

## Perinatal Outcomes and the Risk of Autism Spectrum Disorders-Case Control Study

Melinda Vanya<sup>1\*</sup>, Szili Karoly<sup>2</sup>, Szabina Szucs<sup>3</sup>, Agnes Vetro<sup>3</sup>, Janos Szabo<sup>2</sup> and Gyorgy Bartfai<sup>1</sup>

<sup>1</sup>Department of Obstetrics and Gynaecology, University of Szeged, Albert Szent-Gyorgyi Clinical Centre, Szeged, Hungary

<sup>2</sup>Department of Medical Genetics, University of Szeged, Albert Szent-Gyorgyi Clinical Centre, Szeged, Hungary

<sup>3</sup>Division of Child- and Adolescent Psychiatry, Department of Pediatrics, University of Szeged, Albert Szent-Gyorgyi Clinical Centre, Szeged, Hungary

### Abstract

**Introduction:** Autism spectrum disorders (ASDs) are a neurodevelopmental disorders characterized by social, communication impairments and stereotyped patterns of behaviour. Recent studies to suggest that parental age and obstetric conditions are associated with an increased risk of ASD. Although not proven as independent risk factors for ASD, precise assessments of exposures and potential confounders scarcely have been investigated.

**Methods:** The present retrospective cross-sectional study was designed to assess the effects of maternal age, medical conditions, pregnancy outcomes and prenatal exposure on the risk of ASD. A total of 43 children with ASD clinically diagnosed according to the DSM IV criteria between 2010 and 2012 were recruited. The following data were collected: clinical psychiatric data, data of cognitiv tests, obstetric history of the mother including age, medical conditions, drug use during pregnancy, ultrasonographic measurements each trimester of pregnancy and perinatal outcomes. Statistical comparisons of different parameters on the case group (n=43) and the neurologically healthy control group (n=182) were assessed.

**Results:** The average age of the case and control group were  $29.53 \pm 5.1$  years and  $29.67 \pm 8.54$ . Ultrasonographic parameters (NT:  $1.35 \pm 0.42$ ; CRL:  $53.64 \pm 11.48$ ; thorax:  $23.38 \pm 7.39$ ; length of humerus:  $13.56 \pm 7.57$ ; length of femur:  $13.76 \pm 7.1$ ) were in the normal range. Pre-existing hypertension and diabetes mellitus were more prevalent among the case group than among the healthy women  $p=0.007$ ;  $p<0.001$ . The rate of miscarriages, per vias naturales delivery and pre-eclampsia were significantly higher among the case group than among the control group ( $p=0.001$ ;  $p=0.023$ ;  $p=0.021$ ).

There was no significant difference between the two groups from the aspects of the low birth weight, caesarean section.

**Conclusion:** In contrast with recent publications, there were no significant differences in maternal age, low birth weight and pre-existing hypertension between the two groups. Our results are in accordance with those of previous studies from the aspect of the risk of diabetes mellitus, the elevated risk of miscarriages and caesarean section.

**Keywords:** Autism spectrum disorders; Preterm birth; Intrauterin growth restriction; Caeserean section; Low apgar score

**Abbreviations:** ADI: Autism Diagnostic Interview-Revised; ADOS: Autism Diagnostic Observation Schedule; ASD: Autism Spectrum Disorder; PPD: Pervasive Developmental Disorder

### Introduction

Autism are a neurodevelopmental disorders with definitive male predominance (4:1) characterized by social and communication impairments and deficits and stereotyped patterns of behavior [1]. The prevalence of autism is 5 of every 10000 children, but it have been significantly increased in the last decades [1]. Elberling et al have clearly established the predictors for pervasive developmental disorder in 10 month age infant [2]. Epidemiologic studies suggest the possible interaction of genetic component, and environmental factors in the development of ASD [3,4].

The suggested environmental factors are include E. nutritional and immune function related risk factors such as lack of vitamin D and folic acid supplementation, and metabolic syndrome [3,4]. The purpose of the study was to assess which medical co-morbidity and perinatal factors were associated with ASDs in the children.

### Methods

#### Study population

We conducted a retrospective case-control study in University of Szeged, Hungary to analyse the relationship between perinatal factors

and the risk ASD. A total of 43 children with ASD, who required psychiatric care at the Division of Child- and Adolescent Mental Health, Department of Pediatrics, between 2010-2014 and their mothers have been enrolled in the study. All children have been diagnosed with Autism Diagnostic Interview-Revised (ADI) and Autism Diagnostic Observation Schedule (ADOS) according to the DSM IV. criteria. Ultrasound measurements of the fetus and results of genetical analysis in the Department of Obstetrics and Gynaecology and Medical Genetics have been also reviewed.

The members of the control group were selected at random from among patient with no diagnosis of epilepsy or any other neuropsychiatric disorders and who delivered newborn in the same period at the Department of Obstetrics and Gynaecology. The mother's medical results and their child have been reviewed and followed up (Tables 1 and 2).

**\*Corresponding author:** Melinda Vanya, Department of Obstetrics and Gynaecology, University of Szeged, Albert Szent-Gyorgyi Clinical Centre, Szeged, Hungary, Tel: 00-36-62-54-55-23; E-mail: [vmelinda74@gmail.com](mailto:vmelinda74@gmail.com)

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	Case group	Control group	p-value
	(n=43)	(n=181)	
	n %	n %	
Mean Maternal age (years)	29.53 ± 5.08	29.66 ± 8.52	N. S.
Mean age of children at diagnosis of ASD (years)	6.19 ± 2.72	6.29 ± 5	N. S.
Gestational diabetes mellitus	2 4.65	6 3.31	<0.001*
Pre-existing hypertension	3 6.98	0 0	0.007*
Nuchal translucency at the first trimestre	1.35 ± 0.42	1.5 ± 0.7	N. S.
CRL at the first trimestre	53.64 ± 11.48	54.78 ± 9.5	N. S.
Circumference of the thorax	23.39 ± 7.4	24.0 ± 9.1	N. S.
Length of the humerus	13.56 ± 7.56	15.46 ± 3.2	N. S.
Length of the femur	13.76 ± 7.08	15.81 ± 2.9	N. S.

Table 1: Health characteristics and ultrasound measurements at the first trimester of pregnancy of the mother.

	ASD group	Non-ASD group	p-value
	(n=43)	(n=181)	
	n %	n %	
Miscarriage	4 9.3	0 0	0.001*
Caesarean section	22 51.16	64 35.36	0.029*
Vaginal delivery	21 48.83	117 64.64	0.023*
Pre-eclampsia	2 4.65	0 0	0.021*
Preterm birth	2 4.65	12 6.63	
	1 2.325		
<2500 g	1 2.325	12 6.63	N. S.
<1500 g		0 0	
Mean gestational age (weeks)	38.97 ± 2.17	38.45 ± 2.17	N.S.
Mean birth weight (grams)	2973.33 ± 960.02	3242.74 ± 582.72	0.003*
Mean birth length (cm)	51 ± 6	52 ± 3	N.S.
Umbilical cord blood pH	7.28 ± 0.87	7.18 ± 0.07	N.S.
1 minute Apgar score	8.2 ± 1.5	9.65 ± 0.4	<0.001**
5 minute Apgar score	9.6 ± 0.78	9.8 ± 0.5	<0.001**
10 minute Apgar score	10 ± 5.6	9.75 ± 0.2	<0.001**

Table 2: Description of the prenatal and perinatal characteristics in the case and control group.

## Data collection

Sociodemographic characteristics of the mother, characteristics of the child (age at the diagnosis of ASD, presence of co-morbid disorder, results of psychiatric test) have been evaluated.

The obstetrical characteristics of the mother were as follows:

The mode of delivery (vaginal delivery, vacuum extraction/forceps, elective or emergency caesarean section) history of previous miscarriages and other pregnancy complications of these patients and the existence of any extragenital and congenital disease (previous Down syndrome or ASD in the family) were recorded.

The parameters evaluated were as follows: ultrasound measurements from the first trimester of pregnancy, the mean gestational age at delivery, prematurity, postmaturity, intrauterine growth restriction, small for gestational age and congenital malformations. Parameters of the neonates including the average birth weight, mean birth length of the newborn, umbilical cord blood pH, 1-5-10- minute Apgar score analysed. Data on totals of 43 pregnancies from the case group and 182 pregnancies from the control group are included in our study.

## Statistical analysis

For comparison of the various parameters, univariate ( $\chi^2$  test and

the T-test) were used to identify factors associated with development of ASD (SPSS version 22).

## Ethics

Our retrospective study was approved by the Szeged University Ethics Committee and was in full accordance with the Declaration of Helsinki (1961) (Approval No: 145/2012, University of Szeged Ethics Committee).

## Results

43 children with PDDs were involved in our study. Data on totals of 43 pregnancies from the case group and 182 pregnancies from the control group are included in our study. The average age of children with and without ASD were 6.19 ± 2.72 years and 6.29 ± 5 years, respectively at the time of diagnosis of the disease.

The mean age of the mothers at the time of delivery was 29.53 ± 5.08 years in case group and 29.66 ± 8.52 years in the control group. Hypertension and diabetes mellitus in the past medical history were more common in the case group than in healthy women (p=0.007; p<0.001).

There were no differences in the ultrasound measurements of the fetuses in the first trimester of pregnancy (nuchal translucency (NT), crown-rump length (CRL), circumference of thorax, length of the femur

and humerus) between the foetuses of the case group and the control group.

There were miscarriages in 4 cases (9.3%) in the case group. We found these differences significant compared to the control group ( $p=0.001$ ). Caesarean sections were performed in 22 cases (51.16%) in the case group, and the caesarean section rate was 35.36% in the control group ( $p=0.029$ ). In 20 cases elective caesarean section was indicated by the maternal disease such as hypertension ( $n=3$ ), gestational diabetes mellitus ( $n=2$ ), preterm birth ( $n=2$ ), cephalo-pelvic disproportion ( $n=4$ ) and previous caesarean section in the past medical history of the mother ( $n=9$ ). In the remaining cases, the emergency sections were performed because of pre-eclampsia ( $n=2$ ). Twenty-one children were delivered via vaginal delivery in the case group and 117 children from the control group. There were no cases of vacuum extraction and forceps delivery in our study population. There were 2 pre-eclampsia cases (4.65%), and there was no pre-eclampsia among controls ( $p=0.021$ ). These two pregnancies resulted in emergency caesarean section. There were 2 preterm births (4.65%) in the case group and 12 cases in the controls (6.63%). The differences between the two groups were not significantly different. There were no cases of small for gestational age and birth defects among the children. Only one patient reported Down's syndrome in her previous pregnancy. Her previous pregnancy was terminated by medically indicated induced abortion. The mean gestational age was similar in both groups ( $38.97 \pm 2.17$  vs.  $38.45 \pm 2.17$ ). The umbilical cord pH was also significantly different between the two groups ( $p<0.001$ ). The 1-, 5- and 10-minute Apgar scores were lower in the ASD group than in the non-ASD population ( $p<0.001$ ,  $p<0.001$ ,  $p<0.001$ ).

The mean length of the newborns at birth was  $51 \pm 6$  cm among the newborns to mothers from the case group, and  $52 \pm 3$  cm from the control group. The mean birth weight was  $2973.33 \pm 960.02$  g for the newborns to mothers from the case group and  $3242.74 \pm 582.72$  g from the control group). The birth weight of the children with ASD was less than those of the children without ADS, and the difference in birth weight between the two groups was significant ( $p=0.003$ ). From the aspect of birth length of the children, there was no difference between the two groups.

## Discussion

It can be concluded that rate of caesarean section were significantly higher in the case group than in the control group [5-7].

Our results are in accord with published data. Nilsen et al. was analysed clinical data on large pregnancy cohort in 2014 as concerns the perinatal outcomes and ASD; the results suggest that the caesarean section, prenatal folic acid use, maternal smoking in the prenatal period, low birth weight and preterm birth has increased risk for the development of ASD [6]. Analogous results were found in United States: Shieve et al. was concluded that three perinatal risk factors (preterm birth, small for gestational age, caesarean section) notably contribute to ASD risk [7]. In contrast with recent studies [6-8], the rate of preterm birth was not significantly different between the two groups in our study. There were no cases of small for gestational age and birth defects among the new-born.

The diabetes mellitus were more prevalent among the case group than in the healthy women ( $p=0.007$ ). In 2009, Hjördis et al. was reported similar results from the aspect of 1 type diabetes mellitus and the risk of ASD [9].

We detected an overall previous miscarriage rate of 9.4%. The

rates of miscarriages in the control populations and in case group were significantly different ( $p=0.001$ ). A study by Kolevson et al. was reported the rate of miscarriages was also significantly higher than in the normal population [5].

Our results showed up a significant difference in birth weight ( $p=0.003$ ), but not in length of new-born ( $p=0.0861$ ). Langride was found that mean birth weight were lower among in the case group than in the normal population, but the difference was not significant.

In our research cohort, 1<sup>st</sup>, 5<sup>th</sup> and 10<sup>th</sup> minute Apgar scores were lower among our patients than among the normal population ( $p<0.001$ ,  $p<0.001$ ,  $p<0.001$ ) [10].

Langride was described that the Apgar score and umbilical cord pH did not differ between the children in the case group and those in control one [10].

Langride al. and Polo-Kantola et al. revealed that maternal hypertension associated with a higher risk of ASD [10,11]. Our results were similar from the aspect of pre-existing hypertension and the development of ASD ( $p=0.007$ ). In contrast with their findings, the rate of preeclampsia were significantly higher in the case group than in the control group in our study [10,11]. Ultrasound parameters were in the normal range in both groups. Our results suggest that were no ultrasound markers in early pregnancy to detect of autism spectrum disorders.

Limitation of our study: We did not report the maternal smoking, drug abuse and folic acid intake in the antenatal period and there were few number of epilepsy and toxoplasma infection in our study group. According to our best knowledge, this is the first study to report data in Hungary about the association the perinatal characteristics and the risk of autism spectrum disorder.

## Conclusions

We provided new data about the significant difference between the ASD and not-ASD group from the aspect of the parameters of neonates (birth weight, umbilical cord blood pH and Apgar scores ( $p=0.003$ ,  $p=0.001$ ,  $p=0.001$ )).

We report as first that the ultrasound parameters during the prenatal screening were in the normal range in both groups. Our results suggest that were no ultrasound markers in early pregnancy to detect of autism spectrum disorders.

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