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Perinatal factors associated with autistic spectrum disorder

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Abstract

Background The prevalence of autistic spectrum disorder (ASD) has increased in recent decades. The definitive causes of ASD have yet to be recognized. However, it is believed that both genetic and non-genetic, as well as perinatal and post natal factors influence ASD. Previous studies have shown inconsistent findings.

Objectives To assess for prematurity, birth weight, asphyxia, mode of delivery, bleeding during pregnancy, parental age and education, as prognostic factors for ASD.

Methods We conducted a cross sectional study at schools for autistic children in Yogyakarta between February 2011 to October 2012. The inclusion criteria were children with and without ASD, whose parents consented to participate in this study. Children with genetic abnormalities or who planned to move away during the study period were excluded. A total of 48 subjects with ASD and 96 subjects without ASD were involved in this study. Data were obtained by direct interview using questionnaires. Logistic regression analysis was performed to examine the hypothesis.

Results Multivariate analysis showed that prematurity was not a significant prognostic factor (RR 2.73; 95%CI 0.3 to 15.7) for ASD. However, children born by Caesarean section were 5.4 times more likely to have ASD (RR 5.4; 95%CI 1.3 to 22.8) compared to those who were delivered vaginally or by vacuum extraction. Moreover, asphyxia was also a significant prognostic factor for ASD (RR 8.7; 95%CI 1.9 to 38.6).

Conclusion Prematurity is not a risk factor for ASD. Asphyxia and Caesarean birth should be considered as potential confounders in this study. **[Paediatr Indones. 2014;54:144-8.]**

Keywords: *autistic spectrum disorder, prognostic factor, prematurity, asphyxia, Caesarean section*

The prevalence of autistic spectrum disorder (ASD) has increased in recent years. In the United States, the ASD prevalence was 0.7 in 10,000 children in 1970. The prevalence reportedly increased to 2.5 cases in 10,000 children,[2] then reached 31.2 cases in 10,000 children in 2003.[3] A study carried out by the Centers for Disease Control and Prevention (CDC) estimated that 1 in every 150 American children suffers from ASD, a disease involving autistim and other related disorders such as Asperger syndrome and pervasive developmental disorder not otherwise specified (PDD NOS).[4] In 1966, ASD prevalence in the United Kingdom was 4.1 in every 1,000 children,[5] which increased to 9 cases in every 1,000 children in 1994,[1] and 30.8 in 2000.[6] In Indonesia, ASD prevalence was found to be 11.7 in every 1,000 children in 1997.[1]

The etiology of ASD remains unknown. Many professionals are unable to identify and diagnose ASD, leading to wrong treatment. Autistic spectrum disorder consists of 3 out of 5 pervasive development disorders, namely autistic disorder (autism), Asperger syndrome, and PDD NOS.[7] Since the definitive

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causes of ASD are unclear, many studies have been carried out to identify the factors that increase ASD incidence. Heredity, perinatal factors (low birth weight, prematurity, asphyxia, small for gestational age, or bleeding during pregnancy), a history of parental psychiatric treatment, and parental age of over 40 years, are potential prognostic factors for ASD.[8] These studies, however, showed inconsistent results due to the small sample size and differing methods.[8] In a review of 7 articles concerning risk factors for autism, 2 studies identified Caesarian section as an independent prognostic factor for autism (adjusted RR = 1.6 to 1.8).[10] Other previous studies indicated that prematurity was an important perinatal prognostic factor.[10,14]

Our impetus to conduct this study was the lack of ASD data in our country. Conflicting results about prognostic factors for ASD was another consideration. The aim of this study was to evaluate the role of prematurity and other perinatal and post-natal factors as prognostic factors of ASD in children.

Methods

We conducted a cross sectional study between February 2011 to October 2012 in Yogyakarta involving students from 4 schools for the disabled. Sample size was estimated based on 80% power and α=5%. Our total sample included 48 subjects with ASD and 96 subjects without ASD.

The children with ASD selected from schools for the autistic using consecutive sampling, while non-ASD children consisted of normal children from elementary schools. We defined ASD as fulfilling the diagnostic criteria, which consisted of the 3 of 5 pervasive development disorders, namely autistic disorder (autism), Asperger syndrome and PDD NOS based on Diagnostic and Statistic Manual of Mental Disorder IV (DSM IV). Inclusion criteria was children with ASD whose parents consented to participate. We excluded those with genetic disorders, birth trauma, or those who planned to move out of town. The inclusion criteria for non-ASD group were children with normal development and whose parents consented to participate. Prematurity was defined as a gestational age of less than 37 weeks. We obtained data from medical records or by interviewing parents. Data on parental age and education, family ASD history, mode of delivery, bleeding during pregnancy, asphyxia, gestational age, and birth weight were obtained by questionnaires as well as direct interviews with mothers or other family members. Data were collected by a single observer.

Logistic regression analysis was performed to investigate the relationship between ASD and prematurity, since the dependent variable (ASD) was expressed as a binary variable. Using multivariate logistic regression analysis we evaluated the influence of prematurity on ASD adjusted for other variables (maternal age, paternal age and education, bleeding during pregnancy, mode of delivery, and asphyxia). *STATA/SE 11.1* software (College Station, Texas 77845 USA) was used for statistical analyses.

This study was approved by the Medical and Health Research Ethics Committee, , Universitas Gadjah Mada Medical School.

Results

Basic characteristics of the subjects are shown in **Table 1**.

The mean age of the children with ASD was 8 years 9 months, and ranged from 3 to 15 years, while the mean age of children without ASD was 9 years 4 months, and ranged from 7 to 13 years. The ratio of boys to girls with ASD was 3.4:1.

The relative risks of the possible prognostic variables are shown in **Table 2**. Out of all prognostic variables were seven variables with P values <0.25 included in the multivariate analysis; i.e. paternal age, maternal age, paternal education, bleeding during pregnancy, gestational age, mode of delivery, and asphyxia. Prematurity was not a significant prognostic factor (RR 2.73; 95%CI 0.3 to 15.7). However, children delivered by Caesarean section were 5.4 times more likely to have ASD than those delivered spontaneously or vacuum-assisted (RR 5.4; 95%CI 1.3 to 22.8). Moreover, asphyxia was also a significant prognostic factor for ASD (RR 8.7; 95%CI 1.9 to 38.6).

In our study, the 14 subjects delivered by Caesarian section had the following indications: premature rupture of membranes, oligohydramnios, prolonged second phase of delivery, the presence of myoma, placenta previa, and social indications.

Table 1. Basic characteristics of subjects

Characteristics	ASD group (n=48)	Non-ASD group (n=96)
Mean age (SD), years	8.8 (0.44)	9.4 (0.2)
Gender		
Male, n (%)	37 (77)	74 (77)
Female, n (%)	11 (23)	22 (23)
Paternal age		
<35 years, n (%)	32 (67)	75 (78)
≥35 years, n (%)	16 (33)	21 (22)
Maternal age		
<35 years, n (%)	40 (83)	88 (92)
≥35 years, n (%)	8 (17)	8 (8)
Paternal education		
Low, n (%)	10 (21)	31 (32)
High, n (%)	38 (79)	65 (68)
Maternal education		
Low, n (%)	19 (40)	37 (39)
High, n (%)	29 (60)	59 (61)
Place of birth		
Home/by midwife, n (%)	21 (44)	56 (58)
Hospital, n (%)	27 (56)	40 (42)
Family history of ASD, n (%)	2 (4)	0 (0)
Mode of delivery		
Spontaneously/vacuum-assisted, n (%)	38 (79)	92 (96)
Caesarian section, n (%)	10 (21)	4 (4)

Table 2. Relative risks of prognostic factors for ASD*

Variables	Bivariate			Multivariate	
	RR	95% CI	P value	RR	95% CI
Paternal age					
< 35 years	1			1	
≥ 35 years	1.8	0.8 to 3.9	0.14	1.02	0.34 to 3.03
Maternal age					
< 35 years	1			1	
≥ 35 years	2.2	0.8 to 6.3	0.14	2.06	0.47 to 9.02
Paternal education					
Low	1			1	
High	1.8	0.8 to 4.1	0.15	0.74	0.5 to 1.2
Maternal education					
Low	1				
High	0.96	0.5 to 1.9	0.9		
Bleeding during pregnancy					
No	1			1	
Yes	8.6	0.9 to 79.5	0.057	4.4	0.3 to 59.1
Gestational age					
37-42 weeks (mature)	1			1	
< 37 weeks (premature)	5.5	1 to 29.3	0.04	2.73	0.3 to 15.7
Mode of delivery					
Spontaneously/vacuum-assisted	1			1	
Caesarian section	6.1	1.8 to 20.5	0.004	5.4	1.3 to 22.8
Asphyxia					
No	1			1	
Yes	9.2	2.4 to 34.9	0.001	8.7	1.9 to 38.6

* calculated using logistic regression analysis

Discussion

We found that far more boys than girls had ASD, at a ratio of 3.4:1. This finding is supported by previous studies, with a boy to girl ratio of 4:1.[8,11,12] Neurobiological theory in animals may explain the predominance of boys with ASD. In young male animals, brain neurons contain androgen receptors which bind testosterone, resulting in brain arousal, potentially including the amygdaloid mechanisms for fear and anxiety. A similar mechanism may contribute to the male predomination of autistic children, and the impaired social interactions that define autism. Girls do not have high testosterone levels, hence, they may avoid the such arousal input to the amygdala.[13]

There were no significant differences in demographic characteristics between the ASD and non-ASD children in our study. A previous study demonstrated that a paternal age of 35 years or older did not affect autism in any way.[14] Nevertheless, their results contrasted with those of other studies, in which parents' age of more than 35 years increased the risk of ASD. According to another study, paternal age of more than 39 years increased the risk of ASD by 5.75 times.[15] Maternal age is one of the most frequently observed risk factors. In 6 out of 7 studies, maternal age was highly related to autism risk, before controlling for other confounding factors.[9] Older mothers are at higher risk of obstetric complications due to dysfunctional uterine muscles and the decreased blood supply in the vessels.[16] In addition, a study found that paternal age of above 35 years increased the risk of having children with ASD by 1.6 times.[9] Mothers aged 20 years or younger were found to increase the risk of having children with ASD by 1.8 times.[14] These studies have different sample sizes which may explain the discrepant results to our study.

Our finding similar to previous studies that indicated ASD prevalence in a child who has a sibling with ASD has been found to be 3-5% or 20 times as many as that found in general population.[17] Furthermore, the ASD recurrence risk of a child in a family with one child with ASD was reported to be about 8.6%, and this number increased to 35% if the family had 2 children with ASD.[18]

Other articles summarized that concordance in monozygotic twins is incomplete, leading to the fact that non-genetic factors play role in occurrence of autism. The increase of PDD prevalence for the last 20 years cannot be explained solely by improved PDD detection methods, and underscores the possibility of environmental risk factors. Histological and anatomical distortions in the brain also play important role in PDD etiology. Only a small proportion of PDD cases have major genetic defects. Genetic disorders are found to be nonspecific to autism, instead, they form a collective role as an etiology of intellectual disability and probably schizophrenia.

A previous study also found that low Apgar scores increased the risk of ASD by 3 times.[19] Similarly, another study found that an Apgar score of less than 7 increased the risk of ASD by 3.2 times in healthy babies.[20] Muhartomo *et al.* in Semarang reported that asphyxia was a risk factor for autism, similar to our findings.[21] Some researchers hypothesize that perinatal conditions causing hypoxia in the fetus are the main risk factors for neuropsychological and neuropsychiatric disorders. Murray and Harvey described three areas in the brain sensitive to perinatal disorders, including the basal ganglia, hippocampus and lateral ventricle.[23] The brains of autistic individuals may have abnormal hippocampus morphology.[10]

The relationship between Caesarian birth and ASD should be carefully examined, since there could be confounding factors associated with Caesarian births, such as obstetric complications.[10] In terms of gestational age, our results also differ from a previous study which stated that prematurity increased the risk of ASD by 2.57 times.[14] This discrepancy maybe due to differences in cut-off points for prematurity, with some studies using 35 weeks, while others used 33 weeks.[14,20,24] We used a gestational age of 37 weeks as the cut-off in our study. We also had a smaller number of subjects, which may have affected the results. The significance of the relationship of ASD to Caesarian birth was found to diminish when those who were born after a breech presentation were excluded, as breech is an indication for Caesarian section.[22]

Our study had several limitations. Prevalence, instead of incidence was used in the ASD group population. Observations were performed only in urban area subjects, not rural area children. Therefore, the conclusion should not be generalized to children living in countryside or rural areas. Autisctic spectrum

disorder children were assessed by only one examiner using non-probability consecutive sampling, that may have led to bias. As a questionnaire was used for data collection, recall bias may have been introduced by the children's family members. In conclusion, prematurity is not a prognostic risk factor for ASD. Asphyxia and caesarean section birth should be considered as potential confounders in this study.

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