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CLINICO-EPIDEMIOLOGICAL PROFILE OF CHILDREN WITH DOWN SYNDROME IN A TERTIARY CARE CENTRE OF WEST BENGAL

Paediatric Medicine

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ABSTRACT

Background: Down syndrome (DS) is the commonest chromosomal aneuploidy. The clinical features are quite easily identifiable, but cytogenetic analysis is always better to confirm the diagnosis. Early identification and intervention are important to improve patient care and family counselling. **Objectives:** To determine the pattern and prevalence of clinical features, systemic anomalies and associated epidemiological parameters in children with DS. **Method:** An observational, descriptive study was conducted in the Department of Paediatric Medicine of a tertiary care hospital in Kolkata, West Bengal from March 2020 to August 2021. The children aged between 1 month to 12 years, satisfying the inclusion and exclusion criteria were included. They were subjected to detailed history taking, clinical examination, required hematological & radiological investigations and treatment for the present illness. **Results:** 96 boys (48%) and 104 girls (52%) were analysed giving a male to female ratio of 0.9:1. The commonest age group was 1-12 months (52%). Majority of mothers (42%) were in the age group of 20-24 years & only 10% of mothers were above 34 years of age at conception. None of the mothers underwent antenatal screening for DS. Up slanting palpebral fissure was noted in 92% of them. Children less than 3 years of age had statistically significant lower (<5th percentile) weight for age, height for age and head circumference. 82% had congenital cardiac anomaly. Atrio-ventricular septal defect (AVSD) was the most common (43.9%) cardiac defect. Males had higher prevalence of hypothyroidism than females (p value: 0.011). Cytogenetically, 196 had free trisomy-21 (98%), three had Robertsonian translocation (1.5%) and one had mosaicism (0.5%). **Conclusions:** The study concludes more female affection for DS. Younger mothers had more DS babies. Craniofacial features were most commonly observed. Trisomy 21 was the most common cytogenetic abnormality. AVSD was the major cardiac defect. Male DS children had more hypothyroidism than female.

KEYWORDS

Down Syndrome, Cardiac Anomalies, AVSD, Hypothyroidism, Cytogenetics

INTRODUCTION:

Down syndrome (DS) is the commonest chromosomal aneuploidy with a high life expectancy as compared to other chromosomal aneuploidies[1]. The incidence ranges from 1 in 600 to 1 in 1000 live births and the incidence in India is 0.88–1.09 per 1000.An estimated number of 21,400 infants are born per annum in India with DS[2].Cytogenetically there are three types of DS: Free trisomy- 21, Robertsonian translocation and mosaicism[3]. Free trisomy-21 is characterised by presence of an extra 21 chromosome resulting due to nondisjunction during meiosis and is seen in about 95% of cases[4].Translocations are attributed to 3–4% of the cases, with Robertsonian translocation involving chromosome 14 and 21 being the most common type. Mosaicism is reported in 1% of DS patients and is characterised by cells containing 46 chromosomes and others with 47 chromosomes. An error in cell division soon after conception is thought to be the cause of mosaicism. The cardinal clinical features include flat facial profile, up slanting palpebral fissure, epicanthic fold, flat nasal bridge, protruding tongue, brachycephaly, and high arched palate, low set ears, simian crease, sandal gap, short stubby fingers, hypotonia, congenital heart disease, short stature, and mental retardation[5].DS can cause a variety of medical complications like congenital heart defects, gastrointestinal defects, hip dislocation, ear and eye disease including cataracts and severe refractive errors, hearing loss, obstructive sleep apnoea, leukaemia, thyroid disease[6].Screening tests for DS can be performed in the antenatal period and can be confirmed by cytogenetic analysis in the postnatal period. It is also needed for calculating the risk of recurrence and genetic counselling.

DS represents a major cause of infant morbidity and mortality. The identification of specific types of chromosomal abnormalities in these children is important as it would help in patient management and family counselling. Very few reported studies on clinico-epidemiological profile of DS from a tertiary care centre of West Bengal are available. The existing studies have been conducted around 2000-2012, no recent update of data is available.

OBJECTIVES:

To determine the pattern and prevalence of clinical features and systemic anomalies and associated epidemiological parameters in children with DS from tertiary care centre of West Bengal.

METHODS:

This observational, descriptive study was conducted from March 2020 to August 2021 in a tertiary care hospital in Kolkata, West Bengal. Our study population comprised the children, attended outpatient and inpatient Department of Paediatric Medicine who satisfied the inclusion and exclusion criteria.

Inclusion criteria:

(a) Children aged between 1 month to 12 years (b) Diagnosed cases of DS (confirmed by karyotyping or molecular genetic analysis).

Exclusion criteria:

(a) Phenotypically Down not confirmed by karyotyping or molecular genetic analysis (b) Co-existence of other syndromes.

Sample size:

Considering the last 3 years' outdoor visit and indoor admission rate of DS cases, along with the time bound study period we have taken the convenient sample size of 200 children.

Methodology:

All the study participants were evaluated by thorough clinical examination and treated for the present illness. The study proforma were filled up going through the past medical records supplemented by the history as well as the investigations performed in the course of the study. The collected anthropometric data were put on growth charts for children with DS in the U.S. Paediatrics, for weight, length/height and head circumference and analysed. Under strict aseptic condition, 2 ml peripheral venous blood was collected in ethylenediaminetetraacetic acid (EDTA) vacutainer and serum vacutainer. The EDTA container was sent to Genetic Services Unit, National Institute of Biomedical Genomics, Kolkata for molecular genetic analysis while the serum vacutainer was used for the estimation of thyroid stimulating hormone (TSH) and free T4 (fT4). Following reference ranges were taken to

assess any thyroid abnormality: TSH= 0.5-5.6 mIU/L and free T4= 0.8-2.6 ng/dl [7]. Primary screening like echocardiography, ultra sonogram and skiagram were also carried out. All of these were done at free of cost. Our study variables were: demographic details, phenotypic features, anthropometry, congenital anomalies, thyroid hormone status and cytogenetics.

Ethical issues:

Approval for the study was obtained from the Institutional Ethics Committee of the Institute of Post Graduate Medical Education and Research (No: IPGME&R/IEC/2020/581). Written informed consent from parents or legal guardians of the participating children was taken.

Statistical analysis:

Data was collected, recorded and compiled on Microsoft Excel datasheet, statistical methods (mean, standard deviation) and software was used to analyse the data. Categorical variables are expressed as number of patients and percentage of patients and compared across the groups using Pearson's Chi Square test for Independence of Attributes/ Fisher's Exact Test as appropriate. Continuous variables are expressed as Minimum, Maximum, Mean, Median and Standard Deviation. The statistical software SPSS version 22 has been used for the analysis. An alpha level of 5% has been taken, i.e., if any p value is less than 0.05 it has been considered as significant.

RESULTS:

Two hundred children - 96 boys (48%) and 104 girls (52%) were included in the analysis giving a male to female ratio of 0.9:1. The commonest age group was 1-12 months (52%) and the mean age of presentation was 29.84 months. Only 4% children were born out of consanguineous marriage. Majority of mothers were in the age group of 20-24 years at conception (42%). 10% of mothers were of >34 years of age at conception. The mean maternal age at the time of conception was 25.8 years. Majority of fathers were in the age group of 25-29 years (36%). The mean age of father was 30.9 years [Table:1].

Table 1: Demographic and cytogenetic parameters of the study population (n=200)

Variables		Values
Age distribution	1-12 months	104 (52%)
	>12 months – 5years	64 (32%)
	>5years- 12 years	32 (16%)
Gender	Boys	96 (48%)
	Girls	104 (52%)
Age of child at presentation (months)		29.84 ± 37.63 (1.00, 120.00)
Age of mother at conception (years)		25.8 ± 5.46 (18.00, 40.00)
Age of father at conception (years)		30.9 ± 5.49 (22.00, 45.00)
Cytogenetics	Trisomy 21	196 (98%)
	Translocations	3 (1.5%)
	Mosaicism	1 (0.5%)

Among the various phenotypic features, the common features seen were: up slanting palpebral fissure in 196 children (92%), followed by flat facial profile in 164 children (82%) and hypotonia in 148 children (74%). Other features seen were: protruding tongue (44%), epicanthic fold (54%), hypertelorism (24%), ear abnormality (40%), simian crease (46%), sandal gap (52%), short stubby fingers (28%), clinodactyly (6%) [Figure:1].

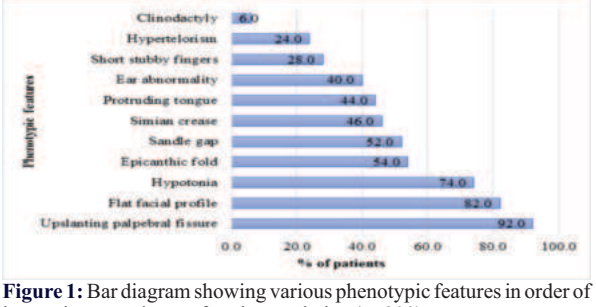

Figure 1: Bar diagram showing various phenotypic features in order of increasing prevalence of study population (n=200)

Majority of the children had weight for age <5th percentile (50%), height for age between 5th – 50th percentile (60%) and head circumference <5th percentile (64%). Interestingly from our study we found children less than 3 years of age had statistically significant lower (<5th percentile) weight for age, height for age and head circumference.

82% had congenital cardiac anomaly. Atrio-ventricular septal defect (AVSD) (43.9%) was the most common cardiac defect seen, followed by ventricular septal defect (VSD) (19.5%) and atrial septal defect (ASD) (12.3%) [Table: 2]. 89.19% of children <3 years of age had cardiac anomalies compared to 61.54% children >=3 years and this was statistically significant (p 0.040). Thus, younger children (<3 years) had more cardiac anomalies compared to older children (>=3 years). Sixteen children had other congenital anomalies (8%). Out of them, 5 had diaphragmatic hernia, 5 had duodenal atresia, 4 had Hirschsprung disease and 2 had eventration of diaphragm.

Table 2: Types and prevalence of congenital heart disease of the study population (n=164)

Type of congenital heart disease	Frequency	Percent
AVSD	72	43.9
VSD	32	19.5
ASD	20	12.3
ASD with PDA	12	7.3
PDA	12	7.3
TOF	8	4.9
DORV with ASD	4	2.4
VSD with PDA	4	2.4
Total	164	100.0

Endocrinal issue as hypothyroidism was seen in 22% of them. Out of them 37.5% of the males had hypothyroidism as opposed to 7.69% of the females, which was statistically significant (p 0.011) [Figure: 2].

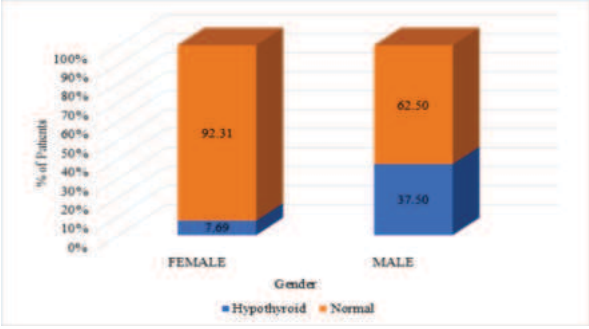

Figure 2: Column diagram showing distribution of thyroid profile and gender (n=200) where 37.50% males had hypothyroidism as compared to 7.69% females.

Out of 200 children, 196 had free trisomy 21 (98%), 3 had Robertsonian translocation (1.5%), 1 had mosaicism (0.5%) [Table:1]

DISCUSSION:

Our study had more number of girls (male to female ratio was 0.9 :1) and this was in contrary to the majority of previous studies [5] [8] which had a higher male sex ratio. It may be due to the change in the perspective towards the female children regarding their care and health. So, now more female children are brought to hospital than before.

The average age at presentation was 29.84 months. It is similar to the study by Sharath et al [5] where the average age of presentation was 30 months. From table:1 it was evident that more than 80.0% of DS cases were diagnosed before the age of 5 years, which indicates that paediatricians and other medical professionals are aware of the clinical phenotype of DS and expedites the cytogenetic confirmation. Late DS diagnosis can result in delayed intervention and appropriate therapy for some risk conditions, such as congenital heart diseases and thyroid dysfunction. These must be detected and treated, otherwise they contribute to morbidity and mortality of these children, in addition, to having an impact in the physical and psychological development.

In our study, mean maternal age at the time of conception was 25.8 years, where it was 28.5 years in Sharath et al study [5] and 26.8 years in the study by Kava et al [9]. Thus, in our study there is an increase in the incidence of DS among younger mothers. This finding was contrary to the previous belief of increased incidence of DS in older mothers. Other risk

factors may be responsible for the increased incidence of DS among younger mothers. Several recent studies have shown relation between the maternal risk factor for DS and genetic polymorphism involved in folate mechanism. Hypomethylation of the centromeric DNA as a result of abnormal folate metabolism leading to abnormal chromosomal segregation and studies point to the role of polymorphisms in some genes involved in homocysteine metabolism as risk factors for DS [10]. Also, culture norms in India are different as most pregnancies occur in younger women, approximately 80% of all babies with DS were born to women under the age of 35. This is very much evident in our study as 90% children with DS were born to mothers below 34 years of age. The mean age of father was 30.9 years which was somewhat similar to Sharath et al study[5]. There is a lack of studies relating paternal age and DS. In study by Hatch et al[11] no evidence of paternal age effects on the trisomy's were found among spontaneous abortions or on chromosomally normal losses. Thus, there is a need for a large sample study to assess the possible relation between paternal age and prevalence of DS.

Very low percentage of DS children (only 4%) were born out of consanguineous marriage. Thus, there was a lower incidence of parental consanguinity in our study as compared to the previous studies [5][12]. Surprisingly, none of the mothers had undergone screening test in the antenatal period. Regardless of age and the familial relationship, screening tests for DS should be offered. First trimester screening includes nuchal translucency ultrasonography and measurement of maternal serum human chorionic gonadotropin (beta-hCG) and pregnancy associated plasma protein A (PAPP-A). Second-trimester screening is available for patients who seek first medical care in the second trimester or in locations where first-trimester screening is not available. The second-trimester screening, often called the quad screen, incorporates maternal age risk with measurement of maternal serum hCG, unconjugated estriol, alpha-fetoprotein (AFP), and inhibin levels [13].

Anthropometric evaluation showed that children less than 3 years of age had weight for age, height for age and head circumference below 5th percentile, which was statistically significant (p value: 0.004, 0.039, 0.043 respectively). Thus, children with DS appear to increase their weight & height with age which is similar to another study Sachdev et al[14]. Since then, there have been no further studies, especially for older children. Therefore, there is a need for the development of standard growth charts for DS children of Indian population along with the need for more anthropometric studies to get a better idea about the growth patterns of children with DS.

The clinical features are quite distinguishing and easily identifiable, but a clinical diagnosis of DS is inaccurate in about one-third of the cases. The knowledge of clinical manifestations of DS is important to make an early postnatal diagnosis. Craniofacial features are the most conspicuous for diagnosis. Comparison between our data and related literature showed considerable variability of the phenotype feature frequencies in Table:3. In addition to environmental factors, the individual and population characteristics also creates variation as India is one of the countries with the different ethnic heterogeneity. Thus, mixed gene population may affect the phenotypic features.

Table:3 Comparison Of Phenotypic Features Of DS In Our Study And Previous Studies

Characteristics	Present study	Sharath et al (5)	Kava et al (9)	Ahmed et al (18)
Up slanting palpebral fissure	92%	64%	83.9%	83%
Flat facial profile	82%	82.6%	50.9%	63%
Hypotonia	74%	-	-	-
Protruding tongue	44%	76%	79.9%	-
Epicanthic fold	54%	-	56.9%	-
Hypertelorism	24%	85.3%	-	86.7%
Ear abnormality	40%	48%	66.9%	45.7%
Simian crease	46%	36%	33.2%	64.7%
Sandal gap	52%	60%	46.2%	46.4%
Clinodactyly	6%	49.3%	36.1%	24.7%

In our study, 82% children had congenital heart disease (CHD) where AVSD was the most common CHD seen in the children (43.9%), followed by VSD (19.5%) and ASD (12.3%). It is comparable with various studies [15][16]. Our study had a much larger number of children with CHD compared to other studies [9][5]. Since our institute is a tertiary referral centre for heart diseases, so we encountered more cases of CHD and this could be a reason for the larger number of DS children with CHD in our study.

Hypothyroidism was found in 22% of the DS children where it was significantly more common (p value: 0.011) in males than female. Both hypothyroidism and hyperthyroidism are more common in patients with Down syndrome than in the general population [17]. However, in our study only hypothyroidism was seen. Therefore, screening for any thyroid abnormality should be done in all children with Down syndrome.

The strength of our study is that we found the lack of awareness regarding antenatal screening, need of DS specific growth chart for Indian population and potentiality of future research to explore any relation between paternal age and DS. The limitation of the study is small sample size and very limited time period. It may not be adequately powered to draw major statistical conclusions. So, the result of this study may not be applicable for the total community. This study was carried in a tertiary care centre, so there may be chance of over representation of CHD cases.

CONCLUSION:

The study concludes that females as majorly affected sex for DS and the mean age of child at diagnosis as 29.84 ± 37.63 months. Younger mothers had more DS babies. Craniofacial features were the commonly observed characteristic in DS children. Trisomy 21 was the most common cytogenetic abnormality. Up slanting palpebral fissure (92%), flat facial profile (82%) and hypotonia (74%) were the common phenotypic features seen. Among CHD's, AVSD was majorly seen. Male DS children had more hypothyroidism than females. Various health problems are more common in Down syndrome than the common population. The parents should be made aware of these complications. Health supervision and timely screening should be done. This can help in reducing the morbidity and mortality. Medical management, home environment, early intervention, education, and vocational training can significantly affect the level of functioning of children and adolescents with Down syndrome and facilitate their transition to adulthood.

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