Association between Prematurity and Autistic Spectrum Disorder

A Thesis

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By

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Sara Ahmed Gaber Osman

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List of Abbreviations

Abbr.	Full-term
ADCY5	**:** Adenylate cyclase 5
ADHD	**:** Attention deficit hyperactivity disorders
ADI-R	**:** Autism Diagnostic Interview-Revised
ADOS-2	**:** Autism Diagnostic Observation Schedule-2nd edition
ADOS-T	**:** Autism Diagnostic Observation Schedule-Toddler Module
ADOS-T	**:** Diagnostic ObservationSchedule-Toddler Module
AGA	**:** Appropriate for gestational age
AGTR2	**:** Angiotensin II Receptor Type 2
aOR	**:** Adjusted odds ratio
AQ	**:** Autism Spectrum Quotient
ART	**:** Assisted reproductive technology
ASD	**:** Autism spectrum disorder
ASSQ	**:** High-functioning Autism Spectrum Screening Questionnaire
BMI	**:** Body mass index
BP	**:** Blood pressure
BPD	**:** Bronchopulmonary dysplasia
BW	**:** Birth weight
CARS-2	**:** Childhood Autism Rating Scale 2nd edition
CAST	**:** Childhood Autism Spectrum Test
CKD	**:** Chronic kidney disease
CP	**:** Cerebral palsy
CPR	**:** Cardiopulmonary resuscitation
CRH	**:** Corticotropin-releasing hormone
CSBS-DP	**:** Communication and Symbolic Behavior Scales Developmental Profile

DBC-ASA : Developmental Behaviour Checklist-Autism Screening Algorithm
DBC-ES : Developmental Behaviour Checklist-Early Screen
DBC-P : Parent/Carer version of The Developmental Behaviour Checklist
DISCO : Diagnostic Interview for Social andCommunicationDisorder
DSM : Diagnostic and Statistical Manual of Mental Disorders
EBF1 : Transcription factor COE1
EEFSEC : Eukaryotic Elongation Factor, Selenocysteine-TRNA Specific
ELBW : Extremely low birth weight
EPT : Extremely preterm
ESAT : Early Screening of Autistic Traits
fFN : Fetal fibronectin
FGR : Fetal growth restriction
FT : Full-term
GA : Gestational age
GARS : Gilliam Autism Rating Scale
GBS : Group B streptococci
HIV : Human immunodeficiency virus
HR : Hazard ratio
ICD : International Classification of Diseases
ID : Intellectual disability
IMR : Infant mortality rate
ITC : The Infant-Toddler Checklist
IVH : Intraventricular hemorrhage
LBW : Low birth weight
LEEP : A loop electrosurgical excision procedure

M-CHAT : Modified Checklistfor Autism in Toddlers
M-CHAT-R/F: Modified Checklist for Autism in Toddlers, Revised with Follow-Up
NCHS : National Center for Health Statistics
NDI : Neurodevelopmental impairment
NEC : Necrotizing enterocolitis
NICHD : National Institute of Child Health and Human Development
NICU : Neonatal intensive care unit
NRN : Neonatal Research Network
OR : Odds ratio
PDA : Patent ductus arteriosus
PMA : Postmenstrual age
POSI : Parent's Observations of Social Interactions
PPROM : Preterm premature rupture of membranes
PT : Preterm
PTB : Preterm birth
PTL : Preterm labor
RAP2C : Member of RAS Oncogene Family
RDS : Respiratory distress syndrome
ROP : Retinopathy of prematurity
RSV : Respiratory syncytial virus
SCQ : Social Communication Questionnaire
sFlt-1 : Soluble fms-like tyrosine kinase-1
SGA : Small for gestational age
SIDS : Sudden infant death syndrome
sPTB : Spontaneous preterm birth
STAT : Screening Tool for Autism in Toddlers and Young Children
SWYC : Survey of Wellbeing of Young Children
VLBW : Very low birth weight

VON : Vermont Oxford Network
VPT : Very preterm
WHO : World Health Organization
WNT4 : Wnt Family Member 4

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Abstract

Objective: *To find association between prematurity and autistic spectrum disorder.*

Methods: *This retrospective study was carried out at Autism center of psychiatric clinic of Abassia Hospital. 138 ASD children from 2-12 years old with Autistic disorder was diagnosed according to diagnostic and statistical manual of mental disorder fourth edition (DSM-IV) published by American Psychiatric Association. Through retrospective the parents of the autistic children were interviewed and asked about gestational age, low birth weight, multiple gestation, previous preterm labor pain during this pregnancy, using of antenatal steroids, prenatal infection, placental abruption, male gender and/or pregnancy induced hypertension.*

Results: *This present study showed that there was statistically significant association between prematurity and autistic spectrum disorder regarding gestational age "≤37wks (55.1%) vs. >37wks (44.9%)", gender "male (78.3%) vs. female (21.7%)", low birth weight "no (45.7%) vs. yes (54.3%). There was no statistically significant association between prematurity and autistic spectrum disorder regarding multiple gestation "no (95.7%) vs. yes (4.3%)", previous preterm labor pain during pregnancy "no" (94.9%) vs. yes (5.1%), using of antenatal steroids "no (98.6%) vs. yes (1.4%)", prenatal infection "no (97.8%) vs. yes (2.2%)" , placental abruption "no (97.1%) vs. yes (2.9%)" and pregnancy induced hypertension "no" (96.4%)) vs. yes (3.6%).*

Conclusion: *In the present study, it is found that there is a good relationship between prematurity and autistic spectrum disorder. Gestational age less than 37 weeks, male gender, low birth weight are important risk factors. Proper antenatal care is needed to decrease incidence of autistic spectrum disorder.*

Keywords: Prematurity, Autistic spectrum disorder

Introduction

Prematurity: Different degrees of prematurity are defined by gestational age (GA), which is calculated from the first day of the mother's last period, or birth weight (BW) ***(WHO, 2012).***

One classification based upon BW includes the following categories: ***(WHO, 2012)***

- Low birth weight (LBW) – BW less than 2500 g
- Very low birth weight (VLBW) – BW less than 1500 g
- Extremely low birth weight (ELBW) – BW less than 1000 g

Prematurity is also defined by GA as follows: ***(WHO, 2012)***

- Late preterm infants: GA between 34 weeks and 36 weeks and 6 days
- Very preterm (VPT) infants – GA at or below 32 weeks
- Extremely preterm (EPT) infants – GA at or below 28 weeks

Neonatal and infant mortality: ***(WHO, 2012)***

Neonatal death is defined as an infant death before 28 days of age. Early neonatal deaths occur before the first seven days from birth, and late neonatal deaths occur between 7 and 27 days of age.

Infant death is defined as a live birth that results in death within the first year of life (<365 days). The infant mortality rate (IMR) is the number of infant deaths less than one year of age (0 to 365 days of life) during a year, divided by the number of live births reported during the same year, expressed per 1000 live births.

Early signs of ASD have been studied with retrospective parental reports and the analyses of home videos of children who were later diagnosed with ASD, with prospective population screening studies of infants who scored positive on early ASD screeners and by longitudinal studies of children in "high-risk" populations for ASD, such as the young siblings of children with ASD ***(Ozonoff et al., 2017).***

Researchers document that, due to early brain plasticity, intensive early intervention programs can improve cognitive and language abilities as well as adaptive behavior in children with ASD ***(Bradshaw et al., 2015).***

Autism spectrum disorder (ASD) is a major neuro-developmental disorder characterized by persistent deficits in social interaction and communication as well as restrictive and repetitive patterns of behavior, interests, or activities ***(APA, 2013).***

A growing focus is thus given to identify prodromal and preclinical signs or indicators that are present very early in life among infants who are later diagnosed with ASD ***(Yirmiya and Charman, 2010).***

We previously reported a prevalence of 21% of ASD risk at 8 months, which decreased to 9% at 12 months, using the Autism Observation Scale for Infants, and to 8% at 18 months, using the Autism Diagnostic ObservationSchedule-Toddler Module (ADOS-T) ***(Agrawal et al., 2018).***

In addition to genetic risk factors for ASD, environmental factors also contribute to the risk of ASD. Identified environmental factors include advanced parental age, birth complications, and pregnancy-related factors such as maternal obesity, maternal diabetes, caesarian section, and perinatal exposure to Oxytocin ***(Modabbernia et al., 2017).***

Premature birth, which is the focus of the current paper, is an additional identified risk factor for ASD ***(Johnson and Marlow, 2014).***

The prevalence of ASD has been estimated as 0.6-2.46% among the general population ***(Baio et al., 2018).***

An increased prevalence of ASD risk (1.8%–41%) has been documented among children who were born preterm (PT), emphasizing the need for the early identification of ASD risk among PT cohorts. Considering the importance of repeated assessments when screening for ASD during the first years of life, the current study focuses on follow-up assessments using gold-standard measures at 24 and 36 months ***(Zwaigenbaum et al., 2018).***

Whereas the association between premature birth and ASD has been documented, there is heterogencity in the reported prevalence of ASD among children born PT, and inconsistent findings regarding the prevalence were reported ***(Agrawal et al., 2018).***

Most researchers employ parental screening report questionnaires or diagnostic interview assessment tools, whereas the use of direct observational assessments is somewhat less frequent, although recently more and more common. Among samples of PT toddlers, the rate of positive screening using parental report questionnaires ranged from 10% to 41%. These rates were significantly reduced if children with sensory-motor difficulties and/or cognitive impairments were excluded and when follow-up interviews were conducted ***(Guy et al., 2015).***

These impairments often overlap with early prodromal symptoms of ASD, which make the differential diagnosis somewhat more complicated ***(Yirmiya and Charman, 2010).***

Most researchers employ parental screening report questionnaires or diagnostic interview assessment tools, whereas the use of direct observational assessments is somewhat less frequent, although recently more and more common. Among samples of PT toddlers, the rate of positive screening using parental report questionnaires ranged from 10% to 41%. These rates were significantly reduced if children with sensory-motor difficulties and/or cognitive impairments

were excluded and when follow-up interviews were conducted ***(Guy et al., 2015).***

Among samples of adolescents born PT, the estimated prevalence rate of ASD was 7.1%, using the ADOS ***(Joseph et al., 2017).***

Few researchers examined the prevalence of ASD by the ADOS, which is a clinical observational instrument. Developmentally, among samples of young children born PT, the estimated prevalence rate of ASD ranges from 1.8% to 12.9%, using the ADOS ***(Pritchard et al., 2016).***

Researchers in multiple narrative reviews have discussed the risk factors and prevalence of ASD in the preterm population; however, there are no meta-analyses or systematic reviews ***(Mahoney et al., 2013)***.