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Cytogenetic and clinical features of down syndrome in malang, east java, indonesia

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ABSTRACT

Introduction: Down syndrome (DS) is the most common chromosomal disorder. DS characterized by multiple congenital anomaly caused by trisomy 21This study was designed to evaluate the karyotype pattern, clinical features and risk factors of patients with Down syndrome.

Method: Data were obtained from a retrospective analysis of a questionnaire from Down syndrome patients.

Result: A total of 34 patients were studied, with 67,6% of males. Out of 34 patients, there were 25 children (73,5%) with no cytogenetic test, 4 children (11,7%) with lost cytogenetic test, 3 children (8,82%) with free trisomy (non-disjunction), 1 (2,9%) with translocation, and 1 (2,9%) with mosaics. Maternal age categories showed one mother less than 20 years, two mothers between 21-25 years, four mothers were between 25 and 30 years, 12 mothers were between 31 and 35 years, ten mothers were between 31 and 40 years, and five mothers were over 41 years of age. The most common clinical features in this study are Congenital Heart Disease (CHD), which was recognized in 9 (26,4%) patients with five patients had Atrial Septal Defect (ASD), two patients had ASD and Ventricular Septal Defect (VSD), two patients had Patent Ductus Arteriosus (PDA). All of them followed by dental problems in 8 (23,5%) patients, ophthalmology problems in 6 (17,6%) patients, digestive problems in 4 (11,7%) patients, seizure in 1 (2,9%) patient, hormonal problems in 1 (2,9%) patient, and hearing problem in 1 (2,9%) patient. There is no significant difference in CHD prevalence between each maternal age group ($p = 0776$, $p>0.05$).

Conclusion: Down syndrome has a higher prevalence in males and is frequently seen among mothers between 31 -35 years of age, yet maternal age did not seem to influence CHD prevalence significantly. Early diagnosis and proper screening should be undertaken among these patients.

Keywords: Clinical Features, Cytogenetic, Down Syndrome (DS), Maternal Age, Sex Ratio

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INTRODUCTION

Down syndrome (DS) is the most common chromosomal disorder. DS characterized by multiple congenital anomaly caused by trisomy 21. Trisomy is characterized by the presence of three complete copies of chromosome 21. DS is causing of intellectual disability with 1 per 600 to 1 per 800 live births worldwide incidence.[1] In Indonesia, DS is a common genetic disorder. Data from the Down Syndrome Association of Indonesia stated at least there are 300,000 cases of Down syndrome in all over the country. According to the Indonesia Health Profile the prevalence of Down syndrome is 0,12%.[2]

DS affects multiple organs and can cause various degrees of intellectual disability, possibly due to defective neuronal precursor proliferation during gestation. DS is characterized by a delayed cognitive process in infancy and childhood, leading to mild-to-moderate mental retardation with an Intelligence Quotient (IQ).[3] The degree of cognitive impairment is variable and may be mild (IQ of 50 – 70), moderate (IQ of 35 – 50), or occasionally severe (IQ of 20 – 35).[4] The most consistent features among trisomy individuals were epicanthic folds, upslanting palpebral fissure and sandal gap.[5] Other commonly exhibit growth abnormalities, including microcephaly, flat face, small nose and distressed nasal bridge.[6]

Children with DS are more prone to congenital heart defects (CHD), gastrointestinal anomalies, endocrinopathies and cognitive impairment because of the presence of extra genetic material from chromosome 21.[4] CHD mostly presented with septal defects, such as Atrial Septal Defects (ASD) and Ventricular Septal Defects (VSD), followed by PDA.[7] Pulmonary Hypertension, Recurrent upper airway infection, endocrinology alterations, hearing problems, neurological abnormalities such as the early manifestation of Alzheimer's disease, immunological deficiency, and elevated risk of leukemia can also be present in DS children.[8,9] It is also documented that patients with DS are at risk of thyroid hormone abnormalities, with 24%.[10]

DS diagnosis can be made by prenatal testing and postnatal testing. Prenatal testing can be done from blood analysis and ultrasound imaging. Some

additional tests such as Chorionic villus sampling and amniocentesis are recommended with testing cytogenetic analysis (karyotype) if DS is suspected.[4] There is also a noninvasive technique for detecting trisomy 21 known as Noninvasive Prenatal Testing (NIPT), which measures the amount of cell-free fetal DNA circulating in maternal serum.[11] The cytogenetic analysis also needs to be performed in postnatal for all patients suspected by DS. Cytogenetic diagnosis is essential for confirming the clinical diagnosis and determining the recurrence risk since this risk differs significantly between the cases. Trisomy is characterized by the presence of three complete copies of chromosome 21. There are three cytogenetic forms of DS: free trisomy 21, mosaic trisomy 21, translocation trisomy 21, and other forms of trisomy 21.[12] Generally, 95% of cases are free trisomy resulting from nondisjunction during maternal meiosis. Translocation is contributed in 3-4% of the cases, and mosaics are reported in 1-2% of the cases.[1] If there is translocation, a balanced translocation must be excluded in the parents.[4]

There are some identified risk factors associated with DS. Advanced maternal age is strongly associated with an increased risk of DS.[13] However, given the fact that there are still DS children born from younger maternal age, suggesting another factor can contribute to influencing DS etiology. Several gene polymorphisms such as MTHFR were suspected,[14] lead to impaired folate metabolism that further increase the risk for chromosome 21 nondisjunction.[15] Another risk category recorded is abnormal serum screening, identifying one or more ultrasound markers at 16 to 22 weeks and detecting a significant fetal anomaly.[16] These risk categories become the guide for obstetricians refer to pediatricians for counseling, diagnosis, providing available treatments and health supervision from birth until early adulthood.[4]

This study was designed to evaluate the karyotype pattern, clinical features and risk factors of patients with Down syndrome in Malang, East Java, Indonesia.

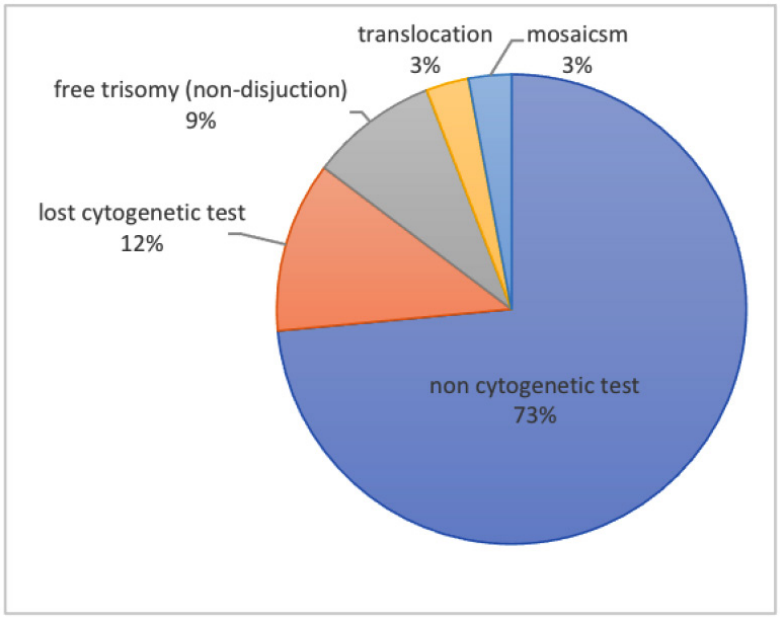

Figure 1. Total of cytogenetic

MATERIALS AND METHODS

The subjects were individuals with Down Syndrome (DS) who visit General Hospital. The subjects were obtained by purposive sampling technique. Data were obtained by using a questionnaire from the parents of a child with Down syndrome. The clinical features, cytogenetic evaluation results, gender, maternal age were recorded from the questionnaire and medical records. The DS diagnosis was made clinically and sometimes combined with cytogenetic testing if the clinical features are insufficient. Data were analyzed using IBM SPSS Statistics for Windows Software, version 20. Research was considered significant when $p<0.05$ was achieved.

RESULTS

A total of 34 records were included in this study. There were 25 children (73,5%) with no cytogenetic test, four children (11,7%) with the lost cytogenetic test. The most common cytogenetic anomalies are free trisomy (non-disjunction) with three children (8,82%), followed by translocation and mosaics with one child (2,9%) each (Figure 1).

Mother maternal age at birth of DS children was also evaluated in this study. Ages are widely varying from less than 20 years to over 41 years. It is further divided into several categories based on age. There are one mother less than 20 years, two mothers between 21-25 years, four mothers were between 25 and 30 years, 12 mothers were between 31 and 35 years, ten mothers were between 31 and 40 years, and five mothers were over 41 years of age (Figure 2).

Down syndrome is often associated with multiple malformations and medical problems. This study's most common clinical features are Congenital Heart Disease (CHD), which was recognized in 9 (26,4%) patients. It can be described with 5 Atrial Septal Defect (ASD), 2 ASD and Ventricular Septal Defect (VSD), and two patients had Patent Ductus Arteriosus (PDA). Dental problems are the second most common clinical features found in 8 (23,5%) patients. Other medical problems that were found in DS patients is ophthalmology problems in 6 (17,6%) patients, digestive problems in 4 (11,7%)

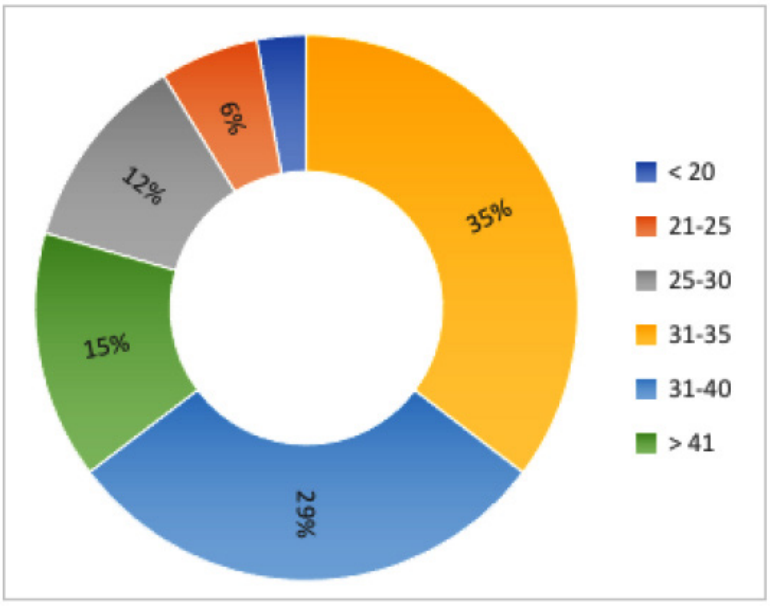

Figure 2. Mother maternity ages of DS

patients, seizure in 1 (2,9%) patient, hormonal problems in 1 (2,9%) patient, and hearing problem in 1 (2,9%) patient.

Further analyses were made to know whether there is an increasing possibility of DS with CHD associated with maternal age. After statistical analysis, It is found that there is no significant difference in CHD prevalence between each maternal age group (p = 0776, p>0.05).

DISCUSSIONS

The result shows that there are 34 children diagnosed with Down syndrome (DS). All case was diagnosed postnatally. This may reflect low awareness of the family as well as a health care provider to recognize DS. DS's prenatal diagnosis is not a routine examination in Indonesia because lack of awareness, and there is no specific guideline or regulation. Cytogenetic is the standard to confirm the diagnosis of DS. Cytogenetic needs to be performed due to possible inherited caused by trisomy 21 and determined the recurrence risk of DS.[5] Nondisjunction, translocation, and mosaics are the classical anomalies of DS. In the present study, free trisomy 21 is most commonly compared with translocation trisomy and mosaics trisomy. In several studies, these findings were also found free trisomy 21 as the most common cytogenetic result of DS.[1,5,17–19] In another study, mothers of translocation trisomy often reported with a history of abortion.[5]

Most (73,5%) of the case in this study were diagnosed without a cytogenetic test. Unfortunately, cytogenetic inaccessible in most cases due to limited facilities and high cost, especially in Indonesia.[2] This condition pushed clinical to make the diagnosis based on clinical features. A careful physical examination is the most sensitive test in the first 24 hours of life because most DS patients have a typical physical appearance. However, the clinical diagnosis of FS by clinical only predicts to be 64% accurate.[20] Five classical exam findings (brachycephaly, ear anomalies, clinodactyly, sandal gap, and excellent neck skin) can be used as initial findings, even probably affected by a certain age and race.[20] Once diagnosed with DS, a patient needs health supervision to evaluate medical problems.[4]

In this study, Congenital Heart Disease (CHD) was the most common clinical features of DS. It is said that patients with DS are 50% at risk of congenital heart defects.[4] In this study, CHD was found in 26,4% of patients with DS. The most common CHD developed was Atrial Septal Defect (ASD), followed by VSD and PDA. The type of congenital heart disease developed in DS is varied from one study to another. Western European countries and the USA reported endocardial cushion defect, which results in AVSD canal defect as the primary abnormality, followed with VSD. In Asia, India, and Egypt, VSD is the most common cardiac defect.[1,4,18]

Meanwhile, in South Korea, the frequencies of ASD were far the most common (28%).[7] Children with severe CHD showed growth retardation during the first year of life.[21] CHD such as atrioventricular septal defect (AVSD) is 1,000-fold higher in DS, leading to high infant mortality in DS patients.[7,22] The high mortality rate observed was associated with many factors, including non-consent parents for surgery and financial problems.[22] The present study also shows there is no significant difference in CHD prevalence between each maternal age group. A study in Sweden shows that higher maternal age was significantly associated with a lower risk of congenital heart defects (CHD). This study shows that maternal obesity, smoking, and infant girls are more likely to risk congenital heart defects.[23] However still, the mechanism of CHD development in DS is still not clearly understood. However, a theory was proposed. The Down syndrome cell adhesion molecule (DSCAM) is involved in the adhesion and fusion of endocardial cushions. There is overexpression of the DSCAM gene in Down syndrome patients that leads to an imbalance in the epithelial-mesenchymal transformation. It can also cause a defect in mesenchymal migration and proliferation that eventually causes several congenital hearts defects.[24]

Other findings in this study are dental problems (23,5%) in inpatient with DS. In

Indonesia, individuals with Down Syndrome showed hypodontia and microdontia as the most common dental anomalies.[6] One patient was found with hearing problem and one patient with an ophthalmology problem. Another study found that hearing loss risk reached 75% in children with DS and followed otitis media (50 – 75%). Meanwhile, eye diseases found in DS children were reached 60%, including cataracts (15%) and severe refractive error (50%).[4]

Other clinical features of DS that had not been measured in this study are low birth weight,[25] pulmonary hypertension,[9] intellectual disability such as narrative skills,[26] haematopoetic disorders, early-onset Alzheimer[27] and cognitive impairment.[4] Another study also shows DS prone to hypothyroidism with a prevalence of 13,6%.[18] Given the comprehensive clinical features and medical problems associated with DS, the American Academy of Pediatrics in their guidelines advised health supervision from birth to early adulthood to evaluate for heart defects, feeding problems, cataract and any other eye anomalies, hearing loss, gastrointestinal tract atresia/stenosis, breathing problems, constipation, hematologic abnormalities, hypothyroidism and many more.[4] It is also suggested that DS has its specific growth chart since known that DS children are shorter than the general population. Several countries have produced their specific centile growth chart, for example, Dutch, United Arab Emirates, and Turkish.[21,28,29]

There are several controversial about the association of maternal conditions and risk of DS. In this study, DS was commonly found among mothers between 31- 35 years of age. Several studies show that infants with DS were mostly born from women 35 years and older.[8,16] This difference could be caused by several factors such as lack of samples and tendency to get pregnant and having a child in the age above 35 is probably lower than any other group. Several hypotheses were proposed to explain the nondisjunction process. It has possibly compromised microcirculation in the perifollicular capillary bed, causing hormonal imbalance. The compromised microcirculation hypothesis explains why women of all reproductive ages may have DS children. Another hypothesis concerning the link between maternal age and nondisjunction is normal biological ovarian aging.[19] This aging probably answers why advanced maternal age is strongly associated with an increased risk of DS.[13]

Several studies suggest an increased risk of giving birth to DS associated with higher parity regardless of maternal age. This association was influential among older women.[13] It supports the theory of an increase in maternal age can increase the possibility of nondisjunction trisomy 21. This also proved with findings mothers of children with nondisjunction DS are significantly older than those of translocation and mosaic children. Meanwhile, the mother of cases of translocation DS was under 35 years.[1] Another study in Egypt found that 17% of the patients with DS were consanguineous marriage products.[1]

Given all of DS's medical condition and burden, it is essential to do early diagnosis and proper screening. Early intervention can be started early before the critical period during pregnancy, the first three years of life, and during puberty to increase life quality. The difference birth length in the infant with DS is 1 SD lower than in the general population,[25] indicating that children with DS already show retarded growth during pregnancy. During puberty, the first three years of life are a critical period of growth that need to be observed in children with and without DS.[21] Surgical intervention is needed for DS children with CHD, especially with life threatening condition.[20] Early DS diagnosis is also followed with early detection of hypothyroidism and will prevent the additional burden of intellectual disability.

CONCLUSIONS

Down syndrome has a higher prevalence in males and is frequently seen among mothers between 31 -35 years of age, yet maternal age did not seem to influence CHD prevalence significantly. Early diagnosis and proper screening should be undertaken among these patients.

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None

CONFLICT OF INTEREST

None

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