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CYTOGENETIC ANALYSIS OF DOWN SYNDROME: A REPORT FROM INDIA.

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ABSTRACT: Down Syndrome (DS) is the commonest autosomal disorder, trisomy 21 in children. It is identified by mental retardation and facial symptoms clinically. This study was conducted on 830 referral cases in our Institute of Ahmedabad Gujarat (India) and compared the epidemiology of this disease with World data available. Karyotype of blood culture of each case was analyzed using Carl Zeiss MetaSystems following WHO manual. A numbers of 82 cases were detected positive of Down Syndrome (9.9%). Amongst, regular/classical free T21 (92.6%) was higher followed translocation (6.0%) and mosaics (1.2%). Maternal age and age independent factors are important for causing this disorder. Males are more affected due to male predominance. Further world survey of frequencies of it indicated regular free 21 is the highest amongst the other types. We hence concluded that identification of this genetic disorder helps an occurrence of mode ofits type. Further, its identity assists genetic screening to suffered families for proper management.
Key words: Referral cases, Cytogenetic analysis, down syndrome, world survey, factors.

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INTRODUCTION

Down Syndrome (DS) is one of the genetic disorders occurring due to aneuploidy in populations having one in 1000 live births (Belmokhtar et al., 2016). It is an autosomal abnormality of 21 with mental retardation. Its diagnosis is easier and has chronologic similarities. So it is identified by clinical features from 73 to 100% occasionally, but is difficult to know in an infant with subtle clinical features. Hence, karyotype is the best confirmatory test. Generally it is caused by three types of chromosomal anomalies classical/regular trisomy 21, translocation and mosaicism. Non-Classical types are rare (Belmokhtar et al., 2016). In Gujarat (India) it occurs with an incidence of 1 per 920 (Sheth et al., 2007). Moreover, it is due to various factors like maternal parity and genetic predisposition (Doria-Rose et al., 2003, Farag and Teebi, 1988). In addition to maternal age,reported by El-Gilany et al.(2011). Hence, we repot our findings of cytogenetic based referral cases of 830 at Supratech Micropath Laboratory Ahmedabad (India) for this autosomal disorder. We also compare word wide survey of this disorder and its status in response to its classification reported in various countries.

MATERIAL AND METHODS

Patients: The suspected cases (830) were referred to Supratech Micropath Laboratory of Ahmedabad, Gujarat for various cytogenetic anomalies from of Jaipur, Kalkota, Chennai, Delhi and Ahmedabad varying in age from 1day to -72 years from 2014 – 2016 (2 Years). Patient consents were taken and this work is approved by Human Ethical Committee of Gujarat University, Ahmedabad.

Karyotype analysis for blood samples was done using the method of Moorhead et al.[1960] These samples were processed with PHA, as mitogen. Harvesting with cholchicine was done before hypotonic treatments. Metaphase plates were prepared and stained with Giemsa stain and karyotypes were done on Carl ZiessMeta Systems Microscope. For each sample 20 metaphase plates were analyzed. The results were carefully analyzed using ISCN Classification [Shaffer et al., 2013].Percent of Down Syndrome karyotypes was calculated and Statistical analysis was also done accordingly using Student's 't' test. A value of $P<0.05$ is considered to be significant.

RESULTS

A number of 82 cases of Down syndrome (9.9%) noticed from a total 830 registered at our Institute. Out of these cases, Free T21 were 76 (92.6%). The second highest was translocation with T21 (6.0%), whereas 01 case was mosaic (1.2%). These translocations were derived from Robertsonian type (21;21) and (14;21) of de novo and familiar types. One was a deletion of chromosome 8 with T21. The age of these cases ranged from 1 day to 12 years. The ratio of male and female was 3.8:1.The maternal age averaged between 26-35 years and was significant ($P<0.05$) in classical T21 compared to others [Table 1]. The pie chart indicated the percent of Down syndrome type distribution [Figure1]. Further a typical karyotypeof free 21 trisomy was presented [Figure 2]. Word wide survey of the frequency of karyotype anomalies of Down Syndrome including our study India, indicate the high incidence of regular, free T21 which was followed by mosaicism, translocations and others [Table 2 and Figures 3, 4].

Table-1: Karyotypes of Down Syndrome (82) Cases.

Regular / Classical (76)		**Age**	**M :F Ratio** (2.5:1)**	**Maternal Age**
47,XY,+21	55	1day to 12 years	3.8:1	35.2± 1.70*
47,XX,+21	21			
Translocation (5)			4:1	30.4± 1.23
46,XX,der(21;21)(q10;q10),+21	1	5 Year		
46,XY,der(21;21)(q10;q10),+21	1	16 Days		
46,XY,der(14;21)(q10;q10),+21	2	6 Month		
47,XY,del(8)(p22),+21	1	1 Year		
Mosaic (01)				26.1± 1.35
47,XY,+21/46,XY	1	1 Month	1:0	

***P<0.05; Figures in parenthesis indicate case number. ** Mean ratio.**

Table-2: Wide survey frequency of different karyotypes among Down Syndrome and pooled data from world.

Country	**Total cases**	**Regular Trisomy**		**Translocation**		**Mosaic**		**Non-classical**	
		Nos	**%**	**Nos**	**%**	**Nos**	**%**	**Nos**	**%**
Iraq (Mokhtar et al.,2003)	30	28	96.4	0	0	2	4.6	0	0
Sudan(Khartoum) (Ellaithi et al., 2008)	5	3	60	2	40	0	0	0	0
Jordan(Amman) (Kawar et al., 2009)	33	28	85	3	9	2	6	0	0
Saudi(Riyadh) (Niazi et al., 1995)	42	37	88	5	11.9	0	0	0	0
Malaysia (Azman et al., 2007)	149	141	94.6	1	0.7	7	4.7	0	0
France (Stoll et al., 1990)	391	368	94.1	14	3.6	9	2.3	0	0
Egypt (Mokhtar et al., 2003)	673	642	95.4	18	2.7	5	0.7	8	1.2
England and Wales (Mutton et al., 1996)	5737	5411	94.3	220	3.8	66	1.2	40	0.7
India with Our Data	8644	7778	91.3	379	4.38	458	5.29	21	0.24
Total Survey	15704	14436	88.78	642	8.45	549	2.75	69	0.23

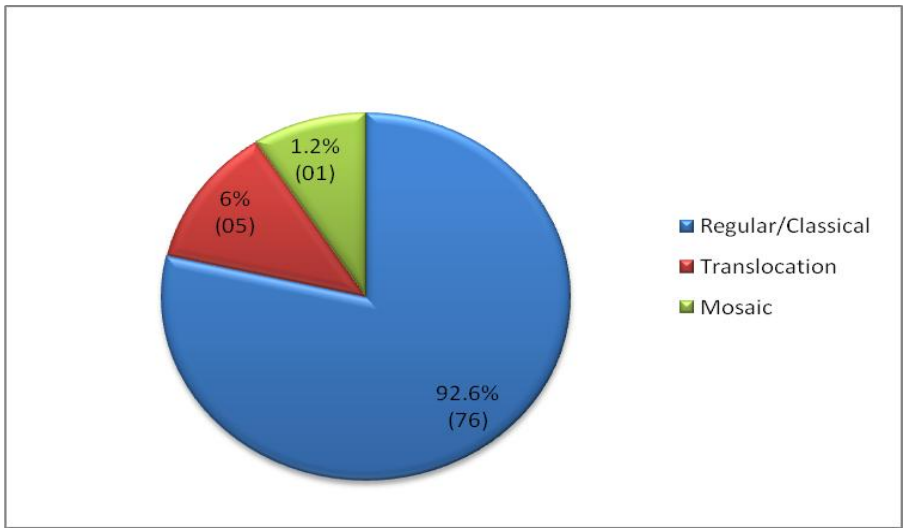

Figure 1: Percent of Down Syndrome types in our study (82).

Figures in parenthesis indicate number of patients.

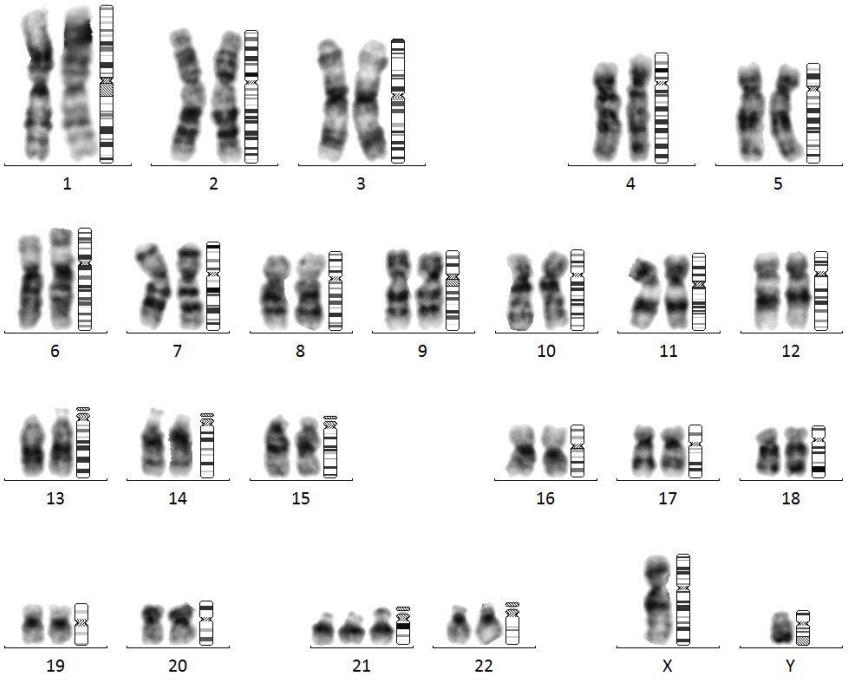

Figure 2: Karyotype of classical free T21.

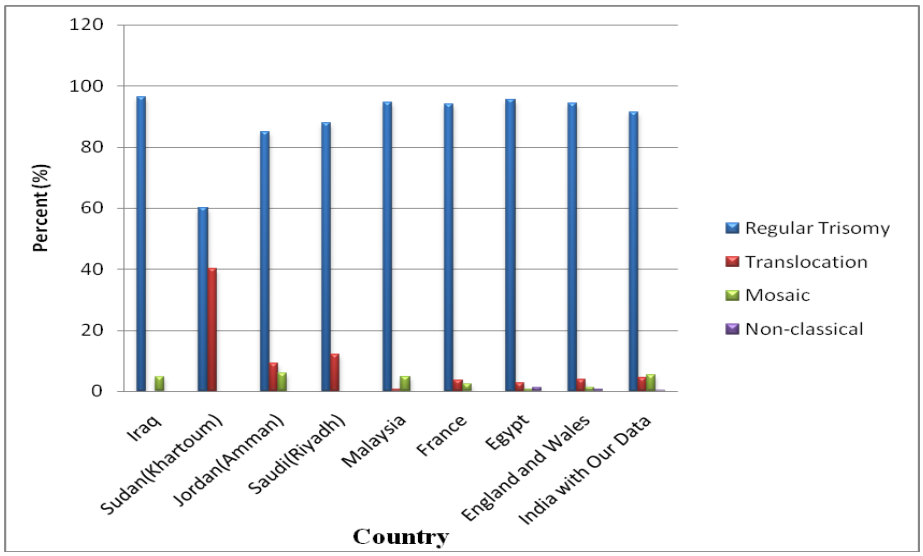

Figure 3: Showing Global Percentage (%) distribution of Down Syndrome of individual countries.

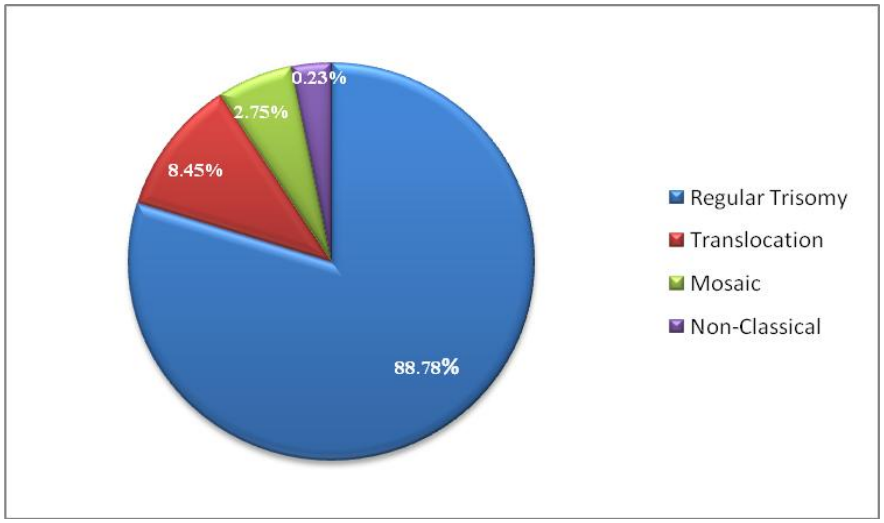

Figure 4: Total average % frequency of Down Syndrome types from global survey.

DISCUSSION

Our study included 830 referral cases for autosomal defects including Down syndrome anomalies. Rajasekhar et al. [2013] reported that genetic anomalies occur in childhood including congenital disorders with an prevalence of 6%. Verma, [2000] reported an incidence of four genetic disorders in population which include Reproductive Genetics (38.9%) Congenital Anomalies (16.7%), Down Syndrome (9.1%), Thalassemia/Haemophilia (8.8%) and Muscular Dystrophy (8.4%).

Present data detected, 82 (9.9%) cases were positive of Down syndrome affected to support the incidence of Verma, [2000] in population. From 82 cases, regular free T21 cases (76) were higher (92.6%) followed by translocations with trisomy 21 (6%) and mosaic cases (1.2%) having 47, XY+21/46, XY. It is documented that T21 free and translocation occur usually more in Gujaratipopulation as reported by Sheth et al. [2007] and others [Azman et al., 2007, Mokhtar et al., 2003, Abdulameer, 2016]. Our Down Syndrome group aged 1 from day to 12 years. Higher incidence of free trisomy 21 is caused by maternal chromosomal non-disjunction during meiosis I and other factors or mitotically after fertilization. It also depends on age dependent factors like decay of spindle fiber, failure in nucleolar break down, radiation accumulation, hormonal imbalance infection and age independent factors, such as chromosomal instability, abnormal segregation, and maternal parity, DNA hypomethylation in support our data [Abdulameer, 2016]. Our study also clearly indicated an increase of this disorder with maternal age, which is one of the age dependant factors with respect to classical type [Belmokhtar et al., 2016].

Such these cases are also prone to have comorbidity having cardiac anomalies and hypothyroidism [El-Gilany et al., 2011]. Further, more Robertsonian translocations (RTs) are involved between (21;21) and (14;21) chromosomes and deletion of chromosome 8 with 21 in our report. These cases may also have hypothyroidism [Azman et al., 2007]. Robertsonian translocations (RTs) are known to be *denovo* (Sporadic) and/familial transmissions. Mosaicism is found in one male case (1.2%) having a mixture of 46 and 47 chromosomal cells. This condition results from mitotic nondisjunction of chromosome 21 during early stages of embryogenesis. The symptoms in such cases are variable and milder dependent on the proportion of abnormal cells [Daimei et al., 2015 and Kumar, 2007] and also associated with hypothyroidism usually. Over all in our report, maleswere more affected by abnormal karyotyping of Down Syndrome. Similar reports were also noticed in Egyptian population [El-Gilany et al., 2011]. Further the cause of this genetic disorder of Down Syndrome is due to non-disjunction, familial/sporadic translocation and mosaic conditions, as documented by these authors [El-Gilany et al., 2011]. Further interesting to note is that male cases of this disorder were more than the opposite sex as mentioned earlier in our investigation. This was also confirmed by other investigators round the globe [El-Gilany et al., 2011 and Mokhtar et al., 2003] and could be due to the genetic mechanisms of male predominance and explained by joint segregation of chromosomes 21 and Y in spermatogenesis and chromosome non-disjunction during the secondary meiotic division of oogenesis [El-Gilany et al., 2011]. If we look into global survey of frequency of Down Syndrome patients, the results were corroborated with our Indian scenario including our present study [Table 2], where regular free T21 was the highest followed by others types ie. translocation/mosaicism and non-classical types. Few authors too observed translocations are higher than mosaics after free T21 as found in our study [Mokhtar et al., 2003, Ellaithi et al., 2008, Kawar et al., 2009, Niazi et al., 1995, Stoll et al., 1990 and Mutton et al., 1996]. Few others, however documented opposite scenario where mosaics were more in their reports globally [Azman et al., 2007 and Abdulameer, 2016] [Figure 3]. This discrepancy may be related to sample size, maternal age, time period, parity and other contributing factors [Abdulameer, 2016, Kumar et al., 2007, and Kumar and Delatycki, 2001]. Considering total incidence of cases world wide, the classical T21 was higher than chromosomal rearrangements and mosaics [Table 2 and Figure 4].

CONCLUSION

Thus our data conclude that abnormal karyotypes with T21 are associated with high frequency of free T21 followed by translocation and mosaicism in support of Word Survey. The causes include age dependant and independent factors. Males are more affected by this disorder due to male predominance. Further data is also called for detecting causative factors, their mechanisms and providing counseling to suffered families for better management.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest in this work.

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