Prenatal and Neonatal Factors

by Desiyani Nani
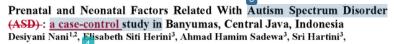
Prenatal and Neonatal Factors Related With Autism Spectrum Disorder (ASD): a case-control study in Banyumas, Central Java, Indonesia

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ABSTRACT

Introduction: Autism spectrum disorder (ASD) is a complicated mental disorder and the etiology is still unknown. Several research showed some possibilities of prenatal and neonatal factors become risk of ASD. This study investigated some prenatal factors such as maternal age, paternal smoking, history of passive smoke during pregnancy, sosio-economic status, history of antenatal care, history of complication during gestation, and parity status. History of newborn weight and history of neonatus cardiopulmonary resucitation (CPR) were also investigated in this research. The aim of this study to seek the possibilities of risk factors in prenatal and neonatal condition that could be related with autism spectrum disorder (ASD).

Method: This study used case control study in Banyumas District Area, Province of Central Java, Indonesia. It included 52 children with ASD as case group and 201 normal children as control group. Data were collected with demographic tools with question about prenatal factors and neonatal factors. Analyzed data used Chi-Square, Fisher Exact, and Regression Logistic.

Result: This study found that father with active smoking, high-income in sosio-economic status, mother with passive smoking during pregnancy, multipara mother, and history of neonatus CPR gained risk to have a children with ASD ($p=0,000$, OR: 0,256; $p=0,000$, OR: 3,23; $p=0,032$; OR:-0,490; $p=0,019$, OR: 2,15; $p=0,000$; OR:-11,760). However, another factors such as history of antenatal care, history of gestation complication and newborn weight were not related significant with ASD ($p>0,05$).

Conclusion: Father with active smoking, high income in socio-economic status, mother with passive smoking during pregnancy, multipara mother and history of neonatus CPR became risk factor of ASD.

Recomendation: A furthermore study are needed to seek the possibilities of another prenatal and postnatal factors in ASD.

Keyword : Prenatal, Neonatal, and autism spectrum disorder

INTRODUCTION

Autism belongs to a spectrum known as autism spectrum disorders (ASDs), it also includes Asperger's syndrome, childhood disintegrative disorder, and pervasive developmental disorder not otherwise specified[1]. ASD present with a range of severity and impairments in social, communication skill, behaviour and interest[2]. Additionally, most two individuals with autism also present intellectual and cognitive impairments[3,4]. There are more than 7,6 million people with ASD and make 0,3% of the global burden of disease[5]. In the other hand, a number of ASD in developing country like Indonesia is not exactly unknown and it showed by a fewer study about ASD[6].

The etiology of ASD is diverse, commonly still unknown, and seems to be the result of genetic and environmental interaction[3,2]. Some previous studies showed 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 neonatal environmental factors. Unfavorable enviromentals during pregnancy and neonatal are likely caused a brain damage. Brain damage being one of prescribed risk factors of ASD[2]. Several studies show prenatal and neonatal factors related with ASD. Those of factors are maternal age, paternal smoking, maternal smoking, complication during gestation, child's birth wieght, and hypoxia[7,8,9]. Considering the potential risk about perinatal factors, this study used a case control study to investigate the association between prenatal and neonatal factors with ASD.

PARTICIPANTS AND METHODS

Study setting and design

This case control study was carried out at community in Banyumas District, Province Central Java, Indonesia. It was conducted over a period four month from October 2017 to January 2018.

Study Population

The sample included 253 children in Banyumas Dictrict, Province of Central Java, Indonesia. Sample divided into case group and control group. Case group was composed of 52 autistic children and previously identified by psychologist in Banyumas Autism Care Project (BACP) event. Control group was composed of 201 normal children. Inclusion criteria consisted children with age between 3-18 years old and willing to be a respondent. Whereas, exclusion criteria consisted children with known neurogenetic conditions (e.g., Down Syndrome, Mental Retardation, Neurofibromatosis).

Sampling design

Sample size

Using sex differences between autism spectrum disorder within boys and girls as risk factor and to detect an odds ratio (OR) of at least 2 with a power of 80% using a 5% level of significance, the sample size was calculated to be 52 cases and 201 controls.

Sample type and selection

Consecutive cases were selected over 4 months, every weekend were allocated to visit the school of special needs children. We invite parents that have children with autism spectrum disorders that independently accepted and confirm the informed consent to permit their children became participant for this study. The location for sampling was in Research center of Faculty of Medicine, Universitas Jenderal Soedirman, Banyumas District, Central Java Province, Indonesia.

Controls were selected from normal children whose came with their parents and also visited by team at schools, till the required sample size was reached.

Measurements

This study used demography tool with questions about perinatal history. It consisted 9 questions about 1) maternal age, 2) paternal smoking, 3) history of smoking during pregnancy, 4) socio-economic status, 5) history of antenatal care, 6) history of complication during pregnancy, 7) parity status, 8) history of newborn weight, and 9) history of neonatus cardio pulmonary resucitation (CPR).

Data Collection

Data collected from parents of children ages 2-18 years old with significantly diagnosed using DSM 4 and DSM 5 by professional practitioners then grouped in case group (children with ASD) and control group (children in normally state) during four month using questionaire consist of demographic factors and risk factors for autism spectrum disorders.

Statistical Analysis

Analysis were first run to describe the data and then to describe the trends resulting from each item. Bivariat analysis used Chi-square explore relationships between variabel. This study also used logistic regression as multivariat analysis to seek the most affecting factor in ASD.

Ethical considerations

Consent was obtained from all parents (mothers/fathers) after an explanation of the study objectives was provided and anonymity of the results was assured. Approval for the study was obtained from Medical Ethical Comittee of the Faculty of Medicine, Universitas Gadjah Mada, Indonesia.

RESULTS

Table 1. Bivariat Analysis Results

		Case Group (n= 52)		Control Group (n = 201)		p	OR	CI95%	
		n	%	n	%			Min	Max
Maternal Age	<20 years	3	5,8	24	11,9	0,332	1,87	0,527	6,639
	21-30 years	29	55,8	124	61,7		ref		
	31-40 years	19	36,5	53	26,4	0,115	2,87	0,774	10,63
	>40 years	1	1,9	0	0				
Paternal Smoking	Active smoking	14	26,9	114	56,7	0,000	3,89	1,957	7,769
	Passive smoking	4	7,7	16	8	0,257	2,036	0,569	6,952
	Not smoking	34	65,4	71	35,3	ref			
History of smoking during pregnancy	Passive smoking	15	28,8	91	45,3	0,032	0,49	0,253	0,949
	Not smoking	37	71,2	110	54,7	ref			
Socio-Economic Status	>Rp 1.549.000,00	37	71,2	87	56,7	0,000	3,23	1,67	6,26
	<Rp 1.549.000,00	15	28,8	114	43,3	ref			
History of Antenatal Care	Not annual	1	1,9	8	4	0,475	2,11	0,26	17,29
	Annual	51	98,1	193	96	ref			
History of Complication During Pregnancy	Present	28	46,2	84	41,8	0,119	1,63	0,88	3,00
	Not Present	24	53,8	117	58,2	ref			
Parity Status	Primipara	18	34,6	102	50,7	ref			
	Multipara	33	63,5	87	43,3	0,019	2,15	1,13	4,08
	Grande-Multipara	1	1,9	12	6	0,484	0,47	0,06	3,86
History of Newborn Weight	<2500	0	0	5	2,5	0,999	0,00	-	-
	2500-4000	49	94,2	191	95	ref			
	>4000 gr	3	5,8	5	2,5	0,256	0,43	0,1	1,85
History of Neonatus Cardio Pulmonary Rescucitation (CPR)	Yes	12	23,1	5	2,5	0,000	11,76	3,93	35,23
	No	40	76,9	196	97,5	ref			

This study included 253 parents, whom 52 were cases (parents with ASD children) and 201 were control (parents with normal children). Table 1 show that mother with age lower than 20 years during pregnancy had a risk to had children with ASD almost two times (1,87). Mother with age between 31-40 years also increased risk of ASD almost three times (OR: 2,87). However, this maternal age category didn't signficantly related with ASD.

Considering the smoking status, when father was an active smoker, the risk of ASD will arise almost four times (OR:3,89) and significantly related with ASD (p=0,000). Father as passive smoker also increased risk of ASD two times, but it not significantly related with ASD.

Mother as passive smoker also related with ASD (*p*=0,032) but it had a low OR value (OR:0,49).

Considering the socio-economic status, 71,2% parents in case group had income above minimum region salary (> Rp 1.589.000,00). Comparing with control group, only 56,7% parents in control group had income above minimum region salary. Parents with income above minimum region salary (>Rp 1.589.000,00) had a risk three times to had a children with ASD (OR: 3,23, CI95%: 1,67-6,26) and it significantly related with ASD (*p*=0,000).

Mother who didn't do routine antenatal care during pregnancy also increased risk of ASD two times (OR: 2,11, CI95%: 0,26-17,29), but it was not statistically significant with ASD (*p*=0,475). Mother with complication during pregnancy such as anemia, hypertension, hyperemesis, etc didn't have significant risk to had children with ASD (*p*=0,119; OR: 1,63; CI95%: 0,88-3,00). Multipara mother with two children or more also significantly related with ASD (*p*=0,019) and two times had risk to have a children with ASD (OR: 2,15, CI95%: 1,13-4,08). Comparing with multipara mother, grande multipara mother with more than four children didn't relate with ASD (*p*=0,484) and also show a lower OR value (OR: 0,47, CI95%: 0,06-3,86).

Table 1 also show the relation between neonatal factor with ASD. Children with history of low newborn weight (<2.500 gr) or macrosomia (>4.000 gr) had no significant relationship with ASD and didn't had a risk of ASD. Another factor like history of neonatus CPR show a higher precentage in case group (23,1%) rather than control group (2,5%). It also had a strong relationship with ASD (*p*=0,000) and 12 times increased risk of ASD.

Table 2. Final Result of Multivariate Analysis with Logistic Regression Model

Variabel	S.E.	Sig.	OR	CI95%	
				Min	Max
History of neonatus CPR	0,628	0,000	10,78	3,151	36,883
Paternal smoking	0,387	0,000	3,872	1,814	8,268
Socio-economic status	0,370	0,008	2,665	1,290	5,504
Parity status	1,197	0,036	12,249	1,174	127,82

Table 2. show the final result of logistic regression model of the significant risk factors related with ASD. After adjusting for prenatal and neonatal factors, it extrated four factors as the most significant predictors of ASD: history of neonatus CPR, paternal smoking, socio-economic status, and parity status. A higher risk of ASD was significantly related with a positive history of neonatus CPR (OR: 10,78; CI95%: 3,151-36,883), father as active smoker

(OR: 3,872; CI95%: 1,814-8,268), higher socio economic status (OR: 2,665; CI95%: 1,29-5,504), and multipara mother (OR: 12,249; CI95%: 1,174-127,82).

DISCUSSION

There was a potential risk between mother with age lower than 20 years during pregnancy and age between 31-40 years to have children with ASD. Maternal ages above 30 years were associated with a greater risk of ASD with intelectual dissabilities with pooled OR was 2.04 (95% CI:1.82–2.30) [10]. Mother with age above 30 years also had a risk almost two times compared with mother with age below 30 years [11] (OR: 1,80, CI95%: 1,27-2,54). However, maternal age did not signficant related with ASD[12,13].

Active somekers father was arise the risk of ASD almost four times (OR:3,89) and significantly related with ASD (p=0,000). Father as passive smoker also increased risk of ASD two times, but it not significantly related with ASD. It consistent with previous study from [14] that said a strong relationship between father with active smoking with ASD (p=0,007) and the risk increased almost three times (OR: 2,6; CI95%: 1,3-5,2). Despite from this result, only fewer study are available that investigate about paternal smoking with ASD and made a lack of mechanism of this variable.

Mother as passive smoker also related with ASD (p=0,032) but it had a low OR value (OR:0,49, CI95%: 0,253-0,949). This study also found that there was no active smoking mother during pregnancy. Several previous studies show a potential risk of maternal smoking with ASD. [15]Exposure of ciggarate during pregnancy associated with a risk of ASD with p<0,000. [16] Passive smoking during pregnancy would increase risk of ASD three times and it had strong relationship with p=0,005 and OR: 2,57, CI95%: 2,57-1,23-5,36. Compared with active smoking, passive smoking became more dangerous and potentially cause ASD by it exposure.

Parents with income above minimum region salary (>Rp 1.589.000,00) had a risk three times to had a children with ASD (OR: 3,23, CI95%: 1,67-6,26) and it significantly related with ASD (p=0,000). [17]Prevalence of ASD with mild impairment increases with income, with prevalence of mild autism significantly higher in the top two income categories than in the lower two (from lowest to highest income, cases per 1000 (95% CI): 1.8 (1.2–2.9); 2.2 (1.8–2.8); 4.6 (3.5–6.2); 5.9 (4.2–8.4), respectively). [18] Most of children with ASD came from high

income family. These finding were surprisingly and still need more investigation to understand the underlying mechanism between socio-economic status and ASD.

Mother without routine antenatal visit care during pregnancy also increased risk of ASD two times (OR: 2,11, CI95%: 0,26-17,29), but it was not statistically significant with ASD (*p*=0,475). Next finding also reported mother with complication during pregnancy such as anemia, hypertension, hyperemesis, etc. didn't have significant risk to had children with ASD (*p*=0,119; OR: 1,63; CI95%: 0,88-3,00). [18] There was no relation between complication such as gestational infection or diabetes mellitus with ASD. [16] There were no association between some pregnancy complication like preeclampsia, fever, or diabetes with ASD. These complication during pregnancy seem not affected ASD becuase the mechanism is still unknowing.

In this present study, multiparous mother with two children or more significant related with ASD (*p*=0,019) and two times had risk to have a children with ASD (OR: 2,15, CI95%: 1,13-4,08). [19] A same result that pregnancy frequencies between two until three were associated with ASD and increased risk of ASD two times. [8] Most of mother with ASD had a parity status more than one and it related with ASD. However, some studied show abstinance significant value of these factors with ASD[20,16].

Investigation at neonatal aspect and its relation with ASD, this study investigate newborn weight and neonatus CPR. Children with history of low birth weight (<2.500 gr) or macrosomia (>4.000 gr) had no significant relationship with ASD and didn't had a risk of ASD. A same result was shown from several studies that reported there was no association between birth weight with ASD[16,11,21]. However, different result was declared by meta-analysis study that reported low birth weight (<2000 gr) was associated with ASD and increased risk two times of ASD (OR: 2,20, CI95%) [22]. Low birth weight was predicted as poor brain development and it associated with risk factor of ASD. Whereas this present study show unsignificant relation between birth weight and ASD, it still need a lot of another study to explain a clear mechanism between birth weight and ASD.

Another neonatal factor such as neonatus CPR show a strong relationship with ASD (*p*=0,000) and 12 times increased risk of ASD (OR: 11,76, CI95%: 3,95-35,23). Logistic regression analysis also show this factor became the greatest risk of ASD (*p*=0,000, OR: 11,78). Several previous studies show a greates risk of neonatus resucitation with ASD. [11] Children with history of neonatus CPR whom it caused by delayed crying or birth asphyxia 11

times get a risk as ASD. [23,13] infant hypoxia trigger neonatus CPR and related significant with ASD. The fact that neonatus CPR became a greatest risk of ASD may cause by a late oxygen and blood delivery to brain. This mechanism well known get a poor brain development and trigger the risk of ASD[24].

As conclusion, this present study consistent with several previous studies about prenatal and neonatal risk factors in ASD. This result suggest neonatus CPR, paternal smoking, socio-economic status, and parity status are associated with ASD. Children with prenatal and neonatal risk factor should be early examined by medical tested to increase the effectivity of therapies. This study also being the first representation from a rural society, especially in Indonesia and becomes noteworthy.

Study Limitation

This present study had several limitation. Complication during pregancy as prenatal factor must be splitted into several variable to made a clear mechanism. Parental nutrional status during pregnancy also could be investigated as prenatal factor in ASD in the next study. A next cohort study about risk factor in ASD in Indonesia will be needed soon.

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