Section: Pediatrics

Research

THE PHENOTYPICAL, CLINICAL AND CYTOLOGICAL PROFILE OF DOWN SYNDROME CHILDREN: A HOSPITAL BASED STUDY IN TELANGANA

Sneha Madasu[1], Santosh Avinash B[1], Lasya Guduru[2], P V K Shastry[3]

[1]Assistant Professor, Department of Pediatrics, Niloufer Institute of Child health, Osmania Medical College, Affiliated to KNRUHS, Telangana, India
[2]Junior Resident, Department of Pediatrics, Dr. D. Y. Patil Medical College, Hospital &Research Centre, Pune, Maharashtra, India.
[3]Former Professor of Pediatrics, MGM Hospital, Kakatiya Medical College, Affiliated to KNRUHS, Telangana, India.

Received : *18/09/2022*
Received in revised form : *14/10/2022*
Accepted : *26/10/2022*

Keywords:
Down syndrome, Trisomy, cardiac anomaly, VSD, dysmorphism

Corresponding Author:
Dr. Sneha Madasu,
Email: sneham89@gmail.com
ORCID: 0000-0002-2072-4095

DOI: 10.47009/jamp.2022.4.5.38

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2022; 4 (5); 177-182

Abstract

Background: There seems to be ethnic variations among Down Syndrome children with the mean maternal age, morbidity profile and dysmorphology profile. **Materials and Methods:** This is a Cross sectional, hospital based, observational, descriptive study conducted at Mahatma Gandhi Memorial hospital, Warangal, Telangana. Inpatients with morphological features suggestive of Down syndrome who also had DS consistent Karyotyping. Their dysmorphology, thyroid profile, echocardiography and morbidity profile have been recorded. **Result:** Mean age at admission was 31.2 months. Most frequent dysmorphic features were features are flat face, generalized hypotonia, loose skin in the nape of neck and oblique palpebral fissure. Dysplastic ear, furrowed tongue, protuberant abdomen are less common. Of the 35 subjects, 34/35 (97.14%) were trisomy 21. Only 1/35 was translocation 14;21(2.85%). No mosaics were identified in this study. Hypothyroidism 10/35 was present in 29.15%.20/35 (57.14%) had cardiac anomolies of which VSD was most common. 3/20 had associated PAH. Among the of phenotypical characteristics, only presence of sandal gap was found to have found significant association with CHD($p<0.05$). Most common condition for which children with DS were admitted was Pneumonia, followed by miscellaneous febrile illness. **Conclusion:** In light of the lower mean maternal age, screening programs need reconsideration in our country. Clinical diagnosis in neonates is not fool proof, especially in neonates. Simian crease, clinodactyly though popular have lesser prevalence. The prevalence of individual dysmorphic feature differs from western studies. Pneumonia is the most common cause of admission. Hypothyroidism and cardiac anomalies were more common than in established literature. Breastfeeding and ENT pathologies are very common. Universal cardiac, thyroid, and hearing evaluation and a multimodal team approach is crucial.

INTRODUCTION

Down syndrome (DS) is the most common chromosomal aneuploidy compatible with life and the most common genetic cause of mental retardation.[1] Literature shows increasing prevalence in the past two decades by nearly a third.[2] Timely screening, medical management, home environment, early intervention and stimulation and education of care giver can significantly affect the life expectancy, morbidity, medical costs and level of functioning of Down syndrome children and facilitate their transition to self-reliant adulthood.

Studies show varying accuracies of clinical diagnosis of DS. There also seems to be an ethnic and geographical variation among phenotypical features and associated morbidities.[3] In light of lower socio-economic demographics, maternal malnutrition and poorer access to healthcare, higher consanguinity and tribal population, the local community might have slightly different phenotype, clinical manifestations and karyotype distribution compared to the western world.

The local socio economic and health systems of the area of this area result in poor follow-ups and preventing care seeking. Thus, pediatrician must be able to maximize the diagnostic accuracy and ensure

ISSN (O): 2687-5365; ISSN (P): 2753-6556

quick and targeted workup when the child is brought for any illness. Being well versed with local variations of physical, biochemical and clinical profile helps optimize care.

MATERIALS AND METHODS

A Cross sectional, hospital based, observational, descriptive study was carried out over 20 months. Consecutive sample of all children between 0 to 12 years who were admitted as inpatients into paediatric department, Mahatma Gandhi Memorial hospital Warangal with morphological features suggestive of Down syndrome were collected over a span of 20 months. Those whose karyotyping was consistent with Down syndrome were included as study subjects.

Inclusion Criteria

- Child should have morphological features suggestive of Down syndrome.
- Children with phenotype and Karyotyping consistent with Down Syndrome.

Exclusion Criteria

- Lack of parental consent
- Karyotyping normal or not consistent with Down Syndrome. (4 such cases excluded)
- Down phenotype Children who died before either of karyotyping/thyroid profile/echo cardiogram could be done.

Ethical committee clearance was obtained.

Methodology

The combination of multiple of the following features were considered for a clinical diagnosis of Down syndrome. Features of epicanthal fold, brachycephaly, up slanted palpebral fissure, single transverse palmar crease, sandal gap, Sydney crease, sandal gap, downturned corners of mouth, protruding tongue. Each dysmorphism was considered based on recommendations by National Human Genome Research Institute. All clinical suspects were subjected to karyotyping. All clinical suspects were tested with thyroid screen and 2DEcho irrespective of clinical findings.

Out of 51 in patients with provisional clinical diagnosis of DS during the study period, consent could not be obtained for 8 subjects, 5 of these children were critically ill when brought and died within a day of admission, before complete evaluation and data collection could be completed.

Karyotyping was done on 43 subjects.4/43 (9.3%) were lost to follow up of karyotyping results and other data. Karyotype results of 39 subjects are available.

4/39(10.2%) had normal karyotype. Only 35 of the available cases were consistent with DS and included in the study. These 16 clinically diagnosed cases of DS were excluded from the study for the reasons mentioned above.

RESULTS

Mean age of presentation was: 31.02 months.60% of the admissions were of children below 2 years of age. 42.8% of the admissions were of children less than one year, of which about half were neonates, i.e22.8% of total subjects (8/35).

62.8%were from rural and 37.14% from urban area. (8.6%) of the children with DS studies belonged to Scheduled tribes irrespective of residence. Mean maternal age was 26.28 yrs. 20%, 8.5%, 2.8% of the subjects were born to mothers of age more than 30,35 and 40 years of age respectively.

Of the 35 subjects, 34/35 (97.14%) were trisomy 21. Only 1/35 was translocation 14;21.(2.85%).No mosaics were identified in this.

Morphological features of Subject

The 8 Items which constitute the fried Index are * asterixed (4/35) 11.4% had frank hypothyroidism of which those with of which only 1 child had overt symptoms before diagnosis. 17.4% of the subjects had subclinical hypothyroidism. Girls (n=6) and boys (n=4) were nearly equally affected.

20/35(57.14%) children had echocardiogram diagnosed congenital heart disease. Most common lesion was VSD which was present in 13 out of the 20 subjects with cardiac anomalies. Of these 11 had isolated VSD and other 2 had ASD + VSD. (5/20) (25%) had Atrioventricular septal defect. 2/20 (10%) children had pure ASD 1(5%) infant had PDA while another 1/20(5%) fallot's physiology. 3/20 had associated PAH (15%) None of the children were yet operated. Among the of phenotypical characteristics, only presence of sandal gap was found to have found significant association with CHD ($p<0.05$).

Table 1: Frequency of each morphological feature in the present study.

Morphological Features	No. of cases	%
Flat face*	33	94.28%
Hypotonia*	33	94.28%
Loose skin –nape of neck*	33	91.4%
Upward oblique palpebral fissure*	32	91.4%
mouth corners turned downward*	18	51.42%
Flat nose	31	88.57%
Sandal gap*	24	68.57%
Hyper flexibility of joints	29	82.85
Epicanthal fold*	21	60%
Narrow palate	26	74.28%
Kennedy's line	24	68.5%

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Clinodactyly	24		68.57%	
Brachydactyly	24		68.57	
Transverse palmar crease	15		44.85%	
Dysplastic ear*	13		37.14%	
Protuberant abdomen	12		34.42%	
Furrowed tongue	11		31.42%	
	age>28 days (n=27)	Age<28 days (n=8)	age>28 days	Age<28 days
Open mouth	17	1	62.9%	12.5%
Brachycephaly	24	2	88.8%	25%
Protruding tongue*	15	1	55.55%	12.5%
Relative macroglossia	19	1	70.3%	12.5%
Short neck	24		88.8%	

Table 2: Morbidity profile among subjects in the current study

Condition	Incidence(n=35)
Ear discharge	17.1%
Hearing loss	11.4%
GERD	20%
Obstructive sleep Apnea	17.1%
Unprovoked Seizures	5.7%
Dry Skin	31.4%
Anaemia	28.5%
Constipation	11.4%
Breastfeeding problems	82.8%
Severe Acute Malnourishment	26%
Stunting	60.8%
Caries (among toothed) (n=20)	25%
Strabismus	17.1%

Incidence of associated medical issues among subjects are tabulated in table

Most common indication of admission in children with DS who were older than one month (n=27) was Pneumonia(62.9%).

Other illnesses were CCF was present in 4 children out of which 3 also had pneumonia. The rest had miscellaneous illness: diarrhoea(2),Viral pyrexia(2) LTB(1),UTI(1),URTI(1),meningitis(1).

(62.96%) of children (excluding neonates) had history of previous hospitalizations, Average number of admissions per child year was 0.75.

Table 3: Comparision of dysmorphology pattern among studies

Morphological Features	Present study	Pueschel et al.[9]	Kava et al,[10]
Flat face	94.28%		50.9%
Hypotonia	94.28%		76.3%
Loose skin –nape of neck	91.4%	81%	
Upward oblique palpebral fissure	91.4%	82%	83.9%
mouth corners turned downward	51.42%		
Flat nasal bridge	88.57%	68%	
Sandal gap	68.57%	68%	46.2%
Hyper flexibility of joints	82.85	73%	
Epicanthal fold	60%	59%	56.9%
Narrow palate	74.28%	76%	
Kennedy's line	68.5%		
Clinodactyly	68.5%	58%	
Transverse palmar crease	44.85%	53%	33.2%
Dysplastic ear	37.14%	50%	66.9%
Protuberant abdomen	34.42%		
Furrowed tongue	31.42%	55%	
Open mouth	62.95%	58%	
Short neck	88.8%	61%	
Protruding tongue	55.5%	47%	
Brachycephaly	88.8%	75%	
Brachydactyly	68.57%		11.1%

Table 4: Medical Problems Common in Down Syndrome in the present study comparison to review by Bull et al.[17]

Condition	AAP Bull et al,[17]	Present study
Obstructive sleep apnea	50–75%	17.14%
Congenital heart disease	40–50%	57.14%
Hypodontia and delayed dental eruption	23%	9.09%

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Thyroid disease	4–18%	29.15%
Seizures	1–13%	5.7%
Anemia	3%	37.03%

Table 5: Distribution of cardiac anomalies among various studies

Cardiac lesion	Present study	Freeman et al,[20]	Kava et al,[10]	Narayanan DL et al,[18]
VSD	65	35	25.80	28.10
AVSD	15	45	0	27.3
PDA	5	7	0	16.8
TOF	5	4	15.5	0
ASD	10	8	12.1	0

Table 6: Comparison of results of karyotyping in various studies.

Type of anomaly	Present Study	Kava (India),[10]	Prustietal (Odisha),[4]	Narayana et al (kerala),[18]	Koshy (Vellore),[26]	L. Devlin,[27]	Zemel (UK),[28]
Trisomy	97.14	95	78	87.8	82.45	94.7	94.9
Translocation	2.85	3.2	4	8.5	7.01	1.45	3.1
Mosiaic	0	1.8	12	3.1	8.7	3.85	2.1

DISCUSSION

In the present study the incidence of consanguinity was 31.4% as compared to 46% reported by Prustiet al.[4] Advanced maternal age is the most well established risk factor. Indian studies show a lower mean maternal age compared to western studies. The mean maternal age was 26.28 years in our study compress to 32.6 and 34 years in studies by Rankin (UK) and Givetic (Crotia).[5,6] Young mothers, (<30 years) comprised of 80% in this study and 75%,90% in studies by Malini et al,[7] Prusti et al,[4] based in India and 22.8% in the western study by Rankin et al.[5]

The priorities of antenatal screening for DS should consider these changes in maternal age as compared to western population. Manikandan et al elucidate the fallacies of current strategy of screening and emphasize an urgent need for nation wise data on risk distribution and establishment of performance of screening tests.[8]

The most consistent features associated with Down syndrome in the present study are: generalized hypotonia, loose skin in the nape of neck and flat face closely followed by flat nose and upward palpebral fissure. When neonates were excluded, brachycephaly and short neck had high prevalence in children with DS.

Simian crease, epicanthal fold though characteristic of Downs has lesser prevalence.

Features like protruding tongue, open mouth, brachycephaly are not very prevalent in neonates as in children.

This is probably indicating that as the child ages the difference in the mouth and the tongue becomes more prominent. Comparison of Morphological features of present study with other major studies is presented under.

There are large differences in reporting of flat facies, dysplastic ear, furrowed tongue and brachydactyly. This highlights the probable ethnic differences between populations studied.

In the present study only 9/35(34.28%) children were classified as "clinically proven" for Fried index. The index seems less sensitive for detecting DS children in this population. None were "clinically disproven". Difference in Dysmorphic characters of dysplastic ear, mouth corners turned downward and protruding tongue were less commonly observed in this study group compared to study based on which the index is based.[11]

Hall's criteria for neonates describes a score of 6 out of 10 giving a probability of DS diagnosis of 89%.[12] All the neonates in the present study had hall's score 6 and above. Average score was7.25.

Hypotonia is present in 94.25%. Similar incidence is found in Indian study by Kava et al76.3%.[10] Feeding problems are quite common probably due to hypotonia, of which GERD (20%) was the most common. 3 out of the 7 children with DS and GERD were admitted for pneumonia. GERD also affects nutrition of the child. Screening for and treating GERD is important due to high incidence and it predisposes to recurrent aspirations and could contribute to pneumonia and impairs feeding.82.8 % (29/35) had breastfeeding difficulties presently or in the past (before 2 years age) and had history of various degrees of top feeding. Breast feeding rate has been reported to be low68.3% in study by Glivetic et al and 48% by Weijerman et al).[6,13]

History of hearing abnormality was forthcoming only in 4/35 (11.42%). No formal audiological assessment was conducted as part of this study.

Obstructive Sleep Apnea was present in 17.14%. Its incidence is reported to be much higher in other studies-50 to 70%.[14] The lower mean age of study population and under reporting because of attributing irritability and sleepiness the mental retardation of the child are possible explanations. Strabismus was found in higher percentage (17.14%) of children compared to study by kava et al(2.7%).[10]

Anemia was found in higher percentage in the study (37.03%) as expected, is much higher compared to western studies 3% but much lower than prevalence of anemia in general population as per the NFHS5 data (67.1%) probably due to more frequent medical contact.[15]

ISSN (O): 2687-5365; ISSN (P): 2753-6556

In the present study 2/35 (5.7%) children had history of unprovoked seizures. It is described in various studies between 5to 15%. It is near 8% of children with Down syndrome in a study by Roizen et al.[16]

A comparison of the morbidity profile as compared to the review by Bull et al has been presented in the table below. Children with Down Syndrome are fraught with many such problems which, though not life threatening, significantly impair quality of life, growth, learning development. Prompt referrals to the specialist to prevent secondary causes of growth and development retardation are essential.

Incidence of CHD was 57.14% compared to63.4% reported by Narayanan et al,[18] in a study conducted at a genetic centre who screened all patients with 2d echo. This is in contrast to just 18.3% reported by Kava et al,[10] in which study, clinical examination was used to diagnose CHD and only a part of the sample was subjected to echocardiography. A study showed that 13% of patients with normal cardiac physical examination had an abnormal echocardiogram and in 27%the physical examination findings did not correctly predict the echocardiographic findings. As per Mc Elhinney et al in neonates with DS The sensitivity of physical examination findings for detection of cardiovascular anomalies was 80% and the specificity was 56%.[19] This highlights the need for routine 2d echo and not relying exclusively on clinical suspicion of CHD. The following table shows distribution of CHD among various studies. Freeman et al was a study based in Atlanta while the others are from India.

Ethnicity appears to be related to the type and frequency of CHD in the DS children.

In a study conducted in the United States of America, Freeman et al,[20] showed that atrioventricular septal defects had the most significant sex and ethnic differences, with twice as many females affected and with twice as many blacks and half as many Hispanics affected compared to whites. In the Saudi population with DS, VSD was the most common (33.3%) followed by AVSD (22.8%), ASD (21.1%), patent ductus arteriosus (14%) and tetralogy of Fallot (11%).[21] In a Turkish sample, the most common single defect was AVSD (34.2%), followed by second ASD (16.7%) and VSD (16.5%).[22] PDA was the most common cardiac malformation observed in children with DS Guatemal(Central Africa), followed by VSD, ASD and then AVSD.[23]

15% of children with DS and CHD in the present study had evidence of PAH in 2d echo in the present study compared to Fudge et al,[24] in which patients with an atrial septal defect had preoperative pulmonary hypertension (6.2%) patients with a ventricular septal defect (8.4%),4.7% for AVSD. This higher incidence could be due to the 2Decho being taken while the child was suffering from lower respiratory tract infections or due to long standing shunt as none of the subjects had undergone surgically correction.

Most common morbidity in DS child having CHD was pneumonia (65%), similar to study by So et al in which respiratory illnesses affected 64.9% of all hospitalized DS children with CHD.[25]

It is important to recognize that the risk is not greater in operating CHD of a DS child.[24] Also the cost benefit ratio favours early surgical correction as uncorrected CHD add substantially to medical costs of a DS child.[25]

Karyotyping among studies from India and two western nationwide studies are compared with the present study in the above table.

Out of 39 clinically diagnosed with DS, 4 (10.2%) had normal karyotyping. Of these 4children 3 were neonates. This highlights the difficulty in precisely diagnosing DS in neonates by physical examination alone. In comparison; study by Devlin et al, (28.7% subjects had normal karyotyping and 6(0.22%) had another abnormality.[27]

Using objective criteria as per recommendations of National Human Genome Research Institute to define dysmorphic features for facial gestalt and use of Photogrammetry may improve clinical precision in babies suspected to have DS.[28,29]

Strengths of the study:

- There has been no study describing Down syndrome in this region (Telangana) earlier. The study has included only karyotyping proven Down syndrome and has attempted to describe a multiple aspect with universal CHD and hypothyroidism.
- Being hospital based, the morbidity pattern could be assessed.
- As karyotype has been included, skewing of data due to wrong diagnosis based on morphology has been avoided. Similarly, 2d echo was used to rule out CHD in order to avoid silent CHD and innocent murmurs confounding the data.

Weaknesses of study:

- Though Down Syndrome is an uncommon disorder, the present sample size is inadequate to come to definitive conclusions on associations and risk factors.
- Being a hospital based rather than population-based study, many of the factors are not truly representative of the Down Syndrome population.
- Only a single visit has been studied. Objective hearing assessment by prescribed methods (BERA) could not be obtained.
- Being a descriptive study relative risk could not be commented upon.

CONCLUSION

Indices for clinical diagnosis of DS, appropriate for the local population need to be formulated.

Prenatal screening protocols should not be limited to women with advanced age. Further research is

ISSN (O): 2687-5365; ISSN (P): 2753-6556

needed in defining risk factors of conception of DS in young mothers. Universal screening among DS children for hypothyroidism and cardiac anomalies irrespective of symptomatology and clinical findings, Ensuring early referral for surgical correction before PAH becomes irreversible. Early referrals and multidisciplinary care is a must for best outcomes Sandal gap, alert the pediatrician to rule out CHD in the child with DS.

REFERENCES

1. Sherman SL, Allen EG, Bean LH, Freeman SB. Epidemiology of Down syndrome. Ment Retard Dev Disabil Res Rev. 2007;13(3):221-7. doi: 10.1002/mrdd.20157.
2. Shin M, Besser LM, Kucik JE, Lu C, Siffel C, Correa A; Congenital Anomaly Multistate Prevalence and Survival Collaborative. Prevalence of Down syndrome among children and adolescents in 10 regions of the United States. Pediatrics. 2009;124(6):1565-71. doi: 10.1542/peds.2009-0745.
3. Kruszka P, Porras AR, Sobering AK, Ikolo FA, La Qua S, Shotelersuk V, et al. Down syndrome in diverse populations. Am J Med Genet A. 2017;173(1):42-53. doi: 10.1002/ajmg.a.38043.
4. Prusti JS, Panda SK, Sahoo SK, Mishra DN, Sahu MC, Das SR, et al. Incidence of down's syndrome with demographic and chromosomal pattern in Odisha. J Evol Med Dent Sci. 2014;3(60):13415–26.
5. Rankin J, Tennant PW, Bythell M, Pearce MS. Predictors of survival in children born with Down syndrome: a registry-based study. Pediatrics. 2012;129(6):e1373-81. doi: 10.1542/peds.2011-3051.
6. Glivetic T, Rodin U, Milosevic M, Mayer D, Filipovic-Grcic B, Seferovic Saric M. Prevalence, prenatal screening and neonatal features in children with Down syndrome: a registry-based national study. Ital J Pediatr. 2015;41:81. doi: 10.1186/s13052-015-0192-9.
7. Malini SS, Ramachandra NB. Possible risk factors for Down syndrome and sex chromosomal aneuploidy in Mysore, South India. Indian J Hum Genet. 2007;13(3):102-8. doi: 10.4103/0971-6866.38984.
8. Manikandan K, Seshadri S. Down Syndrome Screening in India: Are We There Yet? J Obstet Gynaecol India. 2017;67(6):393-399. doi: 10.1007/s13224-017-1042-z.
9. Lin SY, Hsieh CJ, Chen YL, Shaw SW, Lin MW, Chen PC, et al. The impact of Down syndrome screening on Taiwanese Down syndrome births: a nationwide retrospective study and a screening result from a single medical centre. PLoS One. 2013;8(9):e75428. doi: 10.1371/journal.pone.0075428.
10. Kava MP, Tullu MS, Muranjan MN, Girisha KM. Down syndrome: clinical profile from India. Arch Med Res. 2004;35(1):31-5. doi: 10.1016/j.arcmed.2003.06.005.
11. Fried K. A score based on eight signs in the diagnosis of Down syndrome in the newborn. J Ment Defic Res. 1980;24(3):181-5. doi: 10.1111/j.1365-2788.1980.tb00072.x.
12. Hall B. Mongolism in newborn infants. An examination of the criteria for recognition and some speculations on the pathogenic activity of the chromosomal abnormality. Clin Pediatr (Phila). 1966;5(1):4-12. doi: 10.1177/000992286600500102.
13. Weijerman M, Broers CJ, van der Plas RN. New insights into the support of children with Down syndrome. Ned Tijdschr Geneeskd. 2013;157(6):A5330.
14. Shott SR, Amin R, Chini B, Heubi C, Hotze S, Akers R. Obstructive sleep apnea: Should all children with Down syndrome be tested? Arch Otolaryngol Head Neck Surg. 2006;132(4):432-6. doi: 10.1001/archotol.132.4.432.
15. Sanchez I, Vega-Briceño L, Muñoz C, Mobarec S, Brockman P, Mesa T, et al. Polysomnographic findings in 320 infants evaluated for apneic events. Pediatr Pulmonol. 2006;41(3):215-21. doi: 10.1002/ppul.20346. PMID: 16429436.
16. Roizen NJ, Patterson D. Down's syndrome. Lancet. 2003;361(9365):1281-9. doi: 10.1016/S0140-6736(03)12987-X.
17. Bull MJ; Committee on Genetics. Health supervision for children with Down syndrome. Pediatrics. 2011;128(2):393-406. doi: 10.1542/peds.2011-1605.
18. Narayanan DL, Yesodharan D, Kappanayil M, Kuthiroly S, Thampi MV, Hamza Z, et al. Cardiac spectrum, cytogenetic analysis and thyroid profile of 418 children with Down syndrome from South India: a cross-sectional study. Indian J Pediatr. 2014;81(6):547-51. doi: 10.1007/s12098-013-1088-6.
19. McElhinney DB, Straka M, Goldmuntz E, Zackai EH. Correlation between abnormal cardiac physical examination and echocardiographic findings in neonates with Down syndrome. Am J Med Genet. 2002;113(3):238-41. doi: 10.1002/ajmg.10803.
20. Freeman SB, Taft LF, Dooley KJ, Allran K, Sherman SL, Hassold TJ, et al. Population-based study of congenital heart defects in Down syndrome. Am J Med Genet. 1998;80(3):213-7.
21. Al-Jarallah AS. Down's syndrome and the pattern of congenital heart disease in a community with high parental consanguinity. Med Sci Monit. 2009;15(8):CR409-12.
22. Nisli K, Oner N, Candan S, Kayserili H, Tansel T, Tireli E, et al. Congenital heart disease in children with Down's syndrome: Turkish experience of 13 years. Acta Cardiol. 2008;63(5):585-9. doi: 10.2143/AC.63.5.2033225.
23. Vida VL, Barnoya J, Larrazabal LA, Gaitan G, de Maria Garcia F, Castañeda AR. Congenital cardiac disease in children with Down's syndrome in Guatemala. Cardiol Young. 2005;15(3):286-90. doi: 10.1017/S1047951105000582.
24. Fudge JC Jr, Li S, Jaggers J, O'Brien SM, Peterson ED, Jacobs JP, et al. Congenital heart surgery outcomes in Down syndrome: analysis of a national clinical database. Pediatrics. 2010;126(2):315-22. doi: 10.1542/peds.2009-3245.
25. Peterson C, Dawson A, Grosse SD, Riehle-Colarusso T, Olney RS, Tanner JP, et al. Hospitalizations, costs, and mortality among infants with critical congenital heart disease: how important is timely detection? Birth Defects Res A Clin Mol Teratol. 2013;97(10):664-72. doi: 10.1002/bdra.23165.
26. Koshy B, Navamani K, Oommen SP, Srivastava VM. Growth and development profile of Indian children with Down syndrome. Indian Pediatr. 2012;49(8):676-7.
27. Devlin L, Morrison PJ. Accuracy of the clinical diagnosis of Down syndrome. Ulster Med J. 2004;73(1):4-12.
28. Zemel BS, Pipan M, Stallings VA, Hall W, Schadt K, Freedman DS, et al. Growth Charts for Children With Down Syndrome in the United States. Pediatrics. 2015;136(5):e1204-11. doi: 10.1542/peds.2015-1652.
29. Luthra A. Shaping Lips with Fillers. J Cutan Aesthet Surg. 2015;8(3):139-42. doi: 10.4103/0974-2077.167269.

ISSN (O): 2687-5365; ISSN (P): 2753-6556