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Original Research Article

Evaluation of clinical profile to diagnose Down syndrome with respect to karyotyping as gold standard: a cross-sectional study

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ABSTRACT

Background: Down syndrome (DS) is a genetic disorder characterized with trisomy of chromosome 21 with a high prevalence among countries like India. DS patients present clinically with intellectual disability, congenital heart defect and other major abnormalities. Early diagnosis of DS and intervention with supportive care improves the patient care. To study the efficacy/use of Hall's and Fried's scoring system in diagnosing DS confirmed with karyotyping.
Methods: The patients presented with dysmorphology, intellectual disability or other clinical features of DS are assessed for inclusion using Hall's and Fried's scoring in which patients with score ≥3 are included and considered positive. These patients are further confirmed with karyotyping. The results of Hall's and Fried's scoring are comparing against karyotyping results to check for its efficacy.
Results: The cross-sectional study conducted found males as majorly affected sex (60.4%) for DS and the mean age of child at diagnosis as 6.69±4.84 months in infant stage and 61.86±60.16 months after infant stage. Flat face was present in 100% followed by up slanting palpebral fissures, protruding tongue, abundant neck skin and little digit clinodactyly. ID is seen in all the patients with CHD in 48.8% population and GI abnormalities in 9.3%. Among CHD's, VSD is majorly seen followed by AVSD.
Conclusions: The study found using combined criteria of both Fried's and Hall's score/criteria as an excellent screening test to suspect DS in community level compared to an individual score/criteria.

Keywords: Down syndrome, Karyotyping, Hall's and Fried's scoring, Genetic disorder

INTRODUCTION

Down syndrome (DS) is a genetic disorder characterised with trisomy of chromosome 21, presence of either a portion or full of third copy of chromosome.[1] Patients with down syndrome are presented with mild to moderate intellectual disability and growth retardation.[1,2] It dates back to 1866 when Down syndrome was first described by an English physician, John Langdon Down but the association of the disease to the trisomy of chromosome 21 came into light almost a century later in 1959 by Dr. Jerome Lejeune from Paris.[2] With incidence rate of 1 among 650 to 1000 live births, it accounts for most inherited intellectual disability. 12-15% of patients with learning disabilities in developing countries were of down syndrome.[3] 95% of patients with Down syndrome have a karyotype of trisomy of chromosome 21, 4% present translocation and rest 1% shows a mosaic pattern.[4] In India where the consanguineous marriage rates are very high in the enormous population size and the birth rates are high, the prevalence of Down syndrome is also high. Out of 495,000 infants with congenital mutations 21,400 were with down syndrome.[5] Phenotypical complexity of the DS is due to imbalance in the dosage of genes on the chromosome 21 (Has 21).[6] There are 2 hypotheses stated for phenotypical variations and its association with the genotype, viz., gene dosage effect hypothesis and amplified developmental instability hypothesis. The former hypothesis explains the direct cumulative effect of imbalance in the genes located on the extra copy of the

chromosome 21 while the latter explains the disruption of homeostasis as a result of non-specific chromosomal imbalance.[7]

DS affects various organ systems of the body, hence clinical presentations related to different systems are presented by the patients. Signs and symptoms vary greatly from developmental or intellectual disability (neurological features), GI abnormalities, congenital heart defects, hematological abnormalities, morphological abnormalities of feet, face and hands.[8] Among DS infants congenital heart defects is seen in approximately 40-50%, of which approximately half are of atrio ventricular sepal defects (AVSD) (2,000 of 10,000 DS new born patients have AVSD).[9] A locus related to CLERD 1 is located on chromosome 1p31-p21.[10] In terms of neurological abnormality, DS patients often develop clinical features of Alzheimer's disease (AD).[11] The GI abnormalities includes developmental obstructive defects of small intestine and anomalies of colon and anorectal with intestinal duplication.[12] The hematological abnormalities in newborn with Down syndrome (HANDS) includes thrombocytopenia, neutrophilia, polycythemia, thrombocytosis, congenital leukemia and transient myeloproliferative disorder (TMD).[13] Of all the hematological diseases seen, leukemia accounts more which is developed due to GATA 1 mutation.[14]

Diagnosis of DS at an early stage is vital. Prenatal screening for presence of abnormalities/markers of trisomy of 21 associated with the DS can be done in the second trimester using ultrasound screening for the presence of ventriculomegaly, greater nuchal fold thickness, minimal or no hypoplastic nasal bone, short humeral length, echogenic intracardiac focus and bowel along with choroid plexus cyst that can detect DS with a sensitivity of >90%.[15] However, sonogram will predict the risk of foetal abnormalities the women considered as high risk for DS (increased maternal age, biochemical and sonogram abnormalities) are to be further confirmed with invasive procedures like amniocentesis, chorionic villus sampling and cordocentesis which has a false positive rate of 0.2% but with a miscarriage risk of 1-2%.[16] Other methods developed for diagnosing DS include fluorescence in situ hybridization (FISH) that uses probes specific for chromosomes, quantitative fluorescent (QF)-PCR that uses PCR technique and 2 tetranucleotide short tandem repeat markers and paralogous sequence quantification (PSQ), a PCR based technique that uses a paralogous gene of Hsa21.[17] There are few non-invasive procedures used in prenatal screening for estimating the risk of DS which include presence of foetal cells in the maternal bold and also cell free foetal DNA.[1] Recently placental specific epigenetic markers are also identified that are potent markers that can be used as non-invasive prenatal diagnosis of DS.[18]

DS patients presents with physical and intellectual symptoms, the former one includes almond shapes eyes, upward slanting eyes with a skin fold that comes out from upper eyelid and cover inner corner of eye, flattened face, short neck with excess skin fold on the back of the neck, head, mouth and ears, protruding tongue, tiny white spots on the iris of eye (Brushfield spots), palmar crease (single line across the palm), small hands and feet, small pinky figure that curves outwards poor muscle tone and loose joints, shorter height, deep groove between first and second toes and the latter includes short attention span, poor judgement, impulsive behaviour, slow learning and delayed language and speech development.[19]

METHODS

Study design

The study was a cross-sectional study.

Study site

The study was conducted at the department of paediatrics, AIIMS, Rishikesh, Uttarakhand, India.

Setting

Paediatric outpatient department (OPD) and inpatient department (IPD) in All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India.

Duration

The study was conducted over a period of 18 months from July 2020 to January 2022.

Selection of patients

All suspected cases with dysmorphic features, development delay, educationally subnormal presenting to genetic clinic, paediatric clinic/IPD/emergency, AIIMS, Rishikesh was enrolled based on criteria for inclusion and exclusion.

Inclusive criteria

Infants, children and adolescents with features suggestive of Down syndrome (according to Hall's and Fried's criteria), priorly diagnosed with Down syndrome by karyotyping were included in the study.

Exclusive criteria

Patients with clinical features <3 according to Hall's criteria/Fried's criteria, and who gave refusal of consent were excluded.

Sample size

It is a time-bound exploratory study (from July 2020 to January 2022). Convenient sample size is taken for the study, as the prevalence of DS is very low. All the patients

presented to the genetic clinic during the study period are pooled for sample.

Ethical approval

The study was approved by All Indian Institute of Medical Sciences, Rishikesh, institutional ethics committee. Approval no.: ECR/736/Inst/UK/2015/RR-18.

Methodology

All suspected cases with dysmorphic features, development delay, educationally subnormal presenting to the genetic clinic, paediatric clinic/IPD/emergency, AIIMS, Rishikesh were possible subjects. If found to have features of Downs syndrome (using Fried's criteria and Hall's criteria/scoring system) the patients were enrolled in the study after obtaining written informed consent and photography consent from the parents/guardians. This dysmorphology didn't change much with time as per available knowledge from different sources. So, we used both Fried's criteria and Hall's criteria for both children and adolescents to suspect DS. If suspected cases have either three signs from any one of the criteria, then the child were included in the study. Scoring is done by giving score 1, if the clinical feature is found according to Hall's and Fried's criteria, and if not found, then the score 0 was marked to that particular feature. As this scoring is done even in priorly diagnosed children, the observer was blinded to antenatal/karyotype reports in order to have unbiased clinical examination. Any patient with atleast score 3 in any one of the criteria are included in the study and are confirmed by doing karyotyping. Once children have been included in the study, baseline assessment is done that includes the following points.

Relevant history was taken as per the proforma (in the patient's own language).

Relevant physical examination to check for dysmorphology. Certain photographs were taken for dysmorphology features after taking consent from parents, assessing the developmental/cognitive co-morbidities using VSMS under the guidance of the consultant, assessing growth using CDC special growth charts for DS.

Routine investigations like complete blood count (CBC), liver function test (LFT), and renal function test (RFT) were done. Primary screening like echocardiography (echo), ultrasonography (USG) abdomen, and thyroid profile was done if not done earlier.

Confirmatory cytogenetic diagnosis in all suspected DS cases by taking peripheral blood samples in a heparinized vial. While receiving blood samples, informed consent was obtained from parents. The cultivation of cells (lymphocytes) produced from a specimen is the first step in the karyotype process. Colchicine is administered after a period of cell growth and multiplication to arrest the cells in metaphase, poisoning the mitotic spindle. The cells are then exposed to a hypotonic solution, which causes them to explode. The nuclei are then fixed using a chemical fixative, placed on a glass slide, and treated with various dyes to reveal the chromosomes structural properties. G-banding involves treating metaphase chromosomes with trypsin first, then staining them with Giemsa. Trypsin partially digests the chromosomal proteins, thereby relaxing the chromatin structure and allowing the Giemsa dye to access the DNA, revealing chromosomal structural characteristics. Finally, slides were observed under Robotic microscopy.

If the karyotype is found positive, then the sensitivity of these criteria was assessed in diagnosing Down syndrome. Any additional phenotyping features was noted if found in this geographical area.

If the cytogenetic study is unable to find any mosaicism, then the FISH technique was used. If FISH is positive, then the patient was included in the study. The patient was not be charged for any investigation, and it was be self-funding.

Statistical analysis

Primary outcome variables were Fried's score, Hall's score, karyotyping and VSMS. Primary explanatory variable was the clinical profile. For quantitative variables, descriptive analysis was performed using the mean and standard deviation. For categorical variables, frequency and proportion were used. The association between explanatory variables and categorical outcomes was assessed by cross-tabulation and comparison of percentages. Hall's criteria and Fried's criteria was considered as a screening test. Karyotyping was considered as the gold standard. The sensitivity, specificity, predictive values, and diagnostic accuracy of the screening test, along with their 95% CI were presented. P value <0.05 was considered statistically significant. Data was analyzed by using CoGuide software.[20]

RESULTS

After applying both the criteria individually in all patients, the patients with only greater than or equal to 3 score in any of the criteria are included in the study. Of 480 patients screened for DS only 43 were tested positive (score ≥ 3) and are included in the study.

The mean baby age at diagnosis was 6.69±4.84 months in the infant stage and 61.86±60.16 months after the infant stage. Among the study population, 26 (60.47%) participants were male and 17 (39.53%) participants were female. The mean age of mother at conception was 26.02±3.71 years, and age of father at conception was 29.56±4.18 years. All DS participants had CNS involvement as ID while 48.8% had cardiovascular anomalies, as the most common congenital anomaly and 13.95% had endocrinal issue as hypothyroidism. The

incidence of congenital heart diseases in our study was 48.8%. The most common CHD found was VSD followed by ASD and PDA were seen. A sizeable proportion of AVSD (4.65%) seen in our study.

Table 1: Descriptive analysis of baseline parameters in the study population (N=43).

Parameter	Study population (N=43)
Baby age at diagnosed (in months)	
At infant stage (N=21)	6.69±4.84 (0.03, 12.00)
At after infant stage (N=22)	61.86±60.16 (13.0, 182.0)
Gender (%)	
Male	26 (60.47)
Female	17 (39.53)
Age of mother	
Age of mother at conception	26.02±3.71 (20.00, 40.00)
Age of father at conception	29.56±4.18 (24.0, 50.0)
Diagnosis (%)	
Down syndrome with ID	36/36** (100)
Down syndrome with Cardiac disorders (VSD+ASD+PDA+AVSD)	21 (48.8)
Down syndrome with VSD	12 (27.91)
Down syndrome with hypothyroidism	6 (13.95)
Down syndrome with ASD	5 (11.63)
Down syndrome with GIT malformations	4 (9.30)
Down syndrome with PDA	4 (9.30)
Down syndrome with genito urinary disorders	3 (6.98)
Down phenotype	3 (6.98)
Down syndrome with AVSD	2 (4.65)
Down syndrome with myopia, nystagmus	2 (4.65)
Down syndrome with hearing abnormalities	1 (2.33)

** 4 patients were neonates and so ID could not be estimated; 3 children with DS phenotype could not be assessed with VSMS

The majority of 100% participants were reported flat face, followed by hypotonia was 88.40%, up slanting palpebral fissures was 83.70%, protruding tongue was 74.40% and abundant neck skin was seen in 53.50%. The majority of 38 (88.40%) participants had sparse hair, followed by anterior hair line was 28 (65.10%), arched eye brows was 14 (32.60%) and synophrys was seen in 11 (25.60%) cases.

Out of 43 participants, 40 were came to be positive finally after karyotyping. Among the study population, thirty-nine (90.70%) participants had trisomy 21, only one (2.50%) participant had translocation 13 and 21, and three were clinically positive, karyotyping was done and it came out to be normal.

Table 2: Descriptive analysis of clinical parameters in the study population (N=43).

Parameter	Study population (N=43) %
Clinical profile of DS	
Flat face	43 (100.00)
Hypotonia	38 (88.40)
Up slanting palpebral fissures	36 (83.70)
Protruding tongue	32 (74.40)
Abundant neck skin	23 (53.50)
Short fifth digit with clinodactyly	18 (41.90)
Dysplastic ear	15 (34.90)
Simian crease	14 (32.60)
Sandal gap	14 (32.60)
Epicanthic fold	14 (32.60)
Mouth corners turned downwards	4 (9.30)
Poor MORO reflex	4 (9.30)
Hyper flexibility joints	4 (9.30)
Additional phenotypic features	
Sparse hair	38 (88.40)
Anterior hair line (subjective)	28 (65.10)
Arched eye brows	14 (32.60)
Synophrys	11 (25.60)

Table 3: Descriptive analysis of outcome parameters in the study population (N=43).

Parameter	Study population (N=43) %
Karyotyping	
Trisomy 21	39 (90.70)
Normal	3 (6.98)
Translocation 13 and 21	1 (2.33)
Hall score (out of 10)	
2	1 (2.33)
3	11 (25.58)
4	9 (20.93)
5	10 (23.26)
6	10 (23.26)
7	2 (4.65)
Fried's score	
1	1 (2.33)
2	1 (2.33)
3	9 (20.93)
4	15 (34.88)
5	10 (23.25)
6	6 (13.95)
7	1 (2.33)
VSMS	
Mild ID	21 (58.33)
Moderate ID	14 (38.89)
Severe ID	1 (2.78)

Table 4: Comparison of different total scores with karyotyping (n=43).

Clinical criteria	Karyotyping (%)		P value
	Present (N=40)	Absent (N=3)	
Hall's score			
Positive	39 (97.5)	3 (100)	0.782
Negative	1 (2.5)	0 (0)	
Fried's score			
Positive	39 (97.5)	2 (66.67)	0.014
Negative	1 (2.5)	1 (33.33)	
Both score			
Positive	40 (100)	3 (100)	---
Negative	0 (0)	0 (0)	

The difference in the proportion of Hall's score between karyotyping was statistically not significant (p value 0.782).

The difference in the proportion of Fried's score between karyotyping was statistically significant (p value 0.014). Both scores, in karyotyping present 40 (100%) were in positive, 0 (0%) were in negative and in absent 3 (100%) were in positive, 0 (0%) were in negative.

In Hall's score, false positive rate has the maximum predictive validity i.e. 100.00%, it was 97.50% for sensitivity, 92.86% for positive value, 90.70% for diagnostic accuracy, 2.50% for false negative rate and 0.00% for specificity and negative predictive value. In Fried's score, sensitivity has the maximum predictive validity i.e. 97.50%, it was 33.33% for specificity, 66.67% for false positive value, 2.50% for false negative rate, 95.12% for positive predictive value and 50.00% for negative predictive value and 93.02% for diagnostic accuracy. In both score, sensitivity and false positive rate has the maximum predictive validity i.e. 100.00%, it was 0.00% for specificity, false negative rate and negative predictive rate, 93.02% for positive predictive value and 50.00% and 93.02% for diagnostic accuracy.

Table 5: Predictive validity of different total scores with respect to karyotyping (N=43).

Parameter	Hall's score (%)	Fried's score (%)	Both score (%)
Sensitivity	97.50 (86.84, 99.94)	97.50 (86.84, 99.94)	100.00 (91.19, 100.00)
Specificity	0.00 (0.00, 70.76)	33.33 (0.84, 90.57)	0.00 (0.00, 70.76)
False positive rate	100.00 (29.24, 100.00)	66.67 (9.43, 99.16)	100.00 (29.24, 100.00)
False negative rate	2.50 (0.06, 13.16)	2.50 (0.06, 13.16)	0.00 (0.00, 8.81)
Positive predictive value	92.86 (80.52, 98.50)	95.12 (83.47, 99.40)	93.02 (80.94, 98.54)
Negative predictive value	0.00 (0.00, 97.50)	50.00 (1.26, 98.74)	0.00 (0.00, 0.00)
Diagnostic accuracy	90.70 (77.86, 97.41)	93.02 (80.94, 98.54)	93.02 (80.94, 98.54)

DISCUSSION

Our study conducted to formulate the diagnostic efficacy of Hall's and Fried's score/criteria in diagnosing DS so as to surpass routine expensive karyotyping to confirm the same has resulted a greater proportion tested positive using Halls score (97.5%) and Fried's score (97.5%) and are confirmed with same upon karyotyping analysis. Various disorders secondary to DS include 100% population with ID, 48.8% with CHD followed by 9.3% with GI abnormalities. Of all the study participants with ID 58.3% were with mild ID, 38.8% and 2.78% were with moderate and severe respectively. Among CHD, VSD is majorly seen in our study population with 27.9% patients. Clinical presentations are as 100% population presented flat face, followed by 88.4% with hypotonia, 83.7% with slanting palpebral fissure and 74.4% with protruding tongue, 53.5% with abundant neck skin.

A retrospective analytical study conducted by Kava et al included a sample of 524 patients in which males contributed majorly with 57.8% and females of 42.1% which is in great agreement with our study proportions of 60.5% males and 39.5% females, along with few other studies with similarity.[21,22] Most of the DS patients presented trisomy of 21st chromosome with 90.7% which is similar to most of the results published.[22,23] A study conducted by Stoll et al in European population and Jaruratanasirikul et al showed similarity with our study results in terms of proportion of CHD and GI abnormalities seen among DS patients.[24,25] However, the most seen CHD in our study, VSD, varies from the existing evidence of which AVSD is mostly seen.[24,26] A study conducted by Layangool et al reported VSD as the common CHD seen among DS patients.[27]

Falt seen in 100% of our study population but is presented in 94% as in study of Bertelli et al and 82% in the study conducted by Sharath et al.[28,29] The same 2 studies result also published the similarity of our study in terms of proportion of patients presented clinodactyly.[28,29]

The current study is limited with the sample size being small which is due to COVID-19. The current also unable to perform karyotyping in all children who were screened because of logistic constraints, so we might have missed those with atypical phenotype. Hence, the specificity detected in our study might be actually an underestimation

of true specificity which is to be addressed in future studies.

CONCLUSION

The cross-sectional study conducted found males as majorly affected sex for DS and the mean age of child at diagnosis as 6.69±4.84 months in infant stage and 61.86±60.16 months after infant stage. Flat face was present in 100% followed by up slanting palpebral fissures, protruding tongue, abundant neck skin and little digit clinodactyly. ID is seen in all the patients with CHD in 48.8% population and GI abnormalities in 9.3%. Among CHD's, VSD is majorly seen followed by AVSD. The cross-sectional study conducted in a tertiary centre found using combined criteria of both Fried's and Hall's score/criteria as an excellent screening test to suspect DS in community level compared to an individual score/criteria. Despite of low prevalence of DS, awareness of the disease and the importance of early diagnosis and supportive intervention is needed to be created awareness among communities. All the state's health care systems particularly in countries like INDIA where the incidence of genetic diseases is very high, governments should include screening criteria in order to impart basic knowledge to all the residents/staff nurses and staff.

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