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Maternal and paternal Age and Risk of Autism Spectrum Disorder (ASD) in Banyumas district, Central Java, Indonesia

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ABSTRACT
Introduction: The prevalence of autism spectrum disorders has increased in the last three decades. The genetic etiological component of ASD is quite strong and complex. Although genetic factors clearly contribute to ASD risk, environmental, prenatal and post-natal factors are also involved. Father's age and mother's age at the conception of children contribute to the occurrence of autism spectrum disorders in children.
Objective: To explore the association between maternal and paternal age and risk of autis, spectrum disorders (ASD) in Banyumas district, Central Java, Indonesia
Methods: An analytical study with case control approach was conducted. This study used case control method that include 43 children with ASD as case group and 189 normal children as control group. Consecutive cases were selected over 4 months, with every weekend allocated to visit the school of children with special needs. Controls were selected from normal children who came with their parents and were also visited by our team at local schools, until the required sample size was reached.
Results: This study showed that paternal and maternal age at conception onset were not associate with the occurence of asutism spectrum disorders in children based on the statistical annalyzes in every range of paternal and maternal age results p value > 0,05.
Conclusion: Paternal and maternal age were not related with the occurence of autism spectrum disorders

KEYWORDS
Maternal, Paternal, Age, Risk factor for autism

INTRODUCTION

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental disorder in children characterized by disorders and delays in the fields of cognitive, language, behavior, communication and social interaction, accompanied by restrictive and repetitive behaviors and shallow and obsessive interests (American Psychiatric Association (APA), 2013; LoParo and Waldman, 2015). This situation can occur in all racial, ethnic and socioeconomic groups and is seen four times more in boys than girls, the exact cause of ASD has not yet been identified (WHO, 2017).

The overall prevalence of ASD is estimated at 14.7 per 1,000 children (1 in 68) among eight-year-old children in the US (Centers for Disease Control and Prevention (CDC), 2014). The Ministry of Health in 2009 reported that there were 475,000 children diagnosed with autism in 2004, and estimates that one in 150 children (0.67%) in Indonesia in 2009 would be born with a child with autism. Data from the Ministry of National Education in 2010 showed there were 638,000 children diagnosed with autism in Indonesian special schools in 2008, and estimated the prevalence of children with autism in Indonesia increasing by 15% every year (Riany et al., 2016). The increasing prevalence of ASD (Baio et al., 2018) and the etiology of ASD is so complex that most of the etiology is not known with certainty. Alleged interactions between genetic and environmental factors such as prenatal factors that are thought to contribute to the development of ASD (Hallmayer et al., 2011; Jokiranta-Olkoniemi et al., 2016a; Sandin et al., 2014). Prenatal factors that are thought to interact with genetic factors and produce a condition of ASD disorders are maternal maternal age and paternal maternal age

RESEARCH METHODOLOGY

This study is an analytical study with case control design. Consecutive cases were selected over 4 months, with every weekend allocated to visit the school of children with special needs. We invited parents who have children with ASD who independently accepted and confirmed the informed consent of their children to become

participants for this study. Controls were selected from normal children who came with their parents and were also visited by our team at local schools, until the required sample size was reached.
Consisting of 43 children diagnosed with ASD as a case group and 189 normal children as controls. Conducted in the region of Ex Regency Residency Banyumas, namely: Banyumas, Cilacap, Purbalingga, and Kebumen Regencies. Analyzes were first run to describe the data and then to describe the trends resulting from each item. Bivariate analysis used Chi-square tests to explore correlations between variables

RESULTS AND DISCUSSION

Characteristics of Respondents

Respondents in this study were 232 samples including children aged 2-18 years with male sex (n = 114) and women (n = 118). Divided into two groups, namely the case group (n = 43, male = 32 and female = 11) and the control group (n = 189, male = 82 and female n = 107) (Table 1).

Table 1. Characteristics children with and without ASDs and Association of Parental Maternal age with ASDs analyzes.

		Cases Group (n =43)		Control Group (n=189)		*p*	OR	CI 95%	
		n	%	n	%			Min	Maks
Sex of children	Men	32	13,80	82	35,34	0,00	3,80	1,81	7,98
	Women	11	4,74	107	46,12		Ref		
Gestation Age at birth	Preterm	9	3,87	11	4,74	0,049	4,64	1,20	21,00
	Aterm	31	13,36	161	69,39	0,89	1,09	0,30	3,95
	Postterm	3	1,29	17	7,33		Ref		
Paternal Age	<20 year	0	0	5	2,15	-	-	-	-
	20-30 year	20	8,62	99	42,67	0,51	0,71	0,25	1,97
	31-40 year	17	7,32	64	27,58	0,89	0,93	0,32	2,67
	>41 year	6	2,58	21	9,05		Ref		
Maternal Age	<20 year	3	1,29	0	0		Ref		
	20-30 year	26	11,20	25	10,78	0,20	0,42	0,11	1,60
	31-40 year	14	6,03	115	49,56	0,53	0,79	0,38	1,64
	>41 year	0	0	49	21,12	-	-	-	-

Based on the test analysis of the frequency distribution of sex between the case and control groups obtained a significant difference that is indicated by the value of p = 0.00 (p <0.05) with an value of OR = 3.8, which means that male respondents have the possibility (odds) as much as 3.8 times more risk for ASD compared with female respondents.
Neurodevelopmental disorders are more common in male sex. The mechanisms underlying vulnerability to men and protection to women are unknown and are still being studied. Current research in the field of biology-based to examine why autism is greater in someone of male sex and also other neurodevelopmental disorders.
The study carried out a higher genetic burden on women, specific genetic mutations in a particular sex or epigenetic changes that significantly make men more at risk and women more protected. Including the study of sex chromosomes and sex hormones. Specifically, fetal testosterone is involved in many aspects of development and will interact with neurotransmitters, neuropeptides, or pathway pathways that contribute to male vulnerability. Despite the striking heterogeneity in the manifestation and severity of ASD, one finding that is repeatedly found is that this disorder is more common in male sex. The ASD ratio in males compared to females is reported to be 4.5: 1 (Christensen et al., 2018). The large proportion of male risk compared to women in Indonesia in this study is below the proportion found in previous studies in the world. This is due to the relatively small sample size when compared with the sample size in previous similar studies.
Based on the test analysis of the frequency distribution of preterm birth between groups of cases and controls obtained a significant difference that is indicated by the value of p = 0.049 (p <0.05) with an OR value of 4.64, which means that

respondents with a history of preterm birth have the possibility (odds) as much as 4.64 times more risky to experience ASD compared with respondents born at the age of post term and term. Infants with premature gestation get a high exposure to stressors during a critical period and it may affect the brain development. One study reported there were cerebellar lesions in preterm infants at risk of developing autism (Schieve, 2015 cit Nani, et al, 2019b). Preterm infants also had the largest gray matter cluster that included the left angular gyri and the heteromodal association region involved in complex language functions. This brain structure is known to be affected in ASD (Maravić, 2016 cit Nani, et. Al., 2019).

Respondents with a history of being born at preterm gestation, ie born at less than 37 weeks' gestation. Several studies have been conducted to identify whether preterm birth is a risk factor for ASD or not. Children born at 23-27 weeks' gestation compared to those born at term are ten times as likely to experience ASD compared to children born at term. Babies born between 1973 and 2008 in Sweden at 25 weeks' gestation were found to be three times more likely to have ASD in babies born. Babies born at 32 or older are found to be twice as likely to have ASD compared to those at 40 weeks' gestation (D'onofrio et al., 2013).

Studies on children born in 1967 to 1983 in Norway found that children born at 23-27 weeks' gestation had ten times the risk of having ASD compared to children born at term (Moster et al., 2008). Babies born between 1973 and 2008 in Sweden at 25 weeks 'gestation are three times more likely to experience ASD, and babies born at 32 or above are twice as likely to have ASD compared to 40 weeks' gestation (D'onofrio et al., 2013). In 1998-2004 in Canada, children born at 29 weeks' gestation were 2.5 times more likely to develop ASD than those born at term (at term) (Leavey et al., 2013).

A study of children born in 2000-2007 in California found that ASD was experienced three times more in babies born at 27 weeks' gestation than those born at term (Kuzniewicz et al., 2014). The strongest relationship between preterm birth and ASD was found in children born 1980 to 1989. A moderate and stable relationship between gestational age and ASD occurred between preterm birth and ASD in 1990 to 2009

Paternal age (father) and maternal age (mother) during the conception of children diagnosed with ASD in this study did not show significant differences between the case and control groups. In each age range of father and mother, namely age <20 years, 20-30 years, 31-40 years, and> 40 years, between the case and control groups showed a value of p> 0.05, which means that there is no significant difference in the incidence ASD pad child. Thus the study in the Banyumas Ex residency showed no association between father and mother's age at the conception of the child with the occurrence of ASD in children. This is probably due to the local scope of research so that the number of ASD respondents is also limited, so the representation of the number of persons with ASD is not optimal. Significant ASD risk factors in this study are male sex and premature birth so that the child is more at risk of ASD.

There was a potential risk for mothers 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 intellectual disabilities with pooled OR at 2.04 (CI 95%: 1.82–2.30). Mothers with age above 30 years also had a risk almost two times compared with mother with age below 30 years (OR: 1,80, CI95%: 1,27-2,54). However, maternal age was not significantly correlated with ASD (Idring, 2014: Mamidala, 2013: Zhang, 2010; Hadjcakem, 2013 cit Nani, 2019)

These results are different from the study of Parner, 2012 and Croen, 2007. Parner conducted a cohort study and found an association between father's age and ASD, although the mechanism of the combination of father and mother's age was not found to be synergistic to cause ASD in children. Analysis of siblings cannot be calculated due to the complexity of the genetic and environmental causes of ASD. Likewise, the results of Croen's study found that advanced age of fathers and mothers independently each correlated with ASD risk.

RESEARCH LIMITATIONS

Limitations of this study are: (1) Autism spectrum disorder (ASD) is a rare case among the total number of children with disabilities is quite high in the ex-residency area of Banyumas. (2) Several case reports recorded by ASD based on data from the Banyumas District education office after repeated examinations by professional practitioners confirmed developmental disorders and other neurodevelopmental disorders. (3) The diagnosis of ASD requires a long observation time, but in this study confirmation of testing and diagnosis is quite short in one meeting even though it has been measured by experts, namely clinical psychologists. (4) The scope of research is limited in the ex-residency of Banyumas so that the number of persons with ASD obtained is minimal and does not yet represent the total number of persons in Indonesia.

CONCLUSIONS AND SUGGESTIONS

The conclusion of this study is the age of the mother and father's age when conception is not related to the occurrence of ASD in children, but strong risk factors associated with the incidence of ASD in this study are male sex and preterm birth. Suggestions for further research are a wider range of research areas to obtain data on children with ASD with a number that is more representative of the actual data in Indonesia, perhaps by establishing ASD study centers in each province in Indonesia.

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