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DOI: 10.5582/irdr.2023.01103

Critical issue in the identification of Down syndrome and its problems in Central Java, Indonesia: The fact of needing health care and better management

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SUMMARY We conducted a cross-sectional study to describe the health care problems of children with Down syndrome in Central Java, Indonesia. A total of 162 children (81 boys, 81 girls) with Down syndrome were included. Congenital heart defects and hypothyroidism were found in about 50%, followed by vision and hearing problems in 27.7% and 17.3%, respectively. Almost half of cases were diagnosed after the first month of age. Advanced maternal age was identified in more than 50%, and less than 10% was based on karyotype analysis. This study describes the essential issues such as critical co-morbidities, delayed diagnosis, advanced maternal age, and lack of (accessibility to) genetic testing facilities; thus, better health care and management is needed.

Keywords delayed diagnosis, Down syndrome, genetic facilities, limited accessibility, Indonesia

1. Introduction

Down syndrome, also called trisomy 21, is the most common numerical chromosomal aberration found in live-born infants. Down syndrome is characterized by peculiar physical features such as hypotonia, epicanthic folds, up-slanting palpebral fissures, protruding tongue, simian creases, sandal gaps, and intellectual disability. The prevalence of Down syndrome was 1.7 to 2.5 in 1,000 live births, and increases with maternal age. In Indonesia, the prevalence of Down syndrome increased from 0.12% in 2010 to 0.21% in 2018 (*1*).

The frequency of congenital heart disease-associated Down syndrome was about 60%, which leads to early infant death (*2*). Early diagnosis and detection of treatable co-occurring medical conditions, such as hypothyroidism, congenital heart disease, and hearing problems, may minimize the complications, optimize the treatment, and prevent further irreversible conditions. In order to reach maximum beneficial outcomes, recognition of Down syndrome's typical characteristics, and early intervention, should begin shortly after birth (*3*).

Indonesia is the world's fourth-most populous country, with an estimated population of 275 million spread over 17,500 islands. A recently introduced national health insurance system covered almost 75% (203 million) of inhabitants (*4*), and is expected to improve equity and access to health care services, especially in remote areas/islands. However, prioritizing communicable diseases leads to limited access to genetic diseases, including Down syndrome (*5*). In fact, the quality of maternal health care services varies greatly between countries, and in developing countries such as Indonesia, where human resources and care facilities are scarce, this results in inequality of access to maternity and neonatal services (*6*). In developed countries, prenatal screening and diagnosis followed by pregnancy termination were recommended and offered, especially for advanced maternal age (*7*), while in Indonesia, the availability of prenatal diagnosis and termination of pregnancy are extremely low. Therefore, neonatal care, including early diagnosis, prompt intervention, and continued medical issues surveillance, is essential to improve the survival rate and quality of maternal and neonatal health.

Down syndrome based on clinical features, with and without chromosomal testing, is responsible for a significant proportion of infant and childhood

mortality in developed and developing countries but also contributes to chronic health problems and most lifelong disabilities (*8*). Among Down syndrome pregnancies, 63% resulted in a live birth (*9*). Indonesia has the largest Muslim population and religious belief plays an important role in daily life. In addition, the pregnancy termination policy is very strict and mostly offered only for maternity-related health problems; thus, termination in the case of an affected baby is not considered (*10*). Previous studies found that most Down syndrome was suspected on the day of birth, but delayed and appropriate diagnoses were reported (*11*). Therefore, this study aims to describe the healthcare problems in children with Down syndrome. This cross-sectional study was conducted at the Pediatric outpatient clinic of three referral hospitals in Central Java. This study was approved by the Ethics Committee (100/EC/KEPK/FK-UNDIP/VI/2020) and written consent was obtained from all respondents. Down syndrome diagnosis based on the six clinical features, that is, epicanthic folds, hypotonia, up-slanted palpebral fissures, protruding tongue, simian crease, and sandal gap were used for clinical diagnosis of Down syndrome (*12*), with and without chromosomal testing.

2. Clinical data

A total of 162 children with Down syndrome were included in this study, 81 cases were boys and 81 cases were girls, the mean age was 1.75 ± 2.04 in boys and 1.87 ± 2.26 in girls. Subjects were from the middle socio-economic level in almost two-thirds of cases (73.5%), and more than half (52.5%) were from advanced-age mothers at childbirth. Full-term gestational age was the majority of cases in both sexes (77.8%); and pre-term gestational age was found in 21.6%. Vaginal mode of delivery was found in 59.9%, while the remaining cases were born by caesarean section. The obstetrician was the most predominant birth assistant in this study (53.7%), followed by the midwifery-assisted delivery mode in 44.4%. More than 70% were born with normal birth weight; however, 30% were born with low birth weight (Table 1).

Based on Devlin and Morrison (*12*), hypotonia was found to be similarly prevalent in boys (88.8%) and girls (84.0%). Epicanthal fold was found in 96.3% of all cases and up slanted palpebral fissures was 95.1% in both boys and girls. The protruding tongue was observed in 64.2% of boys and 75.3% of girls. Dysmorphism in limbs was found higher in feet, and sandal gap occurrence was found to be similar in boys (91.4%) and girls (88.9%), followed by a single palmar crease observed in 77.8% of both boys and girls. Two characteristics frequently found in addition to Devlin and Morrison clinical criteria, which is flat nasal bridge was found at a higher rate in boys (92.6%) and girls (95.1%). Fifth finger clinodactyly was discovered in 86.4% of boys, and 84.0% of girls Table 2).

Congenital heart diseases and hypothyroidism were found in approximately half of the cases. Hearing problems were found in almost one in five boys (19.8%) and somewhat lower in girls (14.8%), while vision problems were found to be higher in girls (32.1%) compared to boys (23.5%) (Figure 1A).

Table 1. Demographic characteristics

Characteristics	Boys (*n*, %)	Girls (*n*, %)	Total (*n*, %)
Number	81 (50%)	81 (50%)	162 (100%)
Age, years (Mean ± SD)	1.75 ± 2.04	1.87 ± 2.26	-
Parental Socio-economic Status			
< 2,000,000 IDR	22 (%)	21 (%)	43 (26.5%)
≥ 2,000,000 IDR	59 (%)	60 (%)	119 (73.5%)
Maternal Age			
≤ 35 years old	40 (49.4%)	37 (45.7%)	77 (47.5%)
> 35 years old	41 (50.6%)	44 (54.3%)	85 (52.5%)
Gestational Age			
Pre-term (< 39 weeks)	15 (18.5%)	20 (24.7%)	35 (21.6%)
Full-term (39–40 weeks)	66 (81.5%)	60 (74.1%)	126 (77.8%)
Post-term (≥ 41 weeks)	0	1 (1.2%)	1 (0.6%)
Delivery Mode			
Cesarean section	34 (42.0%)	31 (38.2%)	65 (40.1%)
Vaginal delivery	47 (58.0%)	50 (61.8%)	97 (59.9%)
Birth Assistant			
Obstetrician	42 (51.8%)	45 (55.6%)	87 (53.7%)
Midwife	37 (45.7%)	35 (43.2%)	72 (44.4%)
Nurse	0	0	0
Physician	2 (2.5%)	1 (1.2%)	3 (1.9%)
Traditional birth attendant	0	0	0
Birth Weight			
≤ 2,500 gr	23 (28.4%)	25 (30.9%)	48 (29.2%)
> 2,500 gr	58 (71.7%)	56 (69.1%)	114 (70.8%)

IDR, Indonesian Rupiah.

The clinical-based diagnosis was made in most cases (90.1%), while cytogenetic-based testing was only done for less than 10% of cases. The diagnosis was established in the very early postnatal period (0–3 days) in 41.4% of cases and in less than one month in 13% of cases. In infancy (1–12 months), the majority of diagnoses was made within 1–5 months (26.5%) and 13% were made within 6–12 months. The fewest diagnoses (6.2%) were established at the age of 12 months and more (Figure 1B).

Table 2. Physical and clinical characteristics of participants

Characteristics	Boy (*n*, %)	Girl (*n*, %)
Musculoskeletal Problems		
*Hypotonia**	72 (88.9%)	68 (84.0%)
No hypotonia	9 (11.1%)	13 (16.0%)
Head and Neck		
*Epicanthal folds**	78 (96.3%)	78 (96.3%)
*Upslanted palpebral fissures**	77 (95.1%)	77 (95.1%)
*Protruding tongue**	52 (64.2%)	61 (75.3%)
Microcephaly/flat occiput	56 (69.1%)	51 (63.0%)
Flat nasal bridge	75 (92.6%)	77 (95.1%)
Short neck	57 (70.4%)	54 (66.7%)
Hand		
*Simian/single palmar crease**	63 (77.8%)	63 (77.8%)
Clinodactyly	70 (86.4%)	68 (84.0%)
Short of 5th finger	45 (55.6%)	37 (45.7%)
Feet		
*Sandal gap**	74 (91.4%)	72 (88.9%)
Flat foot	45 (55.6%)	46 (56.8%)
Syndactyly	2 (2.5%)	5 (6.2%)

*The main physical features (Devlin and Morrison, 2004).

3. Discussion

The survival rate is critical in children born with Down syndrome, especially in the first year of life, where the morbidity rate is very high (*13*). Sociodemographic characteristics and healthcare accessibility can affect survival rate. Previous report highlights newborn characteristics, including gestational age, birth weight, and comorbidities, because they can predict the survival rate. Individuals with Down syndrome have three times the mortality rate compared to typical individuals, and gestational age is one of the predictors of survival in Down syndrome (*9*). This study showed that most children were born full-term, and only 21% were born pre-term. Normal birth weight is a paramount concern for a baby with Down syndrome. The survival rate is low in Down syndrome for those who are born weighing less than 2,500 grams compared to those with normal birth

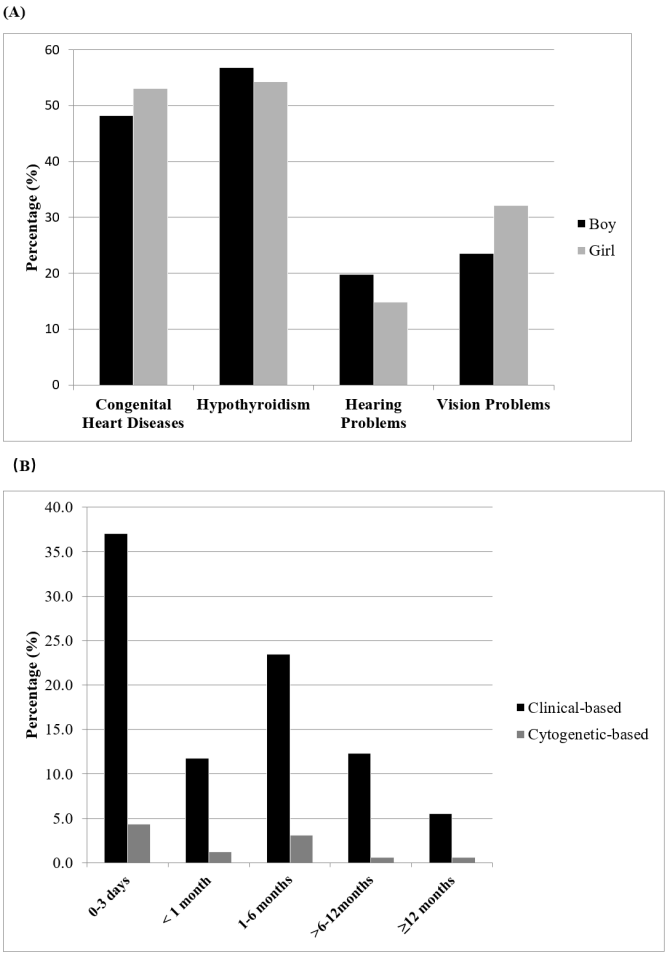

Figure 1. (A) The frequency of associated-medical conditions; (B) Age at diagnosis and frequency of diagnosis-based assessment.

weight. In addition, morbidity was increased in babies with very low birth weight (*9*). Our study counted low birth weight in approximately 30% of cases.

Congenital heart disease is found in about half of the children. A systematic review demonstrated that the prevalence of congenital heart disease in children with Down syndrome is estimated at around 66.1% (*14*). Previously, the mortality rate among Down syndrome with congenital heart disease was 14.1% (*15*). In addition, Down syndrome children have a higher risk of having thyroid disorders; therefore, the American Academic of Pediatrics (AAP) recommends thyroid screening at birth, at six months, and annually starting from one year (*16*). In our study, we found that more than half of the participants had thyroid problems. However, newborn screening is still not widely available in Indonesia; thus, not all children with Down syndrome undergo basic screening, and only some have thyroid examinations. Hearing problems affected almost 20% of cases. This result corresponds with a previous study that found in 22%-30% of cases having transient hearing loss (*17*), there was a double impact on speech and language development, resulting in low cognitive performance and mental age growth and outcome (*18*). In our study, vision problems were more prevalent in girls (32%) than boys (23.5%).

This study found the prevalence of hypotonia, epicanthic folds, up-slanted palpebral fissures, and "sandal gap" to be very high. In addition to Devlin and Morrison's clinical criteria, flat nasal bridge and fifth finger clinodactyly were found in high frequency. This may be due to the variability of clinical characteristics and also the type of Down syndrome karyotype, in which the mosaic cases show a broader spectrum of clinical characteristics. Unfortunately, only 10% of cases in this study were diagnosed based on chromosomal analysis.

In Indonesia, prenatal diagnosis has not been routinely offered in public healthcare facilities (primary or referral) because the national health insurance does not cover prenatal screening and other prevention programs. Moreover, there are still interregional disparities in primary antenatal care in Indonesia (*19*). Consequently, only some individuals who have a risk of having major congenital anomalies can afford to pay out of pocket to do prenatal testing/diagnosis. In our study, advanced maternal age was found in more than half of cases, and none of those completed the prenatal screening during pregnancy. Lacking awareness of healthcare professionals combined with limited health insurance coverage may decrease the opportunity to offer prenatal screening in advanced maternal age, even though international guidelines of prenatal testing recommend performing the aneuploidy screening test for advanced maternal age (*20*).

Regarding the birth assistant, obstetricians were the most prevalent birth assistants (53.7%), followed by midwives at 44.4% of cases in this study. Early postnatal diagnosis of Down syndrome is critical to prompt and early intervention. Our study documented that 41.4% of cases were clinically diagnosed at birth to 3 days after birth. Unfortunately, 6.2% of cases were diagnosed after 12 months of age. The characteristics of Down syndrome are less specific in newborns than in children. Hypotonia is the most striking characteristic, along with the manifestation of feeding problems and failure to thrive in newborns. Besides, small ears, "sandal gap", and nuchal skin fold are the most reliable and discriminative signs (*21*). Delays in diagnosis leads to decreases early identification and management of co-morbidities, which may worsen the clinical conditions.

This study has some limitations. This study was conducted on children with Down syndrome who were admitted to a pediatric clinic due to their critical co-morbidity. Thus, cases from primary care or in the community may not have been accounted for, and the critical problem may be bigger than shown in this study.

In conclusion, this study highlights some crucial issues in terms of Down syndrome in a developing country where the genetic laboratory is not accessible for the majority of the population, leading to delayed diagnosis in almost half of the cases and in increase in the frequency of co-morbidities. Advanced maternal age accounts for the majority of cases, and lack of cytogenetic laboratory assessment to confirm the diagnosis. Furthermore, based on a previous report that the life expectancy for Down syndrome is nearly 60 years, it is worth improving their quality of life by enhancing functional cognitive and adaptive outcomes and preventing their decline by identifying and managing the factors that may contribute to it, such as the co-morbidities.

Funding: Universitas Diponegoro, Semarang, Indonesia, WCRU-No:118-02/UN7.6.6/PP/2021.

Conflict of Interest: The authors have no conflicts of interest to disclose.

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Received November 7, 2023; Revised January 26, 2024; Accepted March 16, 2024.

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Released online in J-STAGE as advance publication April 27, 2024.