≥ 37)**(Schopler et al., 2002).**

Statistical Analysis:-
By using SPSS version 16.0, the differences in categorical variables between cases and control were compared with X2 test. Logistic regression was used to study the risk factors associated with the occurrence of autism.

Results:-

The mean age of autistic children in the present study was 6.88 ± 2.2 years; the mean age of control group in the present study was 6.56± 1.98 years with no statistically significant difference as shown in table (1).

Table 1:- Comparison between case and control group regarding personal data:

		Cases (50)		Control (50)		x2 test	P value
		No	%	No	%		
Sex	Male Female	36 14	72.0 28.0	27 23	54.0 46.0	3.48	0.062
Age (years)	Mean ±SD range	6.88±2.2 4.0-9.0		6.56±1.98 5.0-9.0		St t=0.765	0.446

Parental factors:-
There were statistically significant increase among case than control groups regarding maternal age and paternal age at birth ≥35 years old ($p < 0.05$) and a non-significant difference between both groups regarding positive consanguinity and Positive family history of psychiatric diseases ($p > 0.05$) as shown in table (2).

Table (2): Comparison between case and control group regarding maternal age at birth ≥35, paternal age at birth≥ 35, positive family historyof psychiatric diseases and positive consanguinity.

	Cases (50)	Control (50)	x2 test	P value
Maternal age at birth≥ 35 years Yes No	 11(22.0) 39(78.0)	 3(6.0) 47(94.0)	5.32	0.021*
Paternal age at birth ≥35yeras Yes No	 15(30.0) 35(70.0)	 5(10.0) 45(90.0)	6.25	0.012*
Positive family history of psychiatric diseases	3 (6.0)	1(2.0)	0,26	0,61
+ve consanguinity	6(12.0)	4(8.0)	0.444	0.505

The degree of CARS in autistic children: It was found that half of the studied patients have severe form of the disease (25 patients); while 16% of them have mild form (8 patients) and 34% of them have moderate form (17 patients) as shown in table (3).

Table (3): Distribution of the studied cases regarding CARS score

CARS score (50)	No	%
Mild form (30-<33)	8	16.0
Moderate form (33-<37)	17	34.0
Severe form ((≥ 37)	25	50.0

Perinatal (delivery conditions) risk factors:-

As regarding perinatal risk factors breech and other abnormal presentation during delivery and cesarean section deliveries were found to be statistically significant associated with increased risk for autism while other complications like (PROM, meconium stained amniotic fluid, prolonged labor, induced labor, precipitous labor, forceps or vacuum extraction, cord complications or multiple gestation) show insignificant results as shown in table (4).

Table (4): Comparison between case and control group regarding some perinatal (delivery conditions) risk factors.

	Cases (50)	Control (50)	x2 test	P value
Fetal presentation				
Normal	35(70.0)	46(92.0)	7.86	0.005*
Breech and other Abnormal presentation	15(30.0)	4(8.0)		
Type of delivery				
Cesarean section	20(40.0)	10(20.0)	4.76	0.029*
Normal	30(60.0)	40(80.0)		
Cesarean section				
Elective	16(32.0)	8(16.0)	^0.234	0.628
Emergency	4(8.0)	2(4.0)		
PROM		6(12.0)		
Yes	12(24.0)	39(78.0)	3.87	0.145
No	30(60.0)	5(10.0)		
Missing	8(16.0)			
Meconium stained amniotic fluid				
Yes	5(10.0)	4(8.0)	^1.16	0.56
No	42(84.0)	40(80.0)		
Missing	3(6.0)	6(12.0)		
Prolonged labor	10(20.0)	8(16.0)	0.271	0.603
Induced labor	11(22.0)	12(24.0)	0.056	0.812
Precipitous labor	9(18.0)	10(20.0)	0.065	0.80
Forceps or vacuum extraction	3(6.0)	2(4.0)	^0.0	1.0
Cord complications				
Yes	5(10.0)	6(12.0)	1.57	0.46
No	40(80.0)	35(70.0)		
Missing	5(10.0)	9(18.0)		
Multiple gestation				
Yes	0(0.0)	0(0.0)	-	-
No	50(100)	50(100)		

Neonatal risk factors:-

As regarding neonatal risk factors, preterm baby <37week, low birth weight<2500gm, first baby in the family and neonatal hyperbilirubinemia were found to be statistically significant risk for autism as shown in table (5).

Table (5): Comparison between case and control group regarding some neonatal risk factors.

	Cases (50)	Control (50)	x2 test	P value
Gestational age				
Preterm <37w	15(30.0)	4(8.0)	7.86	0.005*
Full term 38-41w	35(70.0)	46(92.0)		
Birth weight				
<2500gm	17(34.0)	7(14.0)	5.48	0.019*
≥2500gm	33(66.0)	43(86.0)		
Birth weight for gestational age	8(16.0)	10(20.0)		
Small for GA< 10th percentile	38(76.0)	35(75.0)	0.457	0.80
Appropriate for GA	4(8.0)	5(10.0)		

Large for GA> 90th percentile				
Birth order 1st baby 2nd or more	 38(76.0) 12(24.0)	 22(44.0) 28(56.0)	 10.67	 0.001*
Delayed crying Yes No Missing	 7(14.0) 35(70.0) 8(16.0)	 8(16.0) 38(76.0) 4(8.0)	 1.52	 0.47
+ve resuscitation Yes No Missing	 7(14.0) 30(60.0) 13(26.0)	 8(16.0) 33(66.0) 9(18.0)	 0.937	 0.63
Neonatal hypoxia Yes No	 5(10.0) 45(90.0)	 4(8.0) 46(92.0)	 ^0.0	 1.0
Neonatal respiratory complication Yes No	 6(12.0) 44(88.0)	 7(14.0) 43(86.0)	 0.088	 0.77
Birth injury or trauma Yes No	 3(6.0) 47(94.0)	 4(8.0) 46(92.0)	 ^0.154	 0.70
Congenital anomalies or birth defect Yes No	 4(8.0) 46(92.0)	 3(6.0) 47(94.0)	 ^0.154	 0.70
Neonatal sepsis Yes No	 2(4.0) 48(96.0)	 2(4.0) 48(96.0)	 ^0.0	 1.0
Neonatal fever Yes No	 1(2.0) 49(98.0)	 0(0.0) 50(100)	 ^0.0	 1.0
Neonatal seizures Yes No	 2(4.0) 48(96.0)	 1(2.0) 49(98.0)	 ^0.0	 1.0
Neonatal jaundice and admitted NICU Yes No	 15(30.0) 35(70.0)	 3(6.0) 47(94.0)	 9.76	 0.001*
Artificial feeding since birth Yes No	 5(10.0) 45(90.0)	 4(8.0) 46(92.0)	 ^0.0	 1.0

Discussion:-

Autism is a neurodevelopmental disorder in the category of pervasive developmental disorders, characterized by problems of social communication, inflexible language and behavior, and repetitive sensory-motor movements **(Tchacanas and Adesman, 2013).**

In the current study male children reported higher rate of autism than female children that reflects male to female ratio 2.5: 1 respectively.

El-Baz et al. (2011) found 82 male (82%) and 18 female (18%) which reflects male to female ratio **4.5:1** respectively. **El Sawy et al. (2011)** found 38 male (86.4%) and 6 female (13.6%) with **6.3:1** male to female ratio. In **AbdElhameed et al.(2011)** study, autistic children were 12 male (85.7%) and 2 female (14.3%) with **6:1** male to female ratio respectively.

Shu et al. (2000) said that autism is more than twice as common in boys as girls, and this ratio increases to 5:1 at the high-ability end of the autism spectrum.

Parental riskfactors:-

As regard high paternal age (≥ 35 years) at birth was a significant risk factor of autism in the current study as we found that 30% of autistic children parents were ≥35 years at the time of child birth in comparison to 10% of control group.

This agrees with **El-Baz et al., (2011)** who showed that high paternal age (≥35 years) at birth was statistically significant in cases than control group.

Also,**Guinchat and colleagues (2012)** summarized the published studies on this topic and reported that 15 of 20 studies found significant positive results regarding advanced paternal age as a risk factor for ASD.

In contrast to the current study, **El Sawy et al., (2011)** found no association between high paternal age and the risk of developing autism.

The most widely proposed mechanism explaining this association is known as "copy error" hypothesis; after puberty, spermatocytes divide every 16 days, and by the age of 35 years, approximately540 cell division should have occurred. As a result, de novo genetic mutations that result from replication errors and defective DNA repair mechanisms are believed to propagate in successive clones of spermatocytes. These mutations accumulate with advancing paternal age and help to explain how this disorder, which has a large genetic component, can be maintained in the population despite reduced reproduction in affected individuals (**Kolevzon et al., (2007)**.

As regard high maternal age (≥ 35 years) at the child birth is a significant risk factor of autism in the present study, as we found that 22% of autistic children mothers≥35 years at the child birth in comparison to 6 % of control group and the difference was statistically significant.

This agrees with **El-Baz et al., (2011)**,**AbdElhameedet al., (2011)**and **Hultman et al., (2002)** who reported a statistically significant increase risk of autism in the children with highmaternal age.

But **El sawy et al., (2011),Karmel et al., (2010) and Zhang et al., (2010)** they did not found difference between the patient and the control groups in the mother's age at birth in their sample.

As regard Positive family history of psychiatric diseases, we found insignificant result in the present study, as reported in (6%) only in the families of case group, in comparison to 1 (2%) among the controls.

In consistent with our study, **Klauck (2006)** declared that in some cases, parents and other relatives of autistic children show mild impairments in social and communicative skills.

In contrast with the current study, **El-Bazet al., (2011)** and **El Sawy et al., (2011)** found a significant results in their studies.

Delong and Nohna (2008) found that affective or emotional disorders occur more frequently than average within families of people with autism.

Muhle et al., (2007) suggested that families of individuals with autism tend to demonstrate a set of cognitive disorders that are not seen in other family groups.

As regard positive Consanguinity in parents we found it statistically insignificant, as positive consanguinity was reported in 6 autistic children (12%) in comparison to 4 children in control group (8%).

Inconsistent with the current study, **El-Baz et al.,(2011)** and**El Sawy et al., (2011)** found no significant difference between cases and control group.

Also**, Saleh et al., (2009)** in their studydid not provide any evidence of a direct link between consanguinity and autism in Saudi Arabia, also **Sasanfar et al., (2010)** found that consanguinity had no role in a study done on the Iranian population.

On the contrary, other investigatorsfound that possible parenteral consanguinity increases the likelihood of autosomal recessive diseases, autism, learning disorders and behavioral disturbances **(Datta et al., 2009).**

Perinatal (delivery conditions) risk factors for autism:-

In the present study as regard perinatal (delivery conditions) risk factors for autism, we found that:

In the current study caesarean delivery, all indications, is a significant risk factor of autism, as 40% of autistic children were delivered by this mode of delivery in comparison to 20 % of control group.

In systematic review of case–control studies **Guinchat et al. (2012)** they founda significant association between Cesarean birth and autism risk**.**

Also, a nested case–control study in Utah utilizing birth certificate data suggested a positive association between primary (i.e., no previous), but not secondary Cesarean delivery, and autism risk **(Bilder et al. 2009).**

In contrast to the current study, **El-Baz et al.,(2011) and El Sawy et al.(,2011)** found no impact of caesarean delivery on the etiology of autism although most autistic children delivered by this mode of delivery but the difference between the two groups was not statistically significant .

Kolevzon et al., (2007) disapproved that Caesarean section to be accused as a risk factor for autism, despite the obvious increase in its incidence nowadays.

Given the etiologic heterogeneity of Cesarean delivery, it is possible that only a subset of Cesarean deliveries may be related to autism risk. Cesarean delivery may be elected purely for convenience, or it may reflect underlying birth complications, including breech presentation, multiple births, fetal distress, failure to progress, and cord complications. It is possible that some of these factors may be etiologically relevant for autism **(Gardener and Lyall, 2014).**

Caesarean sections were categorized in to elective (scheduled) and emergency caesarean sections, we found insignificant difference between both groups in the present study.

In contrast to our study **Guinchat et al. (2012)** in their systematic review of case–control studies, they found a significant association between scheduled Caesarean sections and autism risk**.**

As regard Breech and other abnormal presentation during delivery we found a significant increase among cases than controls.

According to **Guinchat et al. (2012)** systematic review, breech presentation was associated with autism risk in 7 out of 17 case–control studies included.

In the meta-analysis of peri- and neonatal studies published through March 2007, abnormal presentation was associated with a 44 % increased risk of autism and breech delivery in particular with an 81 % increased risk of autism **(Gardener et al. 2011).**

But **Stein et al., 2006 and Juul-Dam et al., 2001** were in contrast with our study results as they found insignificant results between breech presentation and autism.

Breech delivery and autism share some common risk factors, including congenital malformations, prematurity, advanced maternal age, low birth weight, primiparity, and multiple births, and breech presentation is also associated with low Apgar score **(Maimburg and Vaeth, 2006).**

As regard meconium stained amniotic fluid we found it is insignificant risk factor of autism in the current study.

This result was inconsistent with the study of **Bilder et al., (2009) and Maimburg and Vaeth (2006).**

Small for gestational age $<10^{th}$ percentile is not a significant risk factor of autism in the current study.

This result is inconsistent with the study of **Dodds et al., (2011), HaglundandKallen (2011), and Karmel et al., (2010).**

This result is in contrast with the study of **Buchmayer et al., 2009, Hultman et al., 2011, and Larsson et al., 2005.**

Forceps or vacuum extraction is insignificant risk factors of autism in the current study.**Bilder et al., 2009** confirm the same result.

As regard premature rupture of membrane (PROM) we found it insignificant risk factor of autism in the current study.

Bilder et al., (2009) confirm the same result, while **Zhang et al., (2010)** show that PROM is a significant risk factor of autism.

Induced labor, precipitous labor and prolonged labor are insignificants risk factors of autism in the current study.

Induced labor, precipitous labor and prolonged labor these labor and delivery complications have been associated with an increased risk of autism in more than one study (**Gardener and Lyall, 2014).**

However, a greater number of studies failed to demonstrate these as significant risk factors, and they were not associated with autism in the meta-analysis **(Gardener et al. 2011; Guinchat et al. 2012).**

Umbilical cord complications like prolapsed cord, cord around the neck of the fetus or nuchal cord were insignificant risk factor of autism in the present study.

Inconsistent with the present study according to **Gardener et al. (2011)** meta-analysis study Umbilical cord complications at birth with autism risk show no association in13out of 14 studies included.

In contrast with our study was **zhang et al. (2010)** where Umbilical cord complications were significantly more frequent among children with autism than among the controls.

Nuchal cord may cause fetal deficiency in blood, oxygen and nutrition, which would affect fetal brain development and result in damage to the newborn central nervous system if the inadequate blood flow is severe or lasts long enough**(zhang et al.,2010).**

Neonatal risk factors:-

In the current study Prematurity is a significant risk factor of autism, as 30% of autistic children were delivered as preterm babies (<37 weeks) in comparison to 8% among the controls.

In consistent with the current study, **Rikke et al.,(2007)** demonstrate that Abnormal gestational age, including prematurity and post maturity, and LBW had been associated with an increased risk of autism.

In contrast to the current study, **El-Baz et al., (2011)** found no association between prematurity and the risk of developing autism, as 6% of autistic children were delivered as preterm babies in comparison to 6.5% among the controls.

Studies evaluating neurobehavioral outcomes following preterm birth reveal a "preterm behavioral phenotype" characterized by inattention, anxiety and social interaction difficulties, and learning difficulties **(Limperopoulos, 2009 and Kaindl et al., 2009).**

Low birth weight <2500gm is a significant risk factor of autism in the current study, as 34% of cases their weight at birth were <2500gm in comparison to 14% of control.

Inconsistent with the current study, **El-Baz et al.,(2011)** showed that 10% of autistic children were low birth weight in comparison to 3% among control group.

Also, **Guinchat et al. (2012) and Kolevzon et al. (2007)** showed in their studies a significant association between low birth weight (LBW) of <2,500g with autism.

Lampi et al. (2012) reported that LBW and VLBW increase the risk of childhood autism and PDD but not Asperger syndrome. Being small for gestational age might have different etiologies, and therefore, the reason for an increased risk of ASD among these children is unclear.

In contrast to the current study**, Bilder et al (2009), Mann et al.(2010) and Zhang et al.(2010).**

The association between ASD and LBW might be mediated by several prenatal or neonatal factors, such as maternal age and health conditions, nutrition deficits, hypoxia, and other obstetrical insults. A different explanation for the association of ASD with LBW might be a shared genetic mechanism for both conditions, as well as genetic susceptibility **(Goldenberg et al. 2008).**

History of delayed crying, neonatal hypoxia or positive resuscitation was not significant risk factors of autism in the current study.

There were many case-control studies inconsistent with the present study for example **Sten et al. (2006), Bilder et al. (2009) and Williams et al. (2008).**

El-Baz et al. 2011 found that history of positive resuscitation and hypoxia are a significant risk factor of autism.

AbdElhameed et al. 2011 found that delayed crying is a significant risk factor of autism.

In contrast with the current study were**Guinchat et al., (2012)** in their meta-analysis study as they found 12 of 25 studies included reported a significant increase risk of autism among those with markers of hypoxia.

Several investigators have hypothesized that a set of perinatal conditions that indicate prolonged or acute oxygen deprivation (hypoxia) to the fetus may be a major risk factor for neuropsychiatric disturbance **(Kolevzon et al., 2007).**

There is a hypothesis that dopaminergic activity may be increased as a result of hypoxia and that dopamine over activation may be a feature of autism **(Previc, 2007).**

Despite great variability in the results across studies, evidence exists for various markers of neonatal hypoxia as potential risk factors for autism **(Gardener and Lyall, 2014).**

As regard congenital malformations or birth defects in the present study we found statistically insignificant results between case and control group.

In the neonatal meta-analysis of data published through March 2007, a significant 80 % increased risk of autism was found among those with congenital malformations from the 11 studies included **(Gardener et al. 2011).**

Since then, six additional case–control studies examining this relationship have been published, five of which reported significant associations with relative risks in the 1.60–1.70 range **(Guinchat et al. 2012).**

Another well-conducted study in Western Australia found a twofold increased risk in adjusted analyses of autism in association with birth defects, particularly defects of the nervous system, eyes, ear, face, and neck **(Dawson et al. 2009).**

The association between birth defects and autism risk suggests early pregnancy as one potential sensitive period, as birth defects often arise due to insults in early gestation. The association may also be due to genetic factors. Whether a common etiology, either genetic or environmental, is responsible for the association between congenital malformations and autism requires further study **(Gardener and Lyall, 2014).**

As regard history of injury or trauma during birth we found statistically insignificant results in the present study.

Birth injury and trauma is a rare event and was not associated with autism risk in any of the seven studies that have examined this factor **(Guinchat et al. 2012).**

However, the lack of association in individual studies may have been due to limited power, as a meta-analysis of the effect estimates across studies revealed a potential fivefold increased risk of autism among individuals with birth injury or trauma **(Gardener et al. 2011).**

According to history of neonatal jaundice and admission in incubator the results of the present study show that neonatal jaundice is a significant risk factor of autism.

In consistent with the current study **EL-Baz et al.,(2011)** found a significant result, while **El-Sawy et al.,(2011)**found it insignificant.

Also,**Croen et al. (2005)** Ina large, well-conducted, population-based study using data from medical records found no evidence for an association with hyperbilirubinemia.

Recently **Wu et al. (2016)** in a retrospective cohort study within a large United States birth population, they found no evidence that hyperbilirubinemia or phototherapy play a role in the pathogenesis of autism.

The association between autism and hyperbilirubinemia is worthwhile for several reasons. Hyperbilirubinemia is thought to exert toxicity on the basal ganglia and cerebellum, two structural brain regions that have been identified as important in the development of autism. Also, a disparity exists concerning the management of this condition, and changes in disease management have led to less aggressive treatment. Such a trend could produce an increment of neurodevelopment squeal that may account for the increasing prevalence of autism. Finally, Causes of hyperbilirubinemia in autism require further research **(Guinchat et al., 2012).**

It is not clear whether hyperbilirubinemia represents an independent risk factor for autism or is merely correlated with other complications **(Gardener and Lyall, 2014).**

As regard artificial feeding since birth in the present study we found the difference between the two groups not statistically significant.

But **Stephen et al.,(2006)** found that children who were not breast fed or were fed infant formula without docosahexaenoic acid/arachidonic acid supplementation were significantly more likely to have autistic disorder.

A possible mechanism for these associations is immune system dysfunction. Without breast milk or infant formula supplemented with DHA/ARA, some children's immune systems could be compromised which could in theory lead to autistic disorder. Breast milk provides the infant IgA and other humoral components from the mother which is important for the immune protection of the infant. Also, use of formula with DHA/ARA supplementation could be beneficial to the infant immune system **(Yaqoob, 2004).**

As regard birth order, the first baby in family was a significant risk to develop autism in the current study.

In consistent with the current study, **Bolten et al., (1997)** found that autistic children tend to be first born more commonly than that of control.

In contrast to the current study, **El Sawy et al., (2011)** found no association between birth order and the risk of development of autism.

A birth order effect can arise from both biological (genetic) or demographic (social) causes. Irrespective of etiology, this risk may increase or decrease with birth rank so that the last-borns or first-borns, respectively, are more likely to be affected. The simplest demographic cause of an apparent birth order effect is the curtailment of reproduction after the birth of a child with a serious illness. A second demographic explanation for the birth order effect can be attributed to intense disease surveillance and curtailment within particular reproductive age-groups so that almost all incident cases occur outside that age- group **(Cheslack-Postava et al., 2011).**

Conclusion:-

- Our findings support several perinatal, neonatal and paternal risk factors of autism.
- High parental age, high maternal age, breech and other abnormal presentation and caesarean delivery were identified as significant risk factors of autism
- Preterm < 37 weeks of gestation, low birth weight < 2500 gm., 1st baby in the family and neonatal hyperbilirubinemia were identified as significant risk factors of autism.

Finally, this study show that there is no individual factor in the neonatal and perinatal periods has been consistently validated as a risk factor for autism. However, some have been associated with autism in several studies and should be considered as potential risk factors that provide small contributions to the etiology or causal pathway of autism.

Recommendations:-

- Multiple parallel scientific, epidemiologic and clinical approaches are needed to rapidly improve our understanding of autism, its origin and its prevalence.
- Future studies using larger case group from the same population. In such a replicated sample it would be ideal to have information on autism as well as environmental risk exposures for both parents and children.
- Research to document mechanism of these risk factors in developing or aggravating autism should be done.
- Health education programs about these risk factors should be done to avoid ASDs.
- Dissemination of surveillance and screening algorithm of ASDs to primary health care centers to screen all children with these risk factors at 18- and 24-month well-child doctor visits.
- Proper antenatal care and mothers' education as well as good care of mother and her baby at and after delivery may all be important tools to reduce the occurrence of autism in the future.

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