INTERNATIONAL JOURNAL OF MEDICAL AND APPLIED SCIENCES
Earthjournals Publisher
E-ISSN:2320-3137
www.earthjournals.org

RESEARCH ARTICLE

CLINICO-CYTOGENETIC STUDY OF DOWN SYNDROME

Surendra .H.S*, Sunil.B, Shepur.T.A , Sumanth Amperayani, Preeti.G , Abinandan Dorle

Gurushree Hi- Tech Multispeciality Hospital, Bangalore

Corresponding Author: Dr. Surendra .H.S

Abstract

Background: Down syndrome (DS) is the most common chromosomal disorder and genetic cause of mental retardation with prevalence of 1 in 700 births. The present study is being undertaken to know the clinical features, maternal age correlation, congenital anomalies and cytogenetic of DS. **Methods:** This prospective hospital based study was done in children in the age group of 0 to 12 years admitted to Pediatric Department of a tertiary care hospital in Northern Karnataka, over a period of 1 year (01-11-2011 to 31-10-2012) with clinical suspicion of Down syndrome. **Results:** Out of 37 DS cases, 19 (51.35%) were male and 18 (48.65%) were female. Most common clinical feature was up slanting palpebral fissure (100%). Thirty (81.09%) mothers were less than 30 years of age at the time of conception and 7 (18.91%) mothers were more than 30 years of age. Gastro intestinal anomaly was seen in 1 (2.7%) new born case of DS. 14 (37.84%) children had congenital heart disease (CHD) and ostium secundum atrial septal defect was the commonest (28.57%). Karyotyping results of all cases were trisomy 21. **Conclusion:** Most common clinical feature was up slanting palpebral fissure, followed by full cheeks, flat nasal bridge, narrow and short palate, short and broad hands, microcephaly, flat occiput, epicanthic folds and protruded tongue. Majority of mothers were less than 30 years of age at the time of conception. OS-ASD was most common type of CHD. Karyotyping of all DS cases had trisomy 21.

Key words: Down syndrome, Karyotyping, Maternal age.

INTRODUCTION

Down syndrome (DS) is the most common chromosomal disorder and genetic cause of mental retardation (1). Frequency of Down syndrome in western population is 1 in 700 births (2) and in Indian population, it is estimated to be 1 in 920 births (3). Trisomy 21 is one of the most intensively studied human aneuploid conditions. It is one of the few autosomal trisomies that survive to term, although 80% of conceptions with trisomy 21 are spontaneously aborted (4).Incidence increases with advanced maternal age (>35yr) (1).

In approximately 95% of children with Down syndrome, the condition is because of non-familial trisomy 21. In approximately 3% to 4% of persons with the Down syndrome phenotype, the extra chromosomal material is the result of an unbalanced translocation between chromosome 21 and another acrocentric chromosome, usually chromosome 14. Approximately three fourths of these unbalanced translocations are de novo, and the rest is the result of familial translocations. If the child has a translocation, a balanced translocation must be excluded in the parents. If there is a translocation in either parent, additional familial studies and counselling should be instituted. In the remaining 1% to 2% of persons with the Down syndrome phenotype, 2 cell lines are present: one normal and one trisomy 21. This condition is called mosaicism.

These persons, on average, may be phenotypically less severely affected than persons with trisomy 21 or translocated chromosome 21, but their conditions are generally indistinguishable in all other aspects (5).

As there are no studies done in this part of Karnataka, the present study is being undertaken at KIMS Hospital Hubli, to know the clinical features, maternal age correlation, congenital anomalies and cytogenetics of Down syndrome.

AIMS AND OBJECTIVES

1. To study the clinical features of Down syndrome.
2. To correlate maternal age with Down syndrome.
3. To study the incidence of medical and surgical problems associated with Down syndrome.
4. Cytogenetic study of Down syndrome.

MATERIALS AND METHODS

Children in the age group of 0 to 12 years admitted to Paediatric Department at KIMS Hospital, Hubli over a period of 1 year (01-11-2011 to 31-10-2012) with clinical suspicion of Down syndrome were included in the study. This is a prospective hospital based study.

Inclusion criteria:

All children in the age group of 0 to 12 years admitted to Paediatric Department at KIMS Hospital, Hubli with clinical suspicion of Down syndrome.

Exclusion criteria:

Patients whose parents were not willing to give consent were excluded from the study.

Method of collection of data:

All cases were studied with reference to history, physical examination, systemic examination, Karyotyping and with other necessary investigations in relevant cases. A detailed proforma was used to register the cases.

Parents were explained the need for the study, and written and informed consent was taken.

The following investigations were done in all cases:

1. Complete Haemogram
2. Chest x- ray
3. Ultrasound of abdomen
4. 2D echocardiogram
5. Karyotyping

Karyotyping was done at DNA diagnostic centre, Karnataka University, Dharwad. The definitions for various dysmorphism were taken from universally acceptable definitions (6,7,8).

RESULTS

A total of 49 cases were included in the study and 12 cases whose parents were unwilling to give consent to get involved in the study were excluded. Out of 37 DS cases, 19 (51.35%) were male and 18 (48.65%) were female. Male to female ratio is 1.06:1. Out of 37 mothers, only 2 (5.41%) mothers had history of abortion. 14 children were 1st and 2nd born (37.84%), followed by 3rd (13.51%), 4th (8.11%) and 5th (2.70%) born. Eight (21.62%) and 3 (8.11%) of the 37 DS children had 2nd and 3rd degree consanguineously married parents respectively.

Most common clinical features were up-slanting palpebral fissure (100%), full cheeks (97.30%), flat nasal bridge (94.59%), narrow and short palate (91.89%), short and broad hands

(91.89%), microcephaly (91.89%), flat occiput (89.19%), epicanthic folds (86.49%) and protruded tongue (81.08%). (Table 1)

Table 1:Clinical features (n=37)

Clinical features	**No. of cases**	**Percentage**
Microcephaly	34	91.89%
Flat Occiput	33	89.19%
Small Ears / Low set ear	29	78.38%
Redundant skin nape of neck	16	43.24%
Upslanting palpebral fissure	37	100%
Epicanthal folds	32	86.49%
Brushfield spot	0	0%
Flat nasal bridge	35	94.59%
Narrow, short palate	34	91.89%
Protruding of tongue	30	81.08%
Full cheeks	36	97.30%
Short, broad hands	34	91.89%
Clinodactyly	15	40.54%
Simian line	12	32.43%
Sandal gap	23	62.16%
Increased sole creases	25	67.57%
Hypotonia	26	70.27%
CHD	14	37.84%
GI anomalies	1	2.7%

Maximum numbers of mothers were less than 30years of age. This accounted for 81.09%. Mean age of mothers was 26.6years. Youngest mother was 17years and oldest was 40years. Out of 37 DS cases, 35(94.59%) fathers were less than 40years of age at the time of maternal conception.

Among 37 DS cases, 14(37.84%) had CHD. Among 14 cases of CHD, ostiumsecundum atrial septal defect was most common type (28.57%), followed by TOF (21.43%), and ECD (14.29%). (Table 2)

Table 2: Pattern of Congenital Heart Diseases (n=37)

	No. of cases	Percentage
OS ASD	4	28.57%
VSD	2	14.29%
ASD with VSD	1	7.14%
ECD	2	14.29%
PDA	2	14.29%
TOF	3	21.43%
TOTAL	14	

Out of 37 children, 6 (16.21%) had hypothyroidism. Cytogenetic profiles of all 37 cases (100%) were trisomy 21. Cytogenetic profiles of all 14 cases (100%) were trisomy 21.

DISCUSSION

Out of 37 DS cases, 19 (51.35%) were male and 18 (48.65%) were female. Male to female ratio was 1.06:1. In a similar study by Kava et al (9), Sachdev et al (10)and Jyothi et al (11) male to female ratio were 1.37:1, 1.84:1 and 1.41:1respectievly.

In our study 2 (5.4%) mothers had history of abortion. Hook EB (12) stated that "the younger the mother and the more the number of abortions, the higher the relative risk of a Down syndrome live birth."In our study 11 (29.73%) of the 37 subjectswere children of consanguineously married parents. In Sayee's study (13), the incidence of parental consanguinity was 17.2%. Jyothi (14) et al study showed there was insignificant role of consanguinity in the etiology of DS.

Most common clinical features were up slanting palpebral fissure (100%), full cheeks (97.30%), flat nasal bridge (94.59%), narrow and short palate (91.89%), short and broad hands (91.89%), microcephaly (91.89%), flat occiput (89.19%), epicanthic folds (86.49%) and protruded tongue (81.08%).Redundant skin on nape of the neck was seen in 43.24% and is comparable with 36.8% of Kava et al (9) study. Up slanting palpebral fissure was seen in all 37(100%) cases in our study, where as in Azman et al (15)and Kava et al (9)study it was 89.3% and 83.9% respectively. See Table 3.

Table 3: **Comparison of clinical features of DS with other studies**

Clinical features	Current study (n=37)	Azman et al (15)(n=149)	Kava et al (9) (n=1001)
Microcephaly	91.89%	-	-
Flat Occiput	89.19%	-	-
Small Ears / Low set ear	78.38%	56.1%	66.9%
Redundant skin nape of neck	43.24%	12.2%	36.8%
Upslanting palpebral fissure	100%	89.3%	83.9%
Epicanthal folds	86.49%	17.5%	56.9%
Brushfield spot	0%	-	3.2%
Flat nasal bridge	94.59%	-	-
Narrow, short palate	91.89%	-	-
Protruding of tongue	81.08%	19.2%	29.9%
Full cheeks	97.30%	-	-
Short, broad hands	91.89%	24.5%	-
Clinodactyly	40.54%	19.2%	36.1%
Simian line	32.43%	36.8%	33.2%
Sandal gap	62.16%	33.3%	46.2%
Increased sole creases	67.57%	-	-
Hypotonia	70.27%	52.6%	76.3%
CHD	37.84%	49.3%	11.07%
GI anomalies	2.7%	22.7%	1.33%

Brushfield spot was not seen in any of the cases in our study and is comparable with Wong V et al study at Hong-Kong University, where none of the DS patients had Brushfield spot (16). This can be explained by high prevalence of dark eye in our study. Wallis (17) suggested that there is a low prevalence of Brushfield spots in blue or light colored eyes that darkens with age. A study by Kava et al (9) showed 3.25% Brushfield spot in DS.

In our study clinodactyly was seen in 40.54% cases, which is comparable with 36.1% of Kava et al (9) study. Simian crease was seen in 32.43% cases, where as in Azman et al (15)and Kava et al (9)study it was 36.8% and 33.2% respectively. In our study sandal gap was present in 62.16% cases and in Azman et al (15)and Kava et al (9) study it was 33.3% and 46.2% respectively. Hypotonia was present in 70.27% our cases, which is comparable with 76.3% of cases in Kava et al (9) study.All DS children in our study had global developmental delay. In our study gastro intestinal anomaly (anal atresia) was seen in 1 (2.7%) DS child, which is comparable with 1.33% of Kava et al (9) study.

In our study mean maternal age at conception was 26.6years. In a study by Azman et al (15) mean maternal age at birth was 32.3years, in Irfan Ahmed et al (18) 29.8 years and in Kava MP et al (9)26.8 years.Thirty (81.09%) mothers in our study were less than 30 years of age at the time of conception and 7(18.91%) mothers were more than 30years of age. In Jyothi et al (14)

study, 80.80% mothers were <30years and 19.20% were >30years at conception of children with DS (see Table 4).

Table 4: **Comparison of age of the mother at conception with other study**

Age of the mother at conception in years	Current study (n=37)	Jyothi et al (14) (n=865)
<20	5 (13.51%)	148 (17.11%)
21-25	16 (43.24%)	365 (42.19%)
26-30	9 (24.32%)	186 (21.5%)
31-35	6 (16.21%)	106 (12.26%)
36-40	1 (2.70%)	35 (4.05%)
>40	-	25 (2.89%)

In a study done by Suttur S. Malini et al (19) in south India, 75% of DS children were born to younger mothers whose age ranged from 18-29years. One of the reasons for this may be that Indian women get married and have children earlier when compared to western countries.

In our study, 35 (94.59%) fathers were less than 40years and 2 (5.41%) were more than 40years of age at conception. This is comparable with Jyothi et al (14) study where, 88.32% fathers were less than 40years age at conception of DS children (see Table 5).

Table 5: **Comparison of age of the father at conception with other study**

Age of the father at conception in years	Current study (n=37)	Jyothi et al (14) (n=865)
<20	-	9(1.04%)
21-25	3(8.11%)	134(15.49%)
26-30	11(29.73%)	304(35.140%)
31-35	10(27.03%)	154(17.81%)
36-40	11(29.73%)	163(18.84%)
>40	2(5.41%)	101(11.68%)

Harry Fisch et al (20) study showed there was no parental age influence on DS until the age of 35years and older. Advanced paternal age combined with maternal age significantly

influence the incidence of DS. A paternal age effect was seen in association maternal age of 35years and older, and it was most pronounced when maternal age was 40years and older.

Out of 37 DS children, 14 (37.84%) had CHD. Among 14 cases of CHD, Ostiumsecundum atrial septal defect was most common type (28.57%), followed by TOF (21.43%), ECD (14.29%), VSD (14.29%), PDA (14.29%) and ASD with VSD (7.14%). In a similar study by Bhatia S et al (21) 44% DS children had CHD and most common CHDwas ECD, which accounted for 31.7% and followed by VSD (27.2%), OS-ASD (13.6%), PDA (9.1%), TOF (4.6%).

Among 37 children 6 (16.21%) had hypothyroidism. None of the cases had hyperthyroidism. Prevalence of thyroid disorders varies between 3-54%. The variation in these studies might be related to age variation among the study subjects and / or difference in the diagnostic criteria. Hence thyroid function studies recommended at birth, at 6month and at 12 months of age followed by annually in all DS children (22). In a Somchit et al (23) retrospective study of 295 DS children, thyroid function test was done in 263 cases. Thyroid disorders were found in 30 cases (11.4%). Out of 30 cases, 27 cases were hypothyroidism and 3 cases were thyrotoxicosis.

All children included in our study had cytogenetic confirmation of Down syndrome. Cytogenetic profile of all 37 cases (100%) was trisomy 21. None of the cases had mosaics or translocations. This is comparable with a study by Puri et al (24) where all 69 cases (100%) were trisomy 21. ICMR multicentric studies on mental retardation at Lucknow (1981-1984), all 32 (100%) cases were trisomy 21. See Table 6.

Table 6: **Comparison of Karyotyping study with other studies**

	Current study	Puri et al (24)	ICMR study 1984	Thomas et al (25)	Jyothi et al (14)	Krishnamurthy et al (26)	Verma IC et al (27)	Sheth et al (28)
No. of cases	37	69	32	365	1001	113	645	382
Trisomy 21	100%	100 %	100%	86.5%	87.92 %	80.53%	93%	84.8%
Mosaics	-	-	-	5.75%	7.69%	10.62%	2.6%	3.9%
Translocation	-	-	-	7.67%	4.39%	8.85%	4.1%	8.9%

FISH was done in 14 cases and cytogenetic profiles of all 14 cases were trisomy21.Some rare anomalies observed in our study were, acromelia of left hand in one child and vein of Galen malformation with hydrocephalus in other child.

LIMITATIONS OF THE STUDY

1. Number of cases were less, so general conclusion could not be derived.
2. Complete ophthalmic and hearing assessment was not possible in all cases and follow up was not done.

CONCLUSION

- Most common clinical features were up slanting palpebral fissure, followed by full cheeks, flat nasal bridge, narrow and short palate, short and broad hands, microcephaly, flat occiput, epicanthic folds and protruded tongue.
- Majority of mothers were less than 30years of age at the time of conception.
- Ostiumsecundum atrial septal defect was most common type of CHD.
- Karyotyping of all Down syndrome cases were trisomy 21.

REFERENCES

1. Kleigman RM, Behrman RE, Jenson HB. Abnormalities of Chromosome Numbers. In: Kleigman RM, Behrman RE, Jenson HB, eds. Nelson Textbook OfPediatrics, Vol. 1, 18th Ed, Philadelphia: Saunders, 2008; Pp 506-509.
2. Conn CM, Cozzi J, Harper JC, Winston RM, Delhanty JD. Preimplantation genetic diagnosis for couples at high risk of Down syndrome pregnancy owing to parental translocation or mosaicism. J Med Gent. 1999; 36: 45-50.
3. Verma IC. Genetic causes of mental retardation in India. In: Hook EB, Berg JM, eds. The genetics of mental retardation, biochemical, psychosocial and ethical issues. Dordrecht, The Netherlands: Kluwer AcadPubl; 1988: Pp 99-106.
4. Hook EB, Mutton DE, Ide R, Alberman E, Bobrow M. The natural history of Down syndrome conceptuses diagnosed prenatally that are not electively terminated. Am J Hum Genet. 1995; 57: 875–881.
5. Health Supervision for Children with Down syndrome, American Academy of Pediatrics. Committee on Genetics. Pediatrics. 2001; 107: 442-449.
6. Reardon W. The Bedside Dysmorphologist: Classic Clinical Signs in Human Malformation Syndromes and Their Diagnostic Significance. New York; Oxford University Press, 2008.
7. Ghai OP, Paul VK, Bagga A. Essential Pediatrics. 7th ed. CBS publishers, New Delhi. 2009
8. Da Cunha RP, Moreira JB. Ocular findings in Down's syndrome. Am J Ophthalmol. 1996; 122: 236-244.
9. Kava MP, Tullu MS, Muranjan MN, Girisha KM. Down syndrome: clinical profile from India. Arch Med Res. 2004; 35: 31-35.
10. Sachdev HPS, Menon PSN, Verma IC, Ghai OP. Physical growth of children with Down syndrome in India. Indian J Pediatr .1980; 48: 85-88.
11. Jones K. Smith's recognizable patterns of human malformation. 5th ed. Philadelphia: Saunders; 1997: Pp 8-13.
12. Hook EB, Cross PK. Spontaneous abortion and subsequent Down syndrome live birth. Hum Genet. 1983; 64: 267-270.
13. Sayee R, Thomas IM. Consanguinity, non-disjunction, parental age and Down's syndrome. J Indian Med Assoc. 1998; 96: 335-337.
14. Jyothi A, et al. Cytogenetics studies of 1001 Down syndrome cases from Andhra Pradesh, India. Indian J Med Res. 2000; 111: 133-137.
15. Azman B Z, Ankathil R, Siti Mariam I. Cytogenetic and clinical profile of Down syndrome in Northeast Malaysia. Singapore Med J. 2007; 48: 550–554.
16. Wong V, Ho D. Ocular abnormalities in Down syndrome: an analysis of 140 Chinese children. Pediatric Neurology. 1997; 16: 311-314.
17. Wallis HRE. The significance of Brushfield spots in the diagnosis of mongolism in infancy. Archives of disease in Childhood. 1951; 26: 495-500.

18. Ahmed I, Ghafoor T, Samore NA, Chattha MN. Down syndrome: clinical and cytogenetic analysis. Journal of the College of Physicians and Surgeons Pakistan. 2005; 15: 426-429.
19. Malini SS, Ramachandran NB. Influence of advanced age of maternal grandmothers on Down syndrome. BMC Med Gent. 2006; 7: 4.
20. Fisch H, Hyun G, Golden R, Hensle TW, Carl Olsson A, Liberson GL. The influence of paternal age on Down syndrome. The Journal of urology. 2003; 169: 2275-2278.
21. Bhatia S, Verma IC, Shrivastava S. CHD in Down syndrome. Indian Pediatr. 1992; 29: 1113-1116.
22. Karlsson B, Gustafasson J, Hedov G, Ivarsson SA, Anneren G. Thyroid dysfunction in Down's syndrome: relation to age and thyroid autoimmunity. Arch Dis Child. 1998; 79: 242-245.
23. SomchitJaruratanasasirikul MD et al. Clinical Abnormalities, Intervention Program, and School Attendance of Down syndrome Children in Southern Thailand. J Med Assoc Thai. 2004; 87: 1199-1204.
24. Puri RK, Khanna KK, Bhargava I, Balakrishnan S. Role of consanguinity in chromosomal syndromes. Indian J Med Res. 1997; 65: 859-864.
25. Thomos IM, Rajarangam S, Hegde S. Cytogenetic investigation in Down syndrome patients and their parents. Indian J Med Res.1992; 96: 366-371.
26. Krishna Murthy DS, Patel ZM, Khanna SA, Danthi V, Ambani LM. Frequency of trisomy 21, translocation, mosaicism and familial cases of Down syndrome in Bombay. Indian J Med Res. 1981; 73: 218-22.
27. Verma I C, Mathew S, Elango R, Shukla A. Cytogenetic studies in Down syndrome. Indian Pediatr. 1991; 28: 991-996.
28. Sheth F, Rao S, Desai M, Vin J, ShethJ. Cytogenetic analysis of Down syndrome in Gujarat. Indian pediatr. 2007; 44: 774-777.