DOI: 10.14260/jemds/2014/3789

ORIGINAL ARTICLE

INCIDENCE OF DOWN'S SYNDROME WITH DEMOGRAPHIC AND CHROMOSOMAL PATTERN IN ODISHA

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HOW TO CITE THIS ARTICLE:
Jami Sagar Prusti, Sitansu K. Panda, Santosh K. Sahoo, Dharma N. Mishra, Mahesh C. Sahu, Saurjya R. Das, Priyambada Panda, Sibananda Nayak. "Incidence of Down's Syndrome with Demographic and Chromosomal Pattern in Odisha". Journal of Evolution of Medical and Dental Sciences 2014; Vol. 3, Issue 60, November 10; Page: 13415-13426, DOI: 10.14260/jemds/2014/3789

ABSTRACT: BACKGROUND: To study the age, birth order, consanguinity marriage, reproductive history, demographic pattern of parents and chromosomal pattern of the Down's syndrome (DS) patients of Odisha population coming to the different medical colleges of Odisha. **METHODOLOGY:** Detailed history of the parents was taken by questioners and the DS patients were examined by ink-pad technique and chromosomal analysis methods. **RESULT:** DS more often affects the first and second order births of parents each comprising of 38%. Consanguinity marriage results 46% of DS cases. Ninety percent of DS children were born to mothers of age less than 30 years and 52% of DS were born to father less 30 years of age. There is a high frequency of spontaneous abortion (22%) and still birth (6%) in mothers of DS. Highest incidence (94%) of DS was seen in urban area with working in industry as the occupation of the parents (42%). In karyotypic analysis of DS patients primary trisomy, Mosaic Trisomy, Primary amenorrhea and translocation were 78%, 12%, 6% and 4% respectively. **CONCLUSION:** There is an increase incidence of DS at lower age group of parents. It is tempting to speculate that, the difference in clinical features, abnormal dermatoglyphic patterns etc, are related to the genetic constitution of the Down's syndrome individuals.

KEYWORDS: Chromosomal abnormality, Down's syndrome, Parental age, Trisomy 21.

INTRODUCTION: Down syndrome (DS) is the most commonly recognized human malformation complex and is the foremost known genetic cause of mental retardation. Down syndrome is a genetic disorder that results because of one germ cell has two 21 chromosomes instead of one, so the resulting fertilized egg has three sets of the 21st chromosomes. This abnormality is characterized by specific physical features and limited mental functions, along with several internal organ malformations.

The established risk factors for DS include advancing maternal age and family history of trisomy or relevant chromosomal rearrangements (Bell J 1991, Leck I 1994).[1, 2] Human Chromosome 21 was first mapped in May, 2000 (Hattori M 2000).[3] In general, this leads to an over expression of the genes (Rong et al 2005).[4] Understanding the genes involved may help to target medical treatment to individuals with DS. It is estimated that chromosome 21 contains 200 to 250 genes. Research has identified a region of the chromosome that contains the main genes responsible for the pathogenesis of DS, located proximal to 21q22.3. The search for major genes involved in Down syndrome characteristics is normally in the region 21q21–21q22.3 (Rahmani et al 2005).[5]

Demographic studies in the United States have shown that the number of births to parents older than 35 years has more than doubled in the past 20 years (Fisch et al 2001).[6] This increase in parental age is a public health concern because more infants are being born who are at high risk for

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genetic abnormalities. Determining the potential risks associated with advanced parental age is now more relevant than ever. Trisomy 21 or DS is a common congenital abnormality affecting 1/800 to 1,000 newborns (Cunningham et al 2001).[7] As the most common nonlethal trisomy disorder, it is the focus of genetic screening and testing protocols. Multiple investigations have been done to identify possible risk factors of which, the most common has been parental age. The effect of maternal age as a risk factor for Down syndrome was described as early as 1933 (Penrose et al 1993).[8]

Down syndrome is caused by a gene dosage-imbalance resulting from human chromosome-21 trisomy, and is the most commonly diagnosed congenital malformation/mental retardation syndrome (Jones 2006).[9] The clinical features of DS are comprised of severe cognitive impairment, characteristic facial profile, short stature, speech and developmental delay, chronic ear infections and hearing loss, and hypotonia (Jones 2006).[9] The diagnostic facial profile consists of epicanthal folds, flat nasal bridge, up slanting palpebral fissures, and protruding tongue (Jones 2006).

Approximately 95% of diagnosed Down syndrome cases have a complete trisomy 21 and the remaining 5%either have somatic mosaicism (1%) or chromosome-21 translocations (4%) (Sherman et al. 2007).[10] In this study the age, birth order, consanguinity marriage, reproductive history, demographic pattern of parents and chromosomal pattern of the Down's syndrome (DS) patients of Odisha population coming to the different medical colleges of Odisha were documented.

MATERIALS AND METHODS: The study was carried out in the Department of anatomy and O&G of MKCG Medical College Berhampur, IMS and SUM Hospital Bhubaneswar, SCB Medical College Cuttack and VSS medical college Burla, Odisha, India for 3 years, from 2009 to 2012. Patients attending Pediatrics department with the features of Down's syndrome were asked to report to the Department of Anatomy and O&G. For this study 50 (fifty) clinically diagnosed Down's syndrome cases were selected, irrespective of age and sex.

Their intelligent quiescent from mild to severe categories were drawn from school records, clinics, outdoors, indoors and institutions for mentally retarded children of different areas of Ganjam, Gajapati, Phulbani, Cuttack districts of Orissa. Informed consent was obtained from patient's relatives. The data were collected by using a detailed questionnaire and by personal interview of parents of Down's syndrome children. Detailed history was taken which includes consanguinity marriage, age of the parents at the time of delivery of the patient, birth order of the child and reproductive history of the mother and family history.

The socio-economic status, occupation and locality in relation to urban or rural of the parents were ascertained. In our study both affected and control group contains the consanguineous marriage of parents. It includes, uncle niece type (UN), Daughter married to maternal uncle's son (FSD), son married to maternal uncle's daughter (MBD). For the patient Dermatoglyphic pattern was taken by ink-pad technique, for that different prints are analyzed on white glazed paper by using magnifying lens.

The percentage of different types of finger ball patterns were studied and compared with normal cases (i.e. Control group), Presence of Simian crease was identified and their percentage was calculated. At D angle is calculated and compared finger balls and compared with that of normal cases (Fig 1a-c, Fig 2a-b). Clinical features of the patients of down's syndrome were confirmed by presence of macroglossia, opened mouth, epicanthic fold, short and square nose oblique palpebral fissure and malformed ear (Fig 3).

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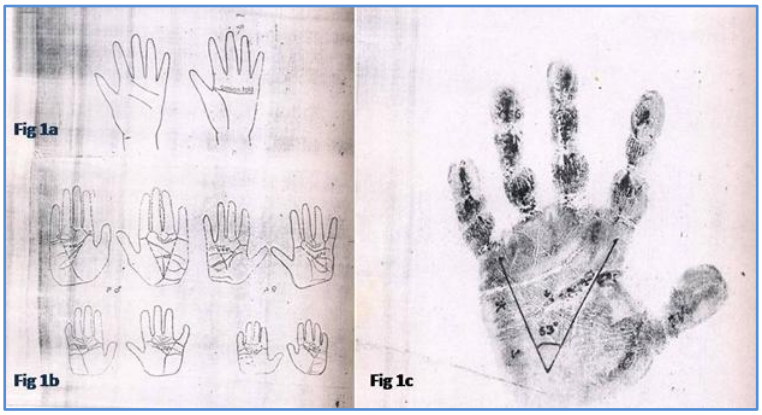

Fig 1a: Simian crease, a single transverse palmar crease, **Fig 1b:** Normal parents, Normal range of AtD angle with Down's syndrome offsprings. (higher range of AtD angle), **Fig 1c:** A Down's syndrome child showing increased AtD angle

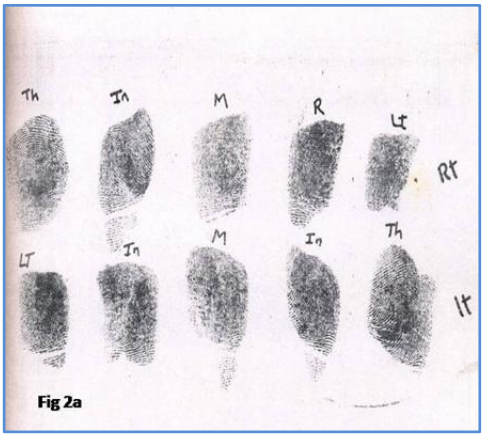

Fig 2a: Finger prints of both hands of a Down's child showing increased incidence of loops.

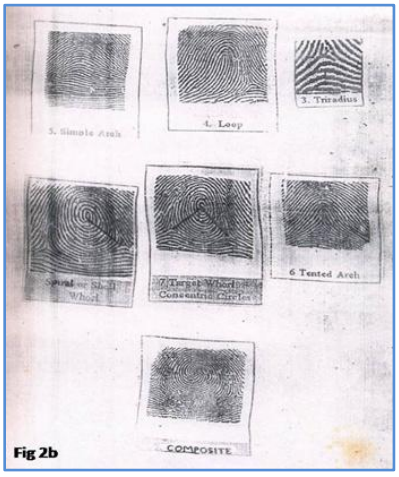

Fig 2b: Types of finger prints and line joining core to the triradius for counting of ridges.

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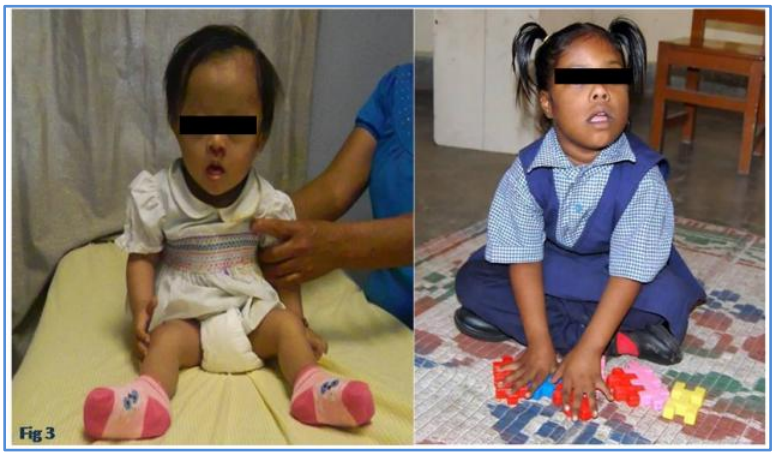

Fig 3: Opened mouth, macroglossia, epicanthic fold, short and square nose oblique palpebral fissure and malformed ear.

For confirmation of Down's syndrome blood sample ware collected from patients for karyotypic analysis. For this 5ml of venous blood are withdrawn in a disposable syringe, with heparinised vial. From that vial 800 µL of blood was used for culture. The culture medium contains a mixture of 7 ml of RPMI, 2 ml of fetal calf serum and 0.2 ml of PHA-M (Phytohaemagglutinin). The pH of the culture was maintained between 7.2 to 7.4. The culture was incubated for 72 hours at 37^0 C in CO_2 incubator (Moorhead et al 1960).[11]

After that 0.2 ml of colcemid was added to the culture, two hours prior to harvest i.e. at 70^{th} hour. Then Culture bottle were removed from the incubator at 72^{nd} hour and the cell suspension was transferred into a 10 ml centrifuge tubes and labelled with marking pencil. It was centrifuged for 8mins at 800 rpm and supernatant was discarded with a micro pipette, resuspend the cells in hypotonic solution (KCI of 0.075 M- pre-warmed at 37^0 C) and incubated for 20mins at 37^0 C. It was centrifuged for 8 mins at 800 rpm and supernatant fluid was removed.

Resuspend the cells in 0.5-1.0 ml of resting fluid. Chilled fixative (3 parts of methyl alcohol, 1 part of glacial acetic acid) is added slowly almost drop-wise, immediately mixed gently with a pipette and kept for 10mins at the room temperature. Centrifuged for 8mins at 800 rpm and supernatant fluid is removed. Again resuspend the cells in fresh fixative and keep in the refrigerator for 2 hours. Centrifuge for 8mins at 800 rpm and supernatant fluid is removed. Re-suspend the cells in few drops of fresh fixative; confirm the cell pellet, (clear white part). If not clear, treat with fresh fixative and repeat step again. The supernatant fixative is removed and finally 0.5 ml to 0.75 ml fresh fixative is added to the cell button (depending on the cell density) to obtain a fairly dense cell suspension.

SLIDE PREPARATION: After fixation, for preparation of slides, the air-drying method, first described by Rothfels and Siminovitch, 1958 (Rothfels and Siminovitch, 1958) [12]is followed. Clean slides are taken and made grease free by dipping in ethyl ether overnight. A drop of fixed cell suspension is then placed on clean slide allowing it to spread out, and then dry it rapidly. The air-drying method at most times yield a higher number of better metaphase. Once the slides are dry, they were coded properly using a pencil.

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The dried and coded slides were kept for 5 to 7 days inside an incubator at 37º C for maturation. The matured slides were treated with Trypsin solution for 20 seconds, which was made in one cuplin jar (trypsin 50 mg /100 ml of distilled water). The trypsin digested slides were rinsed with (NACL 0.9%) twice which were kept in two cuplin jars. The slides were again washed with distilled water and stained with 2 ml of Giemsa stain (4%) which was poured over the slides and kept for I minute after which equal amount of distilled water was added for 5 minutes.

The stained slides were washed with distilled water thoroughly and allowed for air-drying. The stained and air dried slides were examined under light microscope for screening, which shows alternate light and dark bands on the chromosomes. These slides were screened for 20 well spread metaphases, five of them were photographed and one was karyotyped and studied for chromosomal aberrations. The enlarged microphotographs were taken and karyotyped manually by considering the length of the chromosome in decreasing order, position of the centromere, presence of satellite bodies and banding pattern. After that the report was generated for the study (Fig 4).

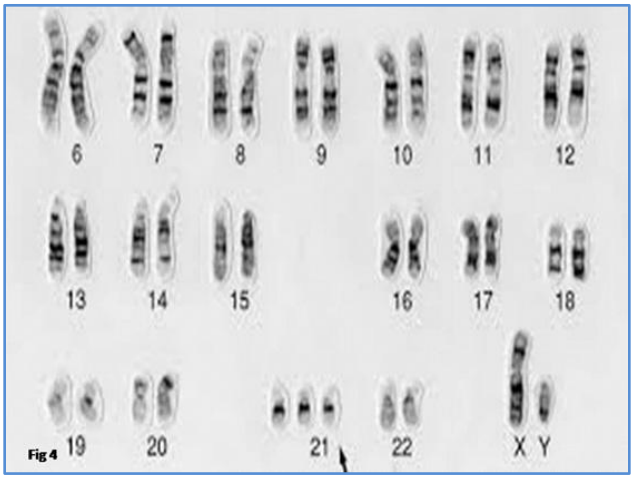

Fig. 4: Karyotypic report of the Down's syndrome patients.

RESULTS: In this study 100 patients were enrolled, among them 50 were case and other 50 were control. Out of 50 Down 's syndrome patients, 34 were males and 16 were females with the sex ratio of 2.12. The highest percentage of down syndrome was 38%, seen in both first and 2nd birth of the mother, where as in the control group birth order of lst and 2nd born were 49% and 47% respectively (Table 1).Table 2 shows are the product of In family history of the patients, it was found that the consanguineous marriage plays a major role for the cause of down's syndrome (46%).

In consanguineous marriage, UN revealed 10%, FSD revealed 14%, while MBD revealed 22% of Down 's syndrome. Where as in the control group 22% consanguineous marriage occurs without any down's syndrome (Table 2). In the study group about 90% of Down 's syndrome patients were from the age group of below 30 years, whereas above 30 years the occurrence is 10%. Highest incidence of Down 's syndrome was seen in between the age group of 21-25 years. In the control group the age of the mother was less than 30 years in 96% of cases. (Table 3). In this study the distribution of paternal age were analyzed. The paternal age was less than 35years in 88% of patients having Down's syndrome.

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At paternal age of 26-30 years the incidence of Down 's syndrome was highest (46%). In the control group 90% of the fathers were below the age of 30 years (Table 4). In the reproductive history, 22 % of mothers having Down 's syndrome baby gave the history of previous abortion, while in control group 8% of mothers gave the history of abortion. Similarly 6% of Down 's syndrome mothers experience still birth baby compared to 2% in control group (Table 5). The impact of living environment, occupation, economic status of parents on the prevalence of Down 's syndrome was studied.

Down's syndrome was seen in 94% of urban population compared to 6 % in rural population. More over parents of Down syndrome mostly work at industry (42%) while in 12% agriculture is their livelihood. Parents of DS have higher socio- economic status 33% compared to 13% of low socio-economic status (Table 6). The karyotype report of the down's syndrome revealed primary trisomy 21 in 39 cases (78%), mosaic trisomy 21 in 6 patients (12%), Down's syndrome primary amenorrhea in 3 cases (6%) whereas translocation46, XY, t (14:21) was the least common which was 2 cases (4%) (Table 7).

Birth order	Study group number percentage (%)		Control group number percentage (%)	
I.	19	38	49	49
II.	19	38	47	47
III.	4	8	3	3
IV.	3	6	1	1
V.	3	6	--	--
VI.	2	4	--	--

Table 1: The distribution of birth order in study group (n = 50) and control group (n = 50)

Types of consanguinity	Study group		Control group	
	Number	Percentage	Number	Percentage
UN	5	10	3	6.00
F.S.D	7	14	2	4.00
M.B.D	11	22	6	12.00
NC	27	54	39	78.00

Table 2: Parental consanguinity in down's syndrome cases

SL. NO	Age group (in yrs).	Study group		Control group	
		Number	Percentage	Number	Percentage
1.	15-20	4	8	3	6
2.	21-25	23	46	36	72
3.	26-30	18	36	9	18
4.	31-35	3	6	2	4
5.	36-40	2	4	--	--
6.	>40	--	--	--	--

Table 3: The distribution of maternal age in study group (n = 50) and control group (n = 50)

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Sl.no	Age group (in yrs).	Study group		Control group	
		Number	Percentage	Number	Percentage
1.	21-25	3	6	4	8
2.	26-30	23	46	41	82
3.	31-35	18	36	5	10
4.	36-40	5	10	--	--
5.	>40	1	2	--	--

Table 4: The distribution of paternal age in study group (n = 50) and control group (n = 50)

Study group	Total cases	Abortions		Premature births		Stillbirths	
		NO	%	NO	%	NO	%
Mother of DS	50	11	22	2	4	3	6
Mother of normal children	50	4	8	5	10	1	2

Table 5: Reproduction history of mothers of down's syndrome cases (n = 50) and normal mothers (n = 50)

		Study group		Control group	
		No	%	No	%
Area	Urban	47	94	50	100
	Rural	3	6	--	--
Locality	Industrial	26	52	50	100
	Other areas	24	48	--	--
Occupation	Agriculture	7	14	--	--
	Industry	21	42	30	60
	Others	22	44	20	40
Economic status	<1500 pm	13	26	2	4
	>1500 pm	33	66	48	96

Table 6: Distribution of down's syndrome cases (n = 50) and normal (n = 50) (habit and habitat of parents of down's syndrome cases).

Sl. no	Types of trisomy	No. of cases	Percentage
1.	Primary trisomy 21 (47,XX or XY+21)	39	78
2.	Mosaic Trisomy 21 (46/47, XX or XY+21)	6	12
3.	Translocation 46, XY, t(14:21)	2	4
4.	Down's Syndrome Primary amenorrhea (47, XX, +21)	3	6

Table 7: Classification of 50 down's syndrome cases according to the karyotype

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DISCUSSION: With the discovery in 1956 that the correct chromosome number in humans is 46, the new era of clinical cytogenetics began its rapid growth. During the next few years, several major chromosomal syndromes with altered numbers of chromosomes were reported, i.e. Down syndrome (trisomy 21), Turner syndrome (45, X) and Klinefelter syndrome (47, XXY). Since then it has been well established that chromosome abnormalities contribute significantly to genetic diseases. They are present in 50% of spontaneous abortions, 6% of stillbirths and in 0.5% of newborns (Frederick 2001).[13]

Some studies suggest that first child infants may be at high risk of DS to older women than a later born child to women of the same age (Alfi et al 1980).[14] This is in contrast to Stene (Stene et al 1981)[15] as he found that the first born infants were at a lower risk of DS than later born infants. It is clear from the table 1 that the first born were found to be more affected (38%) followed by 2nd order, again (38%), where as in the control group birth order of 1st born and 2nd born are 49% & 47% respectively (Table 1). Social factors affecting females are literacy, status of women, employment, general economic development, decreased fertility and adopting small family norms, adoption of family planning etc.

Because of above factors, high frequency of birth order I & II are observed in both study group and control group. Parental consanguinity has been in debate for a long time as one of the cause of non-disjunction. It was observed a fourfold increase in the relative risk of DS children in closely related parents as compared to non-related parents (Alfi et al, 1980).[14] Penrose reported the role of grand parental consanguinity, rather than parental consanguinity as causes of non-disjunction error of chromosome 21 (Penrose 1993).[16] It is observed that, 46% of DS cases are product of consanguineous marriage of some type or other.

The remaining 54% cases are products of affinal marriage (Table 2). Review of literature suggests that incidence of DS is parental age dependant and the maternal age has been incremented more often than paternal age, with the etiology to demonstrates that the increase in trisomy 21 is moderate among young maternal age (Hook 1987).[17] In this present study the mean maternal age of DS cases was estimated as 26.08yrs and that of normal children as 23.51yrs. (Issac, 1984),[18] reported maternal age of DS children as 29.54 + 6.4yrs and that of normal children as 25.75 + 2.12 yrs(Isac 1984)[18]. The reason for maternal age effect is not known.

Several hypotheses have been proposed in particular that of aging or over ripeness of ovum, due to delayed fertilization, maternal endocrine disturbances such as dysthyroidism. In the present study, 90% of DS children were born to mothers, less than 30yrs or is equal to 30yrs of age (Table 3). Data on the distribution of paternal age in study and control group are presented. Earlier investigatiors (Penrose, 1993),[16] did not observe any association of DS with increase paternal age, but (Erickson, 1978)[19] have reported increased incidence of DS with advancing paternal age particularly after the age of 55 years.

In the present study, 2% cases are observed above 40 years of paternal age in DS subjects. (Table 4) Various large United States and European epidemiological studies of Down syndrome show no influence between paternal age and Down syndrome. For example, in one of the largest American studies analyzed birth certificate reports in upstate New York from 1963 to 1974 and reported (Regal et al 1981)[20] no correlation between 853 cases of Down syndrome and paternal age. 13 In contrast, in a study from Canada an examination of 997 cases of Down syndrome revealed a general pattern of increasing relative rate estimates with increasing paternal age. (Verma et al 1998).[21]

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Smaller studies examining Down syndrome data from prenatal diagnosis conflict with regard to a paternal age effect. After evaluating 158 cases of prenatally diagnosed trisomy,[21] including 60 from the Federal Republic of Germany 8 and 98 from the New York State chromosome registry, Stene et al described a paternal age effect (stene et al 1987).[22] However, in a separate analysis of the same 98 prenatally diagnosed cases in New York State, Hook and Cross found no paternal effect (Jyothy et al 2000).[23] The contrast between these 2 conclusions is the result of different methods of statistical analysis and possibly of the small sample size. In our study 48% of DS were born to fathers above 30 yrs of age.

The mean paternal age of DS cases is estimated as 30.79 yrs and that of normal is 27.21 yrs. The study of DS in 118,265 in consecutive birth defects found that 5.3% of DS mothers had two spontaneous abortions compared to 3.7% controls (Stene et al 1987).[22] Recognizable abnormal fetus in younger mothers' uterus is more as compared to older mothers' (Stene et al 1987),[22] as a result the numbers of abortions in younger mothers are higher when compared to older women. The cause of abortions in the present study are not known, however it could be presumed that, the reproductive history shall play a prominent role in the predisposition of the birth of the child with chromosomal defect.

In the present study, it is clear from the table 5, that a high frequency of spontaneous abortions (22%) and still births (6%) are observed in mothers of DS subjects. The scope of the study of living environment, occupation, and economic status of parents is to focus on their impact on the prevalence of DS. 90% of the population, used to be rural in the past, but in the recent years, the trend has changed in India and migration from rural to urban areas become imperative for livelihood and other reasons. Consequently urbanization of population has become more effective, there has been change in occupation and living conditions as well in the population.

A change in the economic status and for the need of comfort in their life with nutrition, health and hygiene, show their effect on the future pregnancy. According to the reported high frequency of DS cases in urban areas (Mikkelsen et al 1980).[24] The increased frequency of DS children in women below 35 years of age has been noticed in industrial and densely populated areas. Low income, big family and poor nutritional standards may have impact on the parental physiology (mainly maternal), may enhance the risk of non-dysjunctional error. In the present study, Exploration of the effect of living conditions, occupation, income nutritional status etc, on the etiology of syndrome could not provide concrete evidence, as the cases studied are less but shall add to the existing data and knowledge. In the coming days, it may aid to pinpoint the environmental effects on the etiology of the DS (Table 6).

The frequency of pure trisomy 21 varies from 83.60% to 100% in 1984. The frequency of mosaic trisomy 21 varies from a minimum of 0.67% Murthy et al 1989 to a maximum of 15%.[14] Similarly, the frequency of translocation trisomy 21 also varies from a minimum of 1.4% to a maximum of 8.85 % (verma 1998).[21] Since the free trisomy 21 is the most common genetic cause of birth of children with Down syndrome it is of great importance to undertake preventive measures in order to reduce the disorder incidence among human population. For prevention purposes, the etiological factors as a cause of birth of children with DS, should be known and reduction measures should be taken to minimize impact. The sequence of chromosome 21 was a turning point for the understanding of Down syndrome. Comparative genomics is beginning to identify the functional components of the chromosome and that in turn will set the stage for the functional characterization of the sequences.

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Animal models combined with genome-wide analytical methods have proved indispensable for unravelling the mysteries of gene dosage imbalance (Stylianos et al 2004).[25] The cytogenetical study conducted on 305 Down syndrome children among Albanian population of Kosovo revealed that free trisomy 21 is significantly more frequent (93.4%) than the other types of trisomy 21. Other authors also indicated high occurrence of free trisomy 21 (92-95%) in children that have Down syndrome (Mutton et al 1986, Owens et al 1983).[26,27] It shows that this chromosomal aberration is presented equally as frequent as in rest of the world.

CONCLUSION: Trisomy 21 or Down's syndrome is a common congenital abnormality affecting 1 in 1,000 newborn. Multiple investigations have been done to identify possible risk factors, of which the most common has been parental age. We defined the parental age effect on Down's syndrome and clarified whether a paternal age effect exists as a risk factor. No relationship between parental age and Down's syndrome is apparent. Early parental age is not immune to down's syndrome as many cases of down's syndrome babies are born to parents less than 35 years.

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DOI: 10.14260/jemds/2014/3789

ORIGINAL ARTICLE

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Date of Submission: 27/10/2014.
Date of Peer Review: 28/10/2014.
Date of Acceptance: 05/11/2014.
Date of Publishing: 08/11/2014.