MORPHOLOGICAL AND KARYOTYPIC ANALYSIS OF DOWN SYNDROME

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CERTIFICATE

This is to certify that the dissertation entitled **" Morphological and Karyotypic Analysis of Down Syndrome"** *submitted by* ***Dr. V. Suba*** *to the Faculty of Paediatrics, The Tamilnadu Dr. M.G.R. Medical university, Chennai in partial fulfillment of the requirement for the award of M.D. Degree Branch VII (Paediatrics) is a bonafide research work carried out by her under our direct supervision and guidance.*

Dean,
Govt. Rajaji Hospital,
Madurai Medical College,
Madurai.

Professor and Head
Institute of Child Health and
Research Centre,
Govt. Rajaji Hospital,
Madurai Medical College,
Madurai.

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CONTENTS

INTRODUCTION

Down syndrome

Down syndrome is the commonest occurring syndrome found in 1:800 live births and was first described by John Langdon Down in 1866[1].

The Syndrome produces a phenotype that includes a characteristic facies, mental handicap and various development anomalies [2].

Individuals with down syndrome are likely to have a variety of other problems, both congenital and acquired which may influence the medical and surgical management.[3]

GENETIC ABNORMALITIES CAUSING DOWN SYNDROME[4]

Proportion of children with Down Syndrome	Genetic Abnormality
95%	Meiotic Nondisjunction
4%	Unbalanced translocation between chromosome 21 and other acrocentric chromosome
1%	Mosaicism – 2 cell lines are present, one normal and one trisomy 21

CERTAIN TERMS REQUIRES DEFINITIONS

Non – disjunction

Failure of chromosomes to disjoin normally during meiosis. Non-disjunction can occur during Meiosis I (or) Meiosis II. The resulting gamete either looks a chromosome (or) has two copies of it producing a monosomic (or) trisomic zygote respectively.[5]

Translocations

2 Types

- ⌘ Reciprocal
- ⌘ Robertsonian

Reciprocal

Is a structural alteration of chromosomes that usually results from breakage of two chromosomes with subsequent exchange of the resultant chromosomal segment.

Robertsonian

Results from centromeric fusion of two acrocentric chromosomes.[6]

Mosaicism

These individuals have some normal somatic cells and some cells with trisomy 21.[7]

The most common cause of Mosaicism for a trisomy is a trisomic conception followed by loss of the extra chromosome in some cells during mitosis in the embryo.[8]

REVIEW OF LITERATURE

A cytogenetic studies of Down Syndrome cases from Andhra Pradesh – India gave the incidence of Down Syndrome to be 1 in 920 births [(9)].

Dr. Aubrey Milunsky, Professor of Human Genetics, Pediatrics, Obstetrics & Gynaecology and Pathology at Boston University School of Medicine makes this statement.

- ★ In general for all women the average likelihood of delivering a child with Down Syndrome is approximately 1 in 800. At age of 30 the average risk is about 1 : 710.

- ★ The risk can be accurately defined when the maternal serum quadruple screen done between 15 & 16 weeks of pregnancy. [(10)]

Male to female ratio in patients of Down Syndrome was 1.4 : 1 as reported by Mutton et al. [11]

Birth order of Down Syndrome revealed a high frequency of first borns (29.7%) followed by second borns 29.13% and 3rd borns 17.10 [(12)]

Most of the translocation Down Syndrome children were born to mother less than 25 years of age and their children were found to be first borns in the birth order. [13]

A study conducted by Sayee R, Thomas IM had revealed that parental consanguinity was observed in 13.8% of cases in parents of Down Syndrome. (n = 865).[14]

In a study conducted by Ishwar C. Verma et al noted that 86.5% of the Down Syndrome patients were last born children. In 24.4% of families the first born child was affected. [15]

96% of babies with Down Syndrome with no heart defects were alive after one year – Hayes C. et al Int. J Epid 26 (4) 822 – 829, 1977. [16]

Infants with Down Syndrome are known to have a high frequency of birth defects, particularly cardiac and Gastrointestinal Tract defects- Fabia and Drolette 1970, Stoll et al 1990, Kallen et al 1996. [17]

A study conducted by Hiji et al had revealed 92.2 % of Down Syndrome subjects without congenital heart disease survived to age 24 years as conducted with 74.6 % of subjects with Congenital Heart Disease. [18]

The AV Canal defect stands out as being the most common defect in Down Syndrome, the risk for this anomaly is increased to 1000 fold among Down Syndrome children.

The cardiac defects such as hypoplastic left heart syndrome, Truncus arteriosus, Transposition of Great Arteries, dextrocardia are not significantly increased in Down Syndrome (Berg JM. Crome L 1960). [20]

Gastrointestinal defects occur about 20 times more commonly in Down Syndrome. [21]

Cardiac disease as high as 4.6 – 7.1 % of those with Down Syndrome.[22]

Tyler CVJ, Zyzanski SJ et al in their study had revealed that there is a risk for gall bladder disease in Down Syndrome children. The risk being 3.52 %. [(23)]

Abnormalities seen in children with Down Syndrome include midface hypoplasia, characterized by malformation of the Eustachian tube, shortened palate, hypoplastic nasal bone, macroglossia, enlarged adenoids and tonsils – Mitchell B, Call C, and Kelly J, 2003 and Stores G 1996. [24]

Persistent obstructive sleep apnea in children with Down Syndrome who have undergone adenoidectomy and tonsillectomy has

multiple causes. The most common include macroglossia, glossoptosis, recurrent enlargement of the adenoid tonsils and lingual tonsils by Donnelly LT, Shoft SR, 2004. [25]

For children with Down Syndrome and Obstructive Sleep Apnea the cine MRI is the best way to identify the case of Obstructive Sleep Apnea. [26]

According to Balkany and colleagues 64 % of patients with Down Syndrome have Binaural hearing loss. In 83% the hearing loss is conductive, and in the remaining sensorineural. [27]

The eyes show numerous abnormalities almost all of which have been encountered in other chromosomal anomalies. [27]

The palpebral fissures are Upslanting and narrow laterally.

According to Donaldson, Brushfield spots are present in 85% of Down Syndrome subjects as compared with 24% of controls. [28]

Cataracts are fifty fold more common in Down Syndrome births – A study by Claudine P. Torfs et al 1998. [29]

Down Syndrome is associated with several autoimmune conditions notably DM type I. An elevation of antithyroid antibody is common and nearly 50% of subjects mostly male have reduced thyroid function in later life. [30]

There is also an increased prevalence of autoimmune thyroiditis. Coleman of Abbassi 1984 – found lymphocytic thyroiditis in 15 of 16 patients. [31]

Javurasanasirikul et al 1998 detected congenital hyperthyroidism in 17 of 112 (15%) of babies with Down Syndrome less than 1 year old. [32]

Gilchrist 1946 described the first case of a person with Down Syndrome with a goitre secondary to hyperthyroidism. [33]

Criscuolo et al 1980 and Sharav et al 1991 have suggested that in patients with Down Syndrome substantial primary hypothyroidism could be diagnosed by testing the hypothalamic pituitary thyroid pathway by detection of an exaggerated and prolonged TSH response to TRH. [34]

Gonadal deficiency progresses from birth to adolescence and becomes manifest in adult life with resultant infertility in virtually all non mosaic male subjects. [35]

Lange BJ, et al in his studies had revealed that acute myeloid leukemia predominates in children with Down Syndrome under 4 years of age where as ALL predominates in older children. [36]

Obsessional slowness was originally described by S. Rachmen in 1974.[37]

In 1994 R.J. Pary described a small number of patients who had both Obsessional slowness and Down Syndrome.

In a study by Charlot L, Fox S, Fried Lander R, had revealed that Obsessional slowness it as an elevated rate in people with Down Syndrome. [38]

New onset of focal weakness in children with Down Syndrome has a broad differential diagnosis. The most common being Atlantoaxial instability and Moya Moya disease – Heffner et al 2004. [39]

Lowry et al reported that atlanto axial instability is seen in 15 - 40 % of patients.[40]

Infantile spasms occur in 2 – 9% (Zelleweger 1977, Romano et al 1990, Stasform et al 1991) [41]

20 –25 % higher incidence of EEG abnormalities, made in younger patients (Ellingson et al 1973). [42]

Bazelon M, et al in his study showed that aside from mental retardation these Down Syndrome children will have generalized muscular hypotonia and hyperextensibility of the joints. [43.]

The dermatoglypic pattern of the patients with Down Syndrome shows several abnormalities of these distally placed triradius is seen in 88% by Paed et al. [44]

Palmar creases develop early in 11^{th} – 12^{th} week of gestation. Absence of palmar crease may indicate problems with early development and may be associated with other developmental disorders like Down Syndrome. [45]

Medical people call single palmar crease or a simian crease. Presence of a simian crease indicates an abnormality physically (or) mentally. However, there are many people with simian drive on one / both hands and don't have any physical (or) mental abnormalities. [46]

Scoliosis developed in 8.7% of patients with Down Syndrome. There was a high rate of cardiac surgery within this population. [47]

Finerman et al 1976, Sigman B (1981) in his studies had revealed that in Down Syndrome children there is narrowing of cervical canal, subluxation of atlanto axial process – an accentuation of which leads to paraplegia (or) tetraplegia. [48]

Functions typically associated with the left hemisphere appear to be more impaired than those associated with right hemisphere – Elliot et al 1987. [49]

In a study by Casaiwva et al 1985 had showed that there is selective loss of cells in basal nucleus of meynert. [50]

Myelination is incomplete or delayed in some cerebrocortical repairs such as fronto temporal lobe especially in the cerebello cortex areas. (Nisniew et al 1986). [51]

Over all decrease in the efficacy of cellular metabolism is noted – Hsia et al 1971. [52]

Significant quantitative deviation from normal lymphocyte surface markers, - serum Ig ; (Gershiun et al 1992) [53]

Strewss D, Eyman RK et al in their study stated that the life expectancy of children with Down Syndrome is still unexplained. It may be due to early appearance of Alzheimer disease which results in a marked survival roles after 35 years of age. [54]

Senalars Kennedy and Brownback introduced a bill into the senate called the “Prenatally Diagnosed Condition Awareness Act”. This bill (S.Fog) states as its goal “To amend the public health service act to increase the provision of scientifically sound information and support services to patients receiving a positive test diagnosis for Down Syndrome or other prenatalty diagnosed conditions.[55]

AIM OF THE STUDY

1. To look for any change in the cytogenetic pattern in Down syndrome cases in the present era of small family norm.

2. To identify any correlation between phenotypic malformation and genotypic abnormality.

DOWN SYNDROME

A BRIEF HISTORY

The formal story began in 1866 when a physician named John Langdon Down published an essay in England in which he described a set of children with common features who were distinct from other children with Mental Retardation.

Down was superintendent of an asylum for children with mental retardation in Surrey, England (1858-68).

He made the first distinction between children who were cretins (later found to have hypothyroidism) and he referred them as mongoloids.

Down based this unfortunate name on his notion that these children looked like people from Mongolia, which then became an ethnic insult.

In early 1960s, the term mongoloids was dropped and instead the condition became called “Down’s Syndrome”.

In the 1970s, an American version of scientific terms changed it simply to “Down syndrome”, while it still is called Down’s in the UK and some places in Europe.

In 1959, Jerome Lejeune and Patricia Jacobs working independently first determined the cause to be trisomy of the 21st chromosome.

Cases of due to translocation and Mosaicism were described over the next 3 years.

- ★ 1973 – National DS Congress
- ★ 1979 – National DS Society were formed.

Down syndrome

Trisomy 21, is the most common aneuploid condition compatible with survival to term.

It is seen in approximately 1 in 800 LB.

Trisomies occur when there are three representatives of a particular chromosome instead of the usual two.

The incidence of Down Syndrome among conception is more than twice as high as it is among live births. More than half of the trisomy 21 conceptions spontaneously abort early in pregnancy. The occurrence of trisomy 21 as well as other autosomal trisomies increases with advancing maternal age.

The chromosomes

Chromosomes are thread like structures composed of DNA and other proteins. They are present in every cell of the body and carry the genetic information needed for that cell to develop. Genes which are units of information are encoded in the DNA.

Human cells normally have 46 chromosomes, which can be arranged in 23 pairs. Of these 23, 22 are alike in males and females and these are called autosomes. The 23rd pair are the sex chromosomes.

Human cells divide in 2 ways. The first is ordinary cell division (mitosis) by which the body grows. In this method one cell becomes 2 cells, which have the exact number and type of chromosomes on the parent cell.

The second method of division occurs in ovaries and testicles, (meiosis) and consists of one cell splitting into two with the resulting cells having half the number of chromosomes of the parent cell. So normal eggs and sperm cells only have 23 chromosomes instead of 46.

Many errors can occur during cell division. In meiosis the pair of chromosomes are supported to split up and go to different spots in the dividing cell – event called 'disjunction'. However occasionally one pair doesn't divide and the whole pair goes to one spot. This means that in the resulting cells, one will have 24 chromosomes and the other will have 22 chromosomes. This accident is called "nondisjunction".

In Down Syndrome 95% of all cases are caused by this event. One cell has two 21st chromosomes instead of one so the resulting fertilized egg has three 21st chromosomes – hence the scientific name trisomy 21.

Three to four percent of cell cases of trisomy 21 are due to Robertsonion translocation. In this case two breaks occur in separate chromosomes, usually the 14th and 21st chromosomes. There is rearrangement of the genetic material so that some of the 14th chromosome is replaced by extra 21st chromosome. So while the number of chromosomes remains normal there is a triplication of the 21st chromosome material. Some of these children may only have triplication of part of the 21st chromosome instead of the whole chromosome, which is called a 'partial trisomy 21'.

The 21st chromsome and Down syndrome

The chromosomes are holders of the genes and those bits of DNA that direct the production of a wide array of materials the body needs. In trisomy 21, the presence of an extra set of genes leads to over expression of the involved genes leading to increased production of certain products.

Down Syndrome Critical Region

One popular theory states that only a small portion of 21st chromosome actually needed to be triplicated to get the effects seen in Down Syndrome called Down Syndrome critical region.

The 21st chromosome may actually hold 200 to 250 genes (being the smallest chromosome in the body in terms of total number of genes).

Genes that may have input into Down Syndrome include :-

- ★ **Superoxide Dismutase (SODI)** – Over expression may cause premature aging and decreased function of the immune system. Its role in senile dementia of the Altzheimer's type (or) decreased cognition is still speculative.
- ★ **COL 6 Al** – Over expression may be the cause of heart defects.
- ★ **ETS 2** – Over expression may be the cause of skin abnormalities.
- ★ **CAF 1 A** – Over expression may be detrimental to DNA synthesis.
- ★ **Cystathione Betasynthase (CBS)** – Over expression may disrupt metabolism and DNA repair.
- ★ **DYRK** – Over expression may be the cause of mental retardation.
- ★ **CRYAI** – Over expression may be the cause of cataracts.
- ★ **GART** – Over expression may disrupt DNA synthesis and repair.
- ★ **IFNAR** – The gene for expression of interferon, over expression may interfere with the immune system as well as other organ system.

Genes can come in different alternate forms called "alleles". The effect of over expression of genes may depend on which allele is present in the person with trisomy 21.

The second reason that might be involved is called penetrance". If one allele causes a condition to be present in some people but not others that is called "variable penetrance" and that appears to be what happens with trisomy 21.

Trisomies, Non disjunction and Maternal Age

Among the mothers younger than the age of 30, the risk is less than 1 in 1000. It increases to approximately 1 in 400 among women at age 35, to approximately 1 % at the age of 40, and to 2% or more after age of 45.

Several hypotheses have been advanced to account for this increase, including the idea that older women are less likely to spontaneous abort trisomic pregnancy. It is most likely that the patient is due to an increase in non-disjunction among older mothers. All of a female's oocytes are formed during her embryonic development. They remain suspended in prophase II until they are shed during ovulation. Thus an ovum produced by a 45 year old women is itself about 45 years old. This long period of suspension in prophase I may impair normal disjunction. However the precise nature of this mechanism is not understood.

Many factors have been examined to determine whether they may affect the frequency of nondisjunction in women. These include hormone levels, cigarette smoking, autoimmune thyroid disease, alcohol consumption, and radiation.

None of these has shown consistent correlations with non-disjunctions in humans.

Numerous studies have tested the hypothesis of a paternal age effect for trisomies and the consensus is that there is little evidence of for such an effect. This may reflect the fact that spermatocytes, unlike oocytes, are generated throughout the life of the male.

Translocation Down Syndrome

Approximately 4% of Down syndrome individuals have a translocation-involving chromosome 21. They account for 9% of the children with Down syndrome born to mothers younger than 30 years of age. Half the translocations arise de novo in the affected individual, where as half are inherited from a translocation carrier parent.

Parents who are carriers of a translocation-involving chromosome 21 produce three types of viable offspring.

1. Normal phenotype and karyotype
2. A phenotypically normal translocation carrier and
3. The translocation trisomy 21

The majority of translocations that give rise to Down syndrome are fusions at the centromere between chromosomes 13,14,15 (or) 21, for example t(13q, 16q) (or) t (21q 21q).

If translocation is identified, parental studies must be performed to identify normal individuals who are translocation carriers with a high recurrence risk for a chromosomally abnormal child and who may also have other family members at risk.

MOSAIC DOWN SYNDROME

The remainder of cases of trisomy 21 are due to Mosaicism. These people have a mixture of cell series some of which have a normal set of chromosomes and other, which have trisomy 21. In cellular Mosaicism the mixture is seen in different cells of the same type. In tissue Mosaicism one set of cells, such as all blood cells, may have normal chromosomes and another type such as all skin cells may have trisomy 21.

CLINICAL MANIFESTATIONS

The clinical picture of Down syndrome is protean and consists of an unusual combination of anomalies.

The birth weight of Down syndrome infants is less than normal and 20% weigh 2.5 kg (or) less. Neonatal complications are more common than normal a consequence of fetal hypotonia and a high incidence of breech presentations.

Physical growth is consistently delayed and the adult Down Syndrome subject is significantly shorter than a normal adult.

The mental age that is ultimately achieved varies considerably. It is related in part to environmental factors, including the age when the individual is institutionalized, the degree of intellectual stimulation and the evolution of presenile dementia even prior to puberty. The patients with Down Syndrome have Intelligence quotient between 25 and 49 with the average about 43.

In mosaics they tend to achieve somewhat higher intellectual development than other types and in particular they possess better verbal and visual perceptual skills.

CNS

They have generalized muscular hypotonia and hyperextensibility of the joints. This is particularly evident during infancy and occurs to a significant degree in 44% of subjects under 9 years of age.

Functions typically associated with the left cerebral hemisphere appear to be more impaired than those associated with right hemisphere.

Evaluation of motor, social and adaptive behaviour of trisomic children suggests developmental regression preceding the first birthday.

Denver development scale studies demonstrate that trisomic infants approximately six months of age typically experience a steady progressive deceleration of development that foretells that mental retardation is readily evident by four years of age.

The language and communication skills are delayed in majority.

In Newborns, the main clinical features being apathy, feeding difficulties, prolonged physiological jaundice, diffuse Hypotonia, hyperextensibility of the joints, slowned response to neonatal reflexes are present.

In children they have unsteady wide based gait. Major motor seizures are seen no more frequently in Down Syndrome infants than in the general population, the association between infantile spasms and Down Syndrome is greater than chance.

Attacks can occur spontaneously on follow treatment with 5-hydroxytryptophan. The electroencephalogram (EEG) demonstrates hypsarrhythmia. A progressive disorganization of the EEG accompanies the evolution of Alzheimer dementia.

Neuro imaging studies characteristically reveals large opercula, an indication of the under developed superior temporal gyrus. Symmetric calcifications in basal ganglia are common, particularly in adults.

In addition to the above mentioned abnormalities patients with Down Syndrome exhibit a number of stigmata. None of these is present invariably, nor are any consistently absent in the normal population, but their conjunction contributes to the characteristic appearance of the subject.

EYES

The eyes show numerous abnormalities almost all of which have been encountered in other chromosomal abnormalities. The palpebral fissures are oblique and narrow laterally. Patients have a persistence of a complete median epicanthic fold.

Brush field spots are an accumulation of fibrous tissue in the superficial layer of the iris. They appear as slightly elevated light spots encircling the periphery of the iris.

Blepharitis and conjunctivitis are common as are lenticular opacifications and keratoconus particularly in older subjects.

EARS

Anomalies of the external ear are also frequent. The ear is small, low set and often ‘c’ shaped with a simple helix and hypoplastic tragus. The cartilage is often deficit. Additionally the diameter of the external auditory meatus is abnormally narrow which precludes good visualization of the tympanic membrane.

Structural anomalies of the middle and inner ear might contribute significantly to the language delay commonly encountered in children with Down Syndrome. Congenital malformations of the sinus of the middle ear, permanent fixation of the stapes, shortening of the cochlear spiral are frequently encountered.

Additionally children particularly infants, are prone to acute and chronic otitis, middle ear effusions, and endolymphatic hydrops with subsequent conductive and neuro sensory hearing loss.

64% of Down Syndrome patients have binaural hearing loss. In 83% the hearing loss is conductive, and in the remainder sensori neural. Brainstem auditory evoked potentials can be used to determine the type and severity of hearing loss in young or uncooperative children. Because of the frequency of impaired hearing a

comprehensive hearing evaluation is indicated during the first six months of life.

LIPS

The lips of the patient with Down Syndrome have radial furrows, and as a consequence of the generalized Hypotonia, the tongue often fissured tends to, protrude because the maxilla is too small and the palate is too narrow to accommodate it.

NECK

The neck is short with redundant skin in the nape of the neck.

EXTREMITIES

The extremities are short. The fifth defect is incurved and the middle phalanx is hypoplastic (Clinodactly).

As a consequence its distal interphalangeal crease is proximal to the proximal interphalangeal crease of the ring finger. Additionally the distal and proximal interphalangeal creases are closely spaced and there might be a single distal crease on the 5^{th} digits. The simian line, a single transverse palmer crease is present bilaterally in 45% of patients. In the feet a diastasis between the first and second toes is the most characteristic anatomic abnormality.

DERMATOLOGICAL PROBLEMS

Since the skin tends to reflect other condition of the body it is not surprising that children and adults with Down Syndrome have more than their share of skin problems.

Newborns with Down Syndrome frequently have bluish discolouration of hands and feet at birth - acrocyanosis.

They also have bluish mottling of the skin called cutis marmorata. It is a response of the capillaries of the skin to being cool. It is common in all newborn but it lasts several months longer in infants with Down Syndrome. Children with Down Syndrome may show all features.

1. Children with Down Syndrome may have dry rough skin **– xerosis.**

2. **Chelitis –** presence of fissures and red, scaly skin at the corners of the mouth and lips. This is due to moisture collecting at the corners of the mouth, but can also be complicated by infection from bacteria (or) the yeast candida.

3. **Atopic dermatitis** – presence of red scaly itchy skin. Most likely to appear on the cheeks behind the ears, behind the knees.

4. **Seborrhea** – Usually greasy and scaly lesions, appearing on the scalp and eyebrows.

5. **Hyperkeratosis –** very thick skin on the palms and sides of the feet.

6. **Syringomas** – Benign skin tumors that arise from sweat duct. They look like very small multiple raised radicals on the skin with varying degrees of yellowish color. Most often seen on the eyelids, neck and chest. They are twice as often in females.

7. **Elastosis Perforans Serpiginosa** – is a disorder of the elastic tissue of the skin, causing deep red raised lesions to appear in alveolar (or) a circular pattern. They tend to occur on the back and

sides of the neck, also seen on the chin, cheeks, arms and knees. They occur in males four times as often as in females.

8. **Vitiligo :** Loss of pigmentation of the skin in well defined areas. Cause – not known, may be caused by acute antibodies destroying melanocytes, which are cells in the skin that produce pigment.

9. **Acanthosis Nigricans** – Is an increase in pigmentation. Most often appears on the back of the neck, hands and groin

10. **Folliculitis -** Is the inflammation and/or infection of hair follicles of the skin and appears as small red bumps (or) yellowish pustules.

11. **Fungal Infection** – May be seen on the groin area, feet, toenails, and fingernails.

12. **Scabies** – In reasons unknown, this infection is a common problem in teens and adults with Down Syndrome.

13. **Alopecia areata** – Is the term used to describe patchy hair loss, which is not due to infection (or) drugs. It is believed to be due to an autoimmune i.e., antibodies against hair follicles.

People with Down Syndrome are more prone to autoimmune diseases such as diabetes, hypothyroidism and celiac disease.

MUSCULO SKELETAL DEFORMITIES

10-20% of all Down Syndrome Children are affected by

- Narrowing of cervical canal
- Decrease of Acetabular and iliac angles
- Subluxation of Atlantoaxial process
- Attenuation of above may cause paraplegia (or) Tetraplegia.

Almost all of the conditions that affect the bones and joints of people with Down Syndrome arise from the abnormal collagen found in Down Syndrome. One of the types of collagen (type VI) is encoded by a gene found on the 21st chromosome. The resulting effect in people with Down Syndrome is increased laxity or looseness of the ligaments that attach bone with bone and muscle to bone.

SPINE

★ **Atlantoaxial instability**

★ **Scoliosis** — Seen in upto half of them as they become adolescents.

★ **Hip** — Subluxation – common between the ages of 3 and 13 years.

Legg-calve-perthes disease – more common. Children will have painless limp and loss of full range of movement of the involved hip and diagnosed through x-rays.

Slipped Capital femoral epiphysis

Here rounded head of the femur slides on the neck of the femur. Femur slides on the neck of the femur.

Can be associated with obesity and hypothyroidism. Appears as a limp with associated pain in the hip (or) knee.

Knees

Instability of the patella – estimated to occur in close to 20% of people with Down Syndrome. Some may develop subluxation, some dislocation.

Foot

a) **Flat foot** also called as pesplanus. In severe cases the heel rotates so that the person is walking in the inside of the heel.

b) **Metatarsus primus varus** – Commonly seen in Down Syndrome. In these conditions the front part of the foot behind the big toe bends inward. This creates obvious deformity of the foot making the task of finding shoes that fit more difficult.

Joint pains in Down Syndrome are mostly due to hyperextensibility of the joints, more primarily due to Juvenile Rheumatoid Arthritis.

Atlantoaxial Instability

Atlantoaxial instability denotes increased mobility at the articulation of the first and second cervical vertebral (Atlantoaxial joint). The causes of Atlantoaxial instability are not well understood but may include abnormalities of the ligaments that maintain the integrity of the articulation, bony abnormalities of the cervical vertebrae (or) both.

In its mildest form, Atlantoaxial instability is asymptomatic and is diagnosed using X-rays.

Symptomatic Atlantoaxial instability results from subluxation that is severe enough to input the spinal cord on from dislocation at the Atlantoaxial joint.

Approximately 15% of youths with Down Syndrome have Atlanto axial instability. The neurological manifestation of symptomatic Atlantoaxial instability includes easy fatiguability, difficulties in walking, abnormal gait, limited neck mobility, torticollis, in - coordination and clumsiness, sensory defects, spasticity and hyperreflexia, and other spinal cord symptoms and signs.

Such symptoms and signs of less remain relatively stable for months (or) years, occasionally they progress then to paraplegia, hemiplegia, quadriplegia (or) death.

The lateral neck x-rays are of potential but unproven value in detecting patients at risk for developing spinal cord injury during sports participation.

ENDOCRINE

Several endocrine abnormalities have also been documented. An elevation of antithyroid antibody is common and nearly 50% of trisomy 21 subjects mostly males have reduced thyroid functions in later life. Congenital hypothyroidism is more common.

Also have primary gonadal deficiency – which progresses from birth to adolescence and becomes manifest in adult life.

The prevalence of iodine in patients with Down Syndrome is 1.4 – 10.6% for higher than in the general population.

CARDIAC

Half of the individuals with Down Syndrome have Congenital Heart Disease of which endocardial cushion defect is more common.

Arrhythmias – Uncommon (usually related to co-existing Congenital Heart Disease (or) its treatment. May be severe and may include complete heart block and sick sinus node, syndrome which necessitate pacemaker implantation.

Reduced risk of coronary artery disease and this was attributed to a favourable blood lipid profile. Other cardiac defects in Down Syndrome include Atrial Septal defect, Ventricular Septal defect, and defects of cardiac valves, Tetralogy of Fallot, Double outlet right ventricle.

GIT

These anomalies are seen in 20% of cases. The following condition may be seen.

- ★ Duodenal atresia
- ★ Tracheo oesophageal Fistula
- ★ Pyloric stenosis
- ★ Meckel's diverticulum
- ★ Hirshsprung disease
- ★ Feeding intolerances
- ★ Gastro eosophgeal Reflexes
- ★ Constipation
- ★ Celiac disease etc.

Gall stones

The rate of gall bladder disease with symptoms requiring removal of the gall bladder was 5 times higher in the adults with Down Syndrome than the control group. Patients with Down Syndrome were more likely to have gall bladder disease were females and there with positive family history of Gall bladder disease.

HEMATOLOGY

10% Incidence of myelo proliferative disorder in New born. Transitory, but may develop into megakaryocytic leukemia, 10-30% fold increase in leukemia.

Macrocytosis, hyposegmentation of WBC's, polycythemia, leukopenia, thrombopenia – seen.

DENTAL

There is a high rate of periodontal disease seen in Down Syndrome. Often seen with onset in the mild to late teen years. This is thought to be related to a lowered host immune response due to the compromised immune system in Down Syndrome.

The teeth most affected are the mandibular incisors and maxillary molars.

Caries – may be due to delayed eruption of the teeth, increased spacing between teeth (or) possible differences in the chemical content of the saliva.

DERMATOGLYPICS

Shows several abnormalities of these a distally displaced triradius the palmer meeting point of three differently aligned crease lines is seen in 88% but in only 10% of controls.

The other features include

- ★ Increased incidence of ulnar loops 83% (n-63)
- ★ Ulnar loops are very high and L shaped.
- ★ Often have 10 ulnar loops 35% (N-5%)
- ★ Reduced incidence of whorls 12% and arches 3%
- ★ Decreased incidence of radial loops but increased incidence of radial loops on fingers.

Palmar features

1. Short, broad palms with short fingers
2. Clinodactly of little finger
3. Hyperflexible thumb joint

4. Presence of simian line (single transverse palmar crease)

ALZHEIMER DISEASE

Early appearance of Alzheimer disease results in a marked drop in survival upto 44 years of age. Deterioration of speech and gait are early findings, epileptic seizures and myoclonus are common.

NEUROPATHOLOGY

- No gross malformation
- There is pronounced and distinctive deceleration of CNS development.
- Mild decrease in brain size and weight
- Frontal lobe, brain stem, especially cerebellum is affected. The most constant abnormalities are those of the cerebellum – which explains the uniform presence of hypotonia.

Gross cortical convolutional pattern are embryonic. A narrow superior temporal gyms, exposed insula resulting from lack of development of the third frontal gyrus, fronto occipital diameter is shortened with steep inclination of both occipital lobes produces significant changes.

Histology

1. Reduction in the number of spines along the apical dendrites of pyramidal neurons.
2. A lack of granular cells with a specific decrease in the population of a specific cell type. Most likely the aspinous stellate granular cell.

3. Reductions of neuronal density in various areas of the cortex, loss of cortical inter neurons, an accumulation of undifferentiated fetal cells in the cerebellum.

The reduction in the number of spines has been interpreted as indicating a reduction in the number of synaptic contacts. Interestingly the dendritic tree is greater than normal in early infancy, but the excessive early outgrowth is followed by atrophy.

Abnormalities of the basal nucleus have received particular attention, because an early and significant, loss of neurons in this area is a feature of both Down Syndrome and Alzheimer disease. In Down Syndrome the cell count is 1/3rd normal even prior to the onset of dementia and it decreases progressively with age. In a few patients particularly those dying in infancy demyelinated patches are observed in the periventricular white matter, where they are accompanied by fat – filled granular cells.

Failure in gyral development and aplasia of the brain stem and cerebellum represent structural anomalies that must be the direct result of the chromosomal disorder.

The most migrating neuropathology observation is the premature development of senile changes within the brain comparable with a morphological diagnosis of Alzheimer disease. The pattern of involvement of the brain by senile plaques and tangles follow that seen in Alzheimer disease. The Amygdala, hippocampus the association areas of frontal, temporal and parietal cortex are particularly vulnerable to these changes.

Microscopic alteration include pigmentary degeneration of neurons, senile plagues, calcium deposits within the Hippocampus, basal ganglia and cerebellar folia. The calcium deposits in the cerebellar folia can be extensive enough to be seen on CT scan.

As in Alzheimer disease the brain of Down Syndrome have reduced choline acetyl transferase activity – not only in areas that contain plaques but also in those that appear microscopically normal.

BIOLOGICAL STUDIES

1. Overall decrease in the efficiency of cellular metabolism.
2. Evidence of immune system derangement leading to increased incidence of ALL, infection, known carrier status for HBs Ag.
3. Significant quantitative deviation from normal lymphocyte surface makers, serum Ig, nitrogen responsiveness, deficiency of T-cells.
4. The localization of the interferon receptor to the 21q22 region has stimulated new conjecture regarding immunological impairment in Down Syndrome.

Diagnosis

Prenatal Diagnosis :

The increased risk of trisomy 21 in women older than 34 years is an indication to offer these woman prenatal diagnosis.

Amniocentesis, (or) chorionic villus sampling to examine the fetal chromosomes is visually offered although maternal serum alpha-

fetoprotein screening recovering fetal DNA (or) cells from maternal blood are being used.

In women younger than 35 years of age maternal serum testing (triple screen) can be efficacious in prenatal screening for Down syndrome.

Low maternal serum and Feto protein concentration, low unconjugated estriol, elevated human chorionic gonadotropin are indicators of Down syndrome.

Detection Rate and the various procedures involved in prenatal screening for Down syndrome.

Procedure	Detection Rate
First Trimester Screening	
Maternal age	32%
Nuchal translucency measurement	74%
First trimester double test (PAPP – A, HCG)	63%
First trimester combined test (Nuchal translucency PAPP-A, HCG)	86%
Second trimester ST (15-19 weeks)	
Maternal age	32%
2^{nd} TM Double test (AFP, HCG)	60%
Triple test (AFP, HCG, UE3)	68%
Quadriple test (AFP, HCG, UE3, tritubin A)	79%
Integrated test (1^{st} TM – Nuchal translucency, PAPP-A, 2^{nd} quadriple test)	95%

★ Amniocentesis (≥ 15 weeks) 100%

- ★ Chorionic villus sampling (11-14 weeks) 100%
  (vs)
  Culture of amniotic fluid takes 2 weeks
  (Preparation of CVS takes 2 days)

Termination

- ★ Surgical dilatation, evacuation (11 to 13 weeks)
- ★ Medical with mifepristone (≥ 14 weeks)

1 week allowed before procedure for counseling.

The nuchal translucency measurement, quadriple test, first trimester combined, and integrated tests represent, the best opinions in terms of effectiveness, cost effectiveness and safety.

a. The diagnosis of Down Syndrome is made by the presence of the characteristic physical anomalies and is confirmed by cytogenetics.
b. Karyotyping of all cases of Down Syndrome is indicated to identify those that result from chromosomal translocation when translocation is present, the karyotype of both the parents must be ascertained to determine whether one of them carries a balanced translocation. Except in the case of the rare 21q/21q translocation recurrence rates for familial translocation range from 5-15% depending on the nature of the translocation and whether it first carried by the mother (or) the father.
c. Antenatal screening is indicated for mother ages 35 (or) older at term; as well as in the young mother who has had a previous child with Down Syndrome. Screening procedures

for low – risk pregnancies can be conducted during the second trimester. Low maternal serum α–fetoprotein, reduction in unconjugated estriol, and elevated chorionic gonadotropins are independent predictors of Down Syndrome and a positive result should prompt a follow up Ultrasonographic study to verify gestational age and anomalies.

Cytogenetic studies of amniotic fluid (or) chorionic villi can be used for the antenatal diagnosis of Down Syndrome as early as the third month of gestation.

Others

- Blood Hb % for anaemia
- Total count, Differential count, peripheral smear – To r/o leukemia
- Thyroid – T3,T4, TSH levels to R/O hypothyroidism
- USG Abdomen – look for
    i. annular pancreas
    ii. Hirsch sprung disease
    iii. Duodenal atresia
- Neuro
    - MRI
    - CT
    - Sleep study
    - O_2 saturation

  To rule out spinal cord compression degenerative changes.
- Dental – to rule out

- Mal occlusion,
- Dental caries
- Periodontal disease

- Cervical spine X rays to rule out Atlantoaxial instability

ECHO - To rule out congenital heart disease

TREATMENT

Despite the number of vigorously advocated regimens, none has proved successful in improving the mental deficit of the Down Syndrome child.

Currently medical intervention is directed toward treatment and prophylaxis of infections, treatment of the hearing deficit and correction of Congenital Heart Disease (or) any other significant malformation.

The early administration of 5-hydroxytryptophan a serotonin precussor, appears to reverse the muscular hypotonia characteristically present in Down Syndrome infant, and in some incidences can accelerate motor milestones. It has no effect on intelligence.

PLASTIC SURGERY

This is done in some centres in order to improve the facial appearance and increase social acceptance procedures include partial glossal resection, correction of the down turned lip, lifting of the nasal bridge, removal of fat from the neck, placing implants in the zygomatic bones, removing the epicanthic folds and making the palpebral fissures more horizontal.

Tongue reduction

The protruding tongue in Down Syndrome is due to a combination of a small oral cavity, enlargement of the portion of the tongue that lies adjacent to the tonsils, and lack of glossal muscle tone. Partial glossectomy for speech improvement and reduction in nasal breathing has no evidence base to date.

Surgical intervention for upper airway obstruction in upper airway obstruction disorders of children with Down Syndrome may include tympanostomy, tonsillectomy, adenoidectomy, Uvulopalato pharyngoplasty and tongue reduction.

Treatment for specific features

GIT

1. Constipation

The usual treatment is dietary increasing of fiber, fruits and vegetables. In bottle fed babies the introduction of stool softener such as corn syrup, malt barley extract (or) Lactulose can be used.

- Increase the amount of fluids the child drinks.
- Decrease the amount of constipating foods (milk products, rice) may also help.

For babies the use of glycerin can be helpful.

2. Hirschsprung disease

The diagnosis is made by first performing a barium enema on the child, confirmed by rectal biopsy. Treatment in the removal of the sequence of colon without the nerve endings.

3. Gall stones - removal

4. Celiac disease – A gluten free diet, vitamin supplements

SKIN

Dermatological problems like xerosis, can be best managed with non drying soaps, adding oils to the bath water and moisturizers.

Dandruff shampoos (or) shampoos with either tar compounds (or) salicylates are used to treat seborrhea of the scalp.

- Hyperkeratosis can be managed with salicylic acid.
- Syringomas can be removed by lasers, shaving (or) scooping out with a curette.
- Fungal folliculitis responds to antifungal drugs like itraconazole (or) topical selenium.
- Boils (or) furuncles requires oral antibiotics.
- Corticosteroids are used in treatment of alopecia areata

MUSCULO SKELETAL ANOMALIES

Requires appropriate treatment such as posterior bone fusion.

ENDOCRINE

Thyroxine treatment may improve development, and growth of young children and it should be considered in Down Syndrome neonates to maximize their early development and growth.

OBSESSIONAL SLOWNESS

(Spending hours each day performing familiar routines like bathing, dressing, and eating). Can be improved with serotonin selective reuplake inhibitors.

DENTAL

For caries : These children should be educated proper oral hygiene and receive the benefits of topical and systemic fluorides.

For periodontal disease : Use of chlorhexidine mouth rinser

- Systemic antibiotics
- Regular dieting and roof planning every 3 months

GENITOURINARY

- PUV junction obstruction
- Hydronephrosis
- Hypospadias
- Undescended testis

Treated accordingly.

RESPIRATORY

- Respiratory upper and lower infections
- Acute and chronic airway obstruction
- Sleep apnea
- Corpulmonale

Treated accordingly

MATERIALS AND METHODS

100 cases of Down syndrome attended as outpatient in Institute of Child Health and Research Centre, Govt. Rajaji Hospital, Madurai and in schools for mentally retarded children in and around Madurai was selected on the basis of clinical suspicion.

Inclusion Criteria

Mainly the following external features are taken.

1. Microcephaly
2. Hypotonia
3. Upslanting palpebral fissure

Exclusion Criteria

- Only cases with features of Down Syndrome are included in this study.

Sample size : 100

Duration of study : 1 year

Children included in this study were undergone following investigations.

1. Complete clinical examination
2. Hematological examination
3. USG – Abdomen

4. Audiological evaluation
5. Ophthalmological evaluation
6. Cardiac evaluation – individualized and
7. Karyotyping

Children with Congestive Cardiac failure, Seizures, Bronchopneumonia, Acute gastro enteritis were treated accordingly.

RESULTS AND ANALYSIS

Table 1

Children – Age wise distribution

S.No.	Age	No. of cases	%
1.	< 1 yr	20	20
2.	1-2 yr	13	13
3.	2-5 yrs	14	14
4.	5-10 yrs	21	21
5	11-12 yrs	32	32

★ In this present study eight cases were detected at the time of birth.

★ Eleven cases were detected in first 6 months, and remaining were at varying time periods.

Table 2

Sex - wise distribution

S.No.	Sex	No. of cases	%
1.	Male	58	58
2.	Female	42	42

In this present study, 58 were males and 42 were females.

Table 3

Maternal – Age wise distribution

S.No.	Mother's Age	No. of cases
1.	< 20 yrs	1
2.	20-30 yrs	53
3.	31 & above	46

The lowest maternal age in this present study was 19 years.

Table 4

Paternal – Age wise distribution

S.No.	Father's Age	No. of cases	%
1.	20-30 yrs	28	28
2.	31 & above	72	72

Table 5

Birth order

S.No.	Birth order	No. of cases	%
1.	I	32	32
2.	II	44	44
3.	III & above	24	24

In this present study there is an increased frequency of Down Syndrome in second order birth, followed by first and third.

Table 6

Mode of delivery

S.No.	Mode of delivery	No. of cases	%
1.	LN	89	89
2.	LSCS	11	11

The indication for LSCS in our present study was Oligohydramnios in 10 cases and one is repeat LSCS.

Table 7

Gestation

S.No.	Mode of gestation	No. of cases	%
1.	Term	90	90
2.	Preterm	10	10

Table 8

Clinical features and %

S.No.	Clinical features	No. of cases	%
1.	Hypotonia	100	100
2.	Microcephaly	100	100
3.	Brachicephaly	100	100
4.	Flat occiput	100	100
5.	Upslanting palpebral fissure	100	100
6.	Depressed nasal bridge	100	100
7.	Protruding tongue	100	100
8.	Clinodactly	100	100
9.	Sandle gap	100	100
10.	Deep plantar crease	94	94
11.	Epicanthic folds	86	86
12.	Brachidactly	82	82
13.	Low set ears	76	76
14.	Short neck	68	68
15.	Short stature	64	64
16.	Simian crease	44	44
17.	Dental carries	40	40

Table 9

Ophthalomological Evaluation

S.No.	Nature of lesions	No. of cases	%
1.	Posterior Capsular Cataract	1	1
2.	Nystagmus	2	2
3.	Myopia	2	2
4.	Ectropion	1	1
5.	Optic Atrophy	1	1

Table 11

Systemic involvement

S.No.	System affected	No. of cases	%
1.	CVS	23	23
2.	CNS	2	2
3.	RS	7	7

In our present study 2 had seizures, one is febrile convulsion and other being convulsion due to cortical venous thrombosis following acute gastro enteritis. 16 cases had recurrent respiratory track infections and 7 were diagnosed to have bronchopneumonia.

Table 12

CVS – Nature of lesion

S.No.	Nature of lesion	No. of cases (n=23)	%
1.	Atrial Septal defect	4	17.4
2.	Ventricular Septal defect	12	52.2
3.	Patent Ductus Arteriosus	4	17.4
4.	Tetralogy of Fallot with Patent Ductus Arteriosus	1	4.3
5.	Endocardial cushion defects	2	8.7

In our present study out of 100, 23 had congenital heart disease and Ventricular Septal Defect appears to be more common.

Table 13

Dermatoglypics

S.No.	Nature	No. of cases (n=80)	%
1.	Ulnar loops in all fingers	37	29.6
2.	Atd angle		
	75^0	38	47.5
	85^0	12	9.6
	90^0	11	13.8
	95^0 and above	19	23.8

Table 14

Karyotyping

S.No.	Types	No. of cases
1.	Meiotic nondisjunction	1
2.	Translocation	1
3.	Mosaicism	8

In this present era of small family norm, from our analysis of 100 cases of Down Syndrome, Mosaicism is found to be more common.

DISCUSSION

The total number of patients included in the present study was 100. This is a cross sectional prospective study conducted over a period of one year.

Out of these 100 patients 58 cases were boys and 42 were girls.

- Eight cases were detected at the time of birth.
- Eleven cases were detected in first 6 months.
- Remaining were detected at varying time periods.
- The lowest maternal age in my study was 19 years of those more than 31 years are 46 cases.
- Birth order of Down syndrome revealed a high frequency of
    - second born – 44 cases
    - followed by first born – 32 cases
    - third borns – 24 cases
- The mode of delivery being labour natural in 89 cases
- Remaining 11 cases were delivered through LSCS
- The indication for LSCS in 10 cases was Oligohydraminos and the one being a repeat LSCS.
- Approximately 15-20% of causes of Oligohydraminos were associated with fetal anomalies and

chromosomal anomalies being commonest one (Pryde and Co 2000, William's Obstetrics – 22nd Edn).

- The number of cases delivered at term being 90
- Remaining 10 were delivered preterm.
- Antenatally USG was done for 7 cases only.
- One case was detected antenatally
- Parental consanguinity was observed in 26 cases

In my study of 100 cases, the most common presenting complaint for which the child was brought to hospital being developmental delay in 72 cases, others being as follows :-

- Recurrent respiratory tract infection – 16 cases
- Congestive cardiac failure – 6
- Seizures – 2
- Failure to thrive - 1
- Acute Gastro enteritis – 1
- Cleft lip and Palate – 1
- Constipation – 1

In this present study the following morphological features were present in all cases.

- Hypotonia
- Microcephaly
- Brachycephaly
- Flat Occiput

- Mongoloid slant
- Depressed nasal bridge
- Clinodactly
- Protruded tongue and
- Sandal gap
- Epicanthic folds were found in 86% cases
- Deep plantar crease in 94 cases.
- Low set ear – 76 cases
- Short neck – 68
- Short stature – 64
- Dental carries – 40
- Simian crease – 44

Infants with Down syndrome are known to have a high frequency of birth defects, particularly cardiac and Gastro intestinal defects (Stru et al 1990, Kallen et al 1996).

In a study conducted by Claudine P Torfs et al revealed that Atrio ventricular canal defect stands out as being the most common defect in Down syndrome.

In this present study of 100 cases, 23 cases were found to have congenital heart disease.

- The commonest being – Ventricular Septal defect – 12 cases

- Others
    - Atrial Septal defect – 4
    - Patent Ductus arteriosus – 4
    - Endocardial cushion defect – 2
    - Tetralogy of Fallot with Patent ductus arteriosus – 1

The overall rate of congenital heart defects is 55.9% in a study by Khouny and Erickson in 1992.

Gastrointestinal defects occurs about 20 times were commonly in Down Syndrome – Torfs CP, Curry CJR, Bateson TF, 1995) Teratology 52 : 220 to 232. In our present study no gastrointestinal anomalies were noted.

Infantile spasms were noted in 2.9% of cases in a study conducted by Stafstron et al 1997. In our study there are 2 cases admitted with seizures, one had febrile convulsions and other being convulsions due to cortical venous thrombosis following acute gastroenteritis.

In the present study 16 cases was brought with c/o recurrent respiratory tract infections and bronchopneumonia was diagnosed in 7 cases.

Hangai S, Tanka Y – 1999 revealed the visual problems in Down syndrome as follows:-

- Myopia – 30%
- Strabismus – 27%
- Cataract – 15%

In our present study following findings were detected by ophthalmological evaluation.

1. Posterior capsular cataract – 1
2. Primary optic atrophy – 1
3. Nystagmus – 2
4. Myopia – 2
5. Ectropion – 1

Baxter et al (1975) found a rate of 66% of hypothyroidism in a sample size of 11 people with Down syndrome. In our present study all cases were screened and one found to have hypothyroidism.

In the first 3 years of life, non lymphoid leukemia is the most common form of leukemia. In our study of 100 cases no children had evidence for leukemia. One child had hypochromic microcytic anemia.

Atlanto axial instability was to be present in 15% of cases By V. Grech – An overview of update regarding medical problems in down syndrome. In this present study of 100 children, no one had difficulties

in walking, abnormal gait, decreased neck mobility, sensory defects, spasticity etc suggestive of at Atlanto axial instability.

Most of the patients with Down syndrome have Intelligence Quotient(Iq) between 25 and 49 with the average of approximately 43.

In our case Iq assessment is done for 46 cases, 24 had Iq in the range of 30-49 and 22 had Iq more than 70.

Del BO, R et al in their study had revealed that a distally placed triradius, the palmar meeting point of three differently aligned finger creases is seen in 88% but only in 10% of controls.

Baby BJ et al in their study pointed out that the percentage of various demographic features as follows.

- Increased incidence of ulnar loops in 83%.
- Displaced axial triradius – 85% of cases (4% in controls).

In our present study demographic study were done for 80 cases.

- Ulnar loops present in all fingers – 37 cases
- Atd angle :-
  - 75^0 – 38 cases
  - 85^0 – 12 cases
  - 90^0 – 11 cases
  - 100^0 – 19 cases

Karyotyping is needed only to ascertain whether nondisjunction / translocation / Mosaicism is the underlying mechanism of chromosomal abnormality, as the clinical profile for DS are characteristic (Sweimann – Textbook of Neurology).

Karyotyping was done in 10 cases, for whom mother's age is below 30 years, except for 2 cases.

- Mosaicism – found in 8 cases
- Translocation – 1 case
- Meiotic non disjunction – 1 case

Carrier status of parents were not done in translocation case.

LIMITATIONS

1. Dermatoglypics was done in 80 cases.
2. Chromosomal analysis was done for 10 cases as the investigation was cost effective.
3. Karyotypic analysis was not done for the patients for the above said reason.

CONCLUSION

The following conclusions were made based upon the observations in this study.

1. **In the era of small family norm, from our analysis of 100 cases of Down syndrome, we find Mosaicism to be common, but karyotyping should be done in larger number of children to confirm this finding.**
2. **In our analysis, we find that there was no correlation between phenotypic malformation and genotype.**
3. **Eight cases were detected at the time of birth.**
4. **Eleven cases were detected in first 6 months.**
5. **Remaining were detected at varying time periods.**
6. **Lowest maternal age in my study was 19 years.**
7. **Birth order revealed a high frequency in 2nd borns followed by first and third borns.**
8. **Majority of the presenting c/o is developmental delay.**
9. **Congenital heart disease was found in 23 cases, and Ventricular Septal Defect – found to be most common.**
10. **No seizure disorder, GIT anomalies, leukemia were detected in this study.**
11. **No atlanto axial dislocation was made out.**
12. **Hypothyroidism is found in one case.**

RECOMMENDATIONS

1. Prenatal screening tests for Down Syndrome should be done for all mothers on the incidence of Down Syndrome children is increasing in mother with younger age group.
2. As half of the individuals with Down Syndrome have Congenital Heart Disease, Echo is a must for all cases before the age of 6 months.
3. In newborn, all Down Syndrome cases should have their complete hematological work up to rule out neonatal transient leukemoid reaction, as there is a risk of malignancy.
4. USG – Examination of abdomen should be done in neonates to rule out Gastro intestinal anomalies.
5. As these children have the propensity to develop autoimmune antibodies, thyroid screening should be done at birth, 4-6 months, 12 months and then annually.
6. Vision should be checked at birth, 3 months, 6 months and then annually.
7. As most of them develop constipation, dietary advice should be insisted specifically.
8. All children with Down Syndrome who wish to participate in sports should have cervical spine X-rays.
9. When the distance on X-ray between the atlas and odontoid process is more than 4.5 mm, restriction on sports is advised.

10. Repeated X-rays are not indicated for children with Down Syndrome who have previously had normal neck X-rays.
11. Patients with atlantoaxial subluxation and dislocation and neurological signs should be restricted from all strenuous activities.
12. Parents must be taught about the symptoms of Atlantoaxial instability that indicate the need to seek immediate medical care.
13. Thyroxine treatment should be considered in Down Syndrome neonates to maximize their early development and growth.
14. Sensorineural and conductive hearing loss is seen in children with Down Syndrome. The routine follow up include a hearing test at 6 to 8 months of age and as needed afterward.
15. It is appropriate to refer children with Down syndrome to preschool programs to provide intervention for developmental disabilities.

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MORPHOLOGICAL AND KARYOTYPIC ANALYSIS OF DOWN SYNDROME

PROFORMA

Name :

Mother's age at the time Of conception

State of Nutrition of the Mother

Father's age at time of Conception

Age / Sex :

Address :

Informant :

Birth order

Reliability :

Diagnosed at the age of :

PRESENTING COMPLAINTS :

H/O PRESENT ILLNESS :

RESPIRATORY TRACT :

	Yes	No
• Cough		
• Running nose		
• Difficulty in breathing		
• Fever		

CARDIOVASCULAR SYSTEM :

	Yes	No
• Excessive sweating		
• Puffiness of face		

	• Oliguria • Cyanosis		
ABDOMEN	:	Yes	No
	• Vomiting • Jaundice • Abdominal distension • Abdominal pain • Malaena • Hemetemesis • Bleeding per rectum • Constipation		
CENTRAL NERVOUS SYSTEM	**:**	Yes	No
	• Seizures • Incontinence • Gait disturbances • Mental retardation		
DEVELOPMENTAL DELAY	**:**	Yes	No
FAILURE TO THRIVE	**:**	Yes	No
BLEEDING MAINFESTATIONS	**:**	Yes	No
	• Purpura • Petechiae • Ecchymosis		
EYE	:	Yes	No
	• Defective vision • Squint • Discharge • Nystagmus • Cataract		
EARS	:	Yes	No
	• Discharge • Hearing loss		
DENTAL	:	Yes	No

- Caries
- Bleeding gums
- Swelling

MISCELLANEOUS : Yes No

Bones – Fractures / Others : Yes No

Behavioural problems : Yes No

ANTENATAL HISTORY :

USG :

NATAL HISTORY :

- **T**erm/Preterm/Post Term
- Labor Natural
- LSCS
  - Indication
- Birth weight
- Events during delivery

POST NATAL HISTORY :

- Jaundice Yes/No
- Convulsions Yes/No
- Constipation Yes/No

DEVELOPMENTAL HISTORY :

- Social smile
- Head control
- Sitting
- Walking
- Others

IMMUNISATION HISTORY :

NUTRITIONAL HISTORY :

FAMILY HISTORY :

Close Relations with DS

CONTACT HISTORY :

EXAMINATION

Anthropometry

HC :
CC :
HT :
WT :

General	Yes	No
• Hypotonia		
• Protruded tongue		
• Hyperflexibility of joints		
• Diastasis recti		
• Mental retardation		

CRANIOFACIAL	Yes	No
• Brachycephaly		
• Microcephaly		
• Flat occiput		
• Upslanting palpebral fissures		
• Hypertelorism		
• Epicanthic folds		
• Small nose		
• Depressed nasal bridge		

HAIR	Yes	No
• Fine		
• Sparse		
• Soft		

EYES	Yes	No
• Brush field spots		
• Refractive errors		

- Nystagmus
- Cataract
- Squint
- FUNDUS

EARS Yes No

- Low set ears / EAR anomalies
- Hearing loss
- Discharge

DENTITION Yes No

- Caries
- Bleeding
- Others

TONGUE Yes No

- Hypertrophy of papillae
- Scrotal tongue

NECK Yes No

- Short
- Webbed

HANDS Yes No

- Clinodactly
- Simian crease
- Brachydactly

FEET Yes No

- Sandal gap
- Deep plantar crease between 1st and 2nd toes

SKIN Yes No

- Loose folds in posterior neck
- Dry hyperkeratotic skin

GENITALIA ANUS

- Imperforate anus
- Others

SYSTEMIC EXAMINATION Yes No

CVS

- Congenital heart disease
- Nature
- Medical / Surgical intervention
- Needed

CNS Yes No

- Seizures
- MR
- Treatment

ABDOMEN Yes No

- Protruded abdomen
- Umbilical hernia
- Bleeding

RESPIRATORY TRACT : Infection – Specific
Medical / Surgical intervention needed

BONES BEHAVIOUR : Anomalies
Sociable
Music lovers
Aggressive

INVESTIGATIONS : Blood profile
Chest X-ray

X-RAY CERVICAL SPINE AP AND LATERAL VIEW

1. Atlandoaxial instability
2. Hypoplasia of posterior arch

X-RAY PELVIS AP VIEW

1. Dislocation / Hypoplasia
2. Outward lateral flare of iliac margins
3. Avascular Necrosis
4. Shallow Acetabular angle
5. Iliac Index

CT BRAIN : Cerebellar Hypoplasia

MRI BRAIN :

ECG :

ECHO :

THYROID PROFILE :

USG ABDOMEN : Tracheo oesophageal fistula
Duodenal atresia
Pyloric stenosis
Annular pancreas
Hirschprung disease
Omphalocele

ENT OPINION :

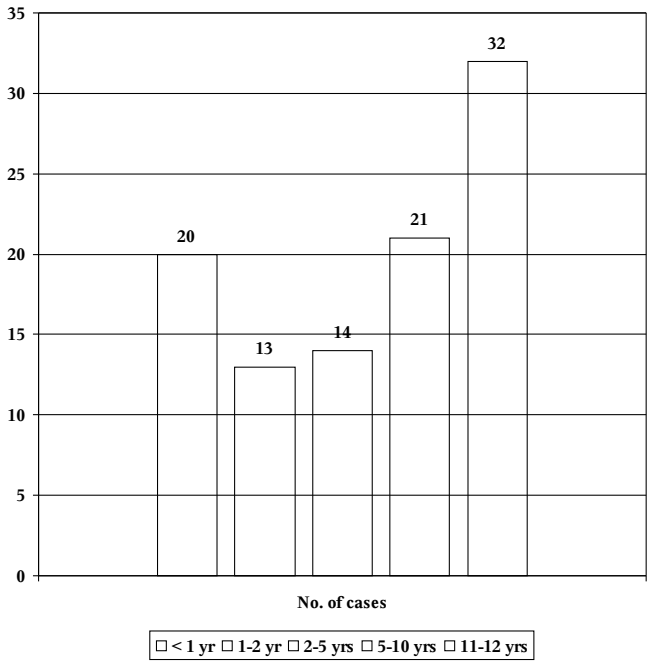
OPTHAL OPINION :

CHROMOSOMAL ANALYSIS :

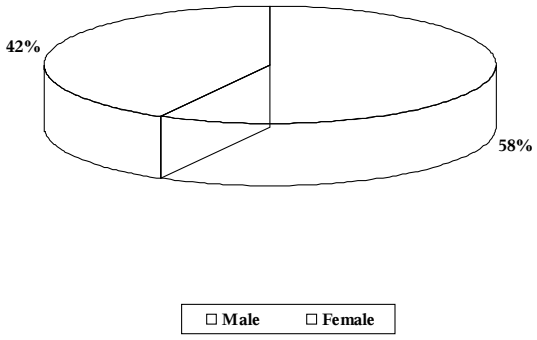
Translocation
Meiotic non dysjunction
Mosaicism

DERMATOGLYPICS :

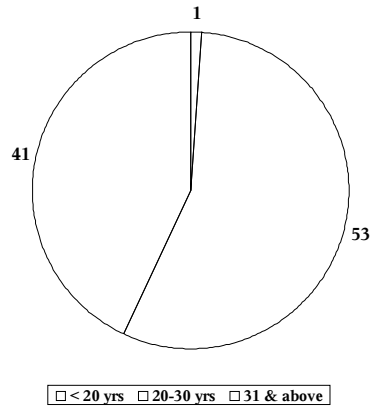
Children – Age wise distribution



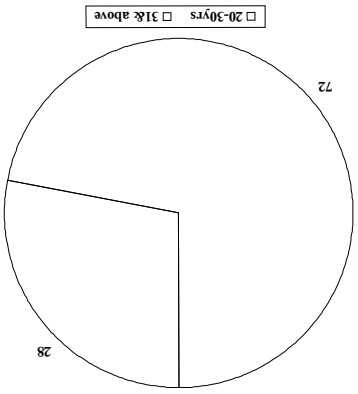
Sex – wise distribution



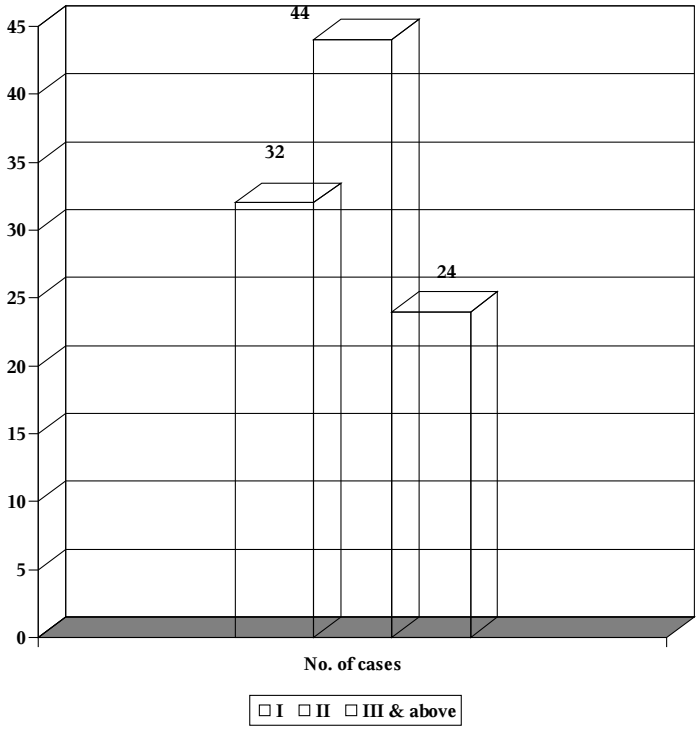
Maternal – Age wise distribution



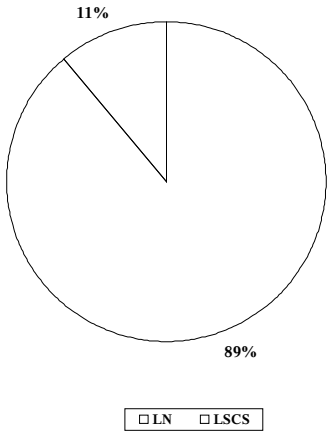
Paternal – Age wise distribution



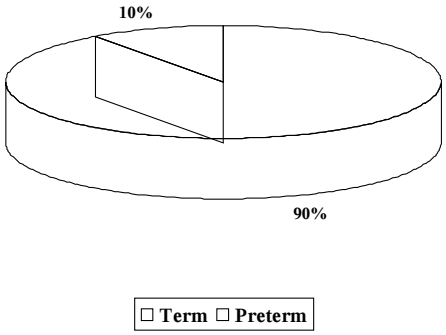
Birth order



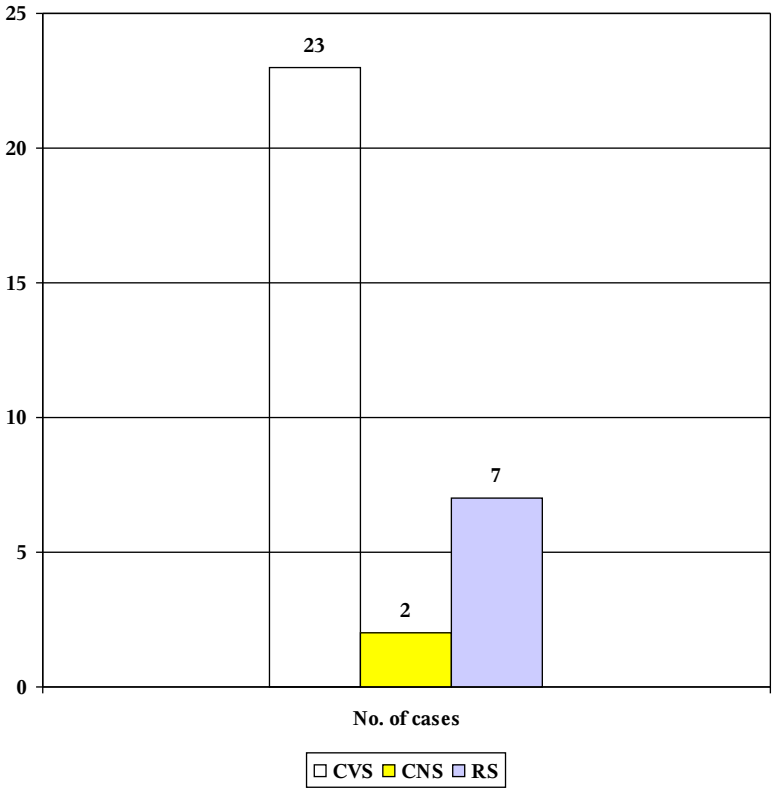
Mode of delivery



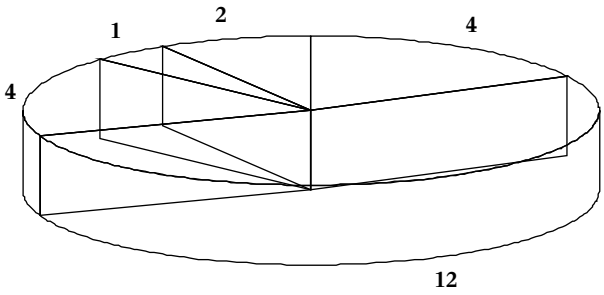
Gestational Age at birth



CF – Systemic involvement

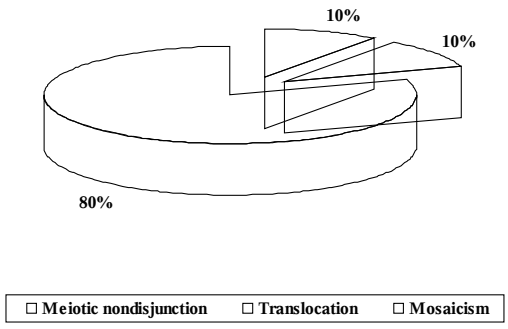


CVS – Nature of lesion



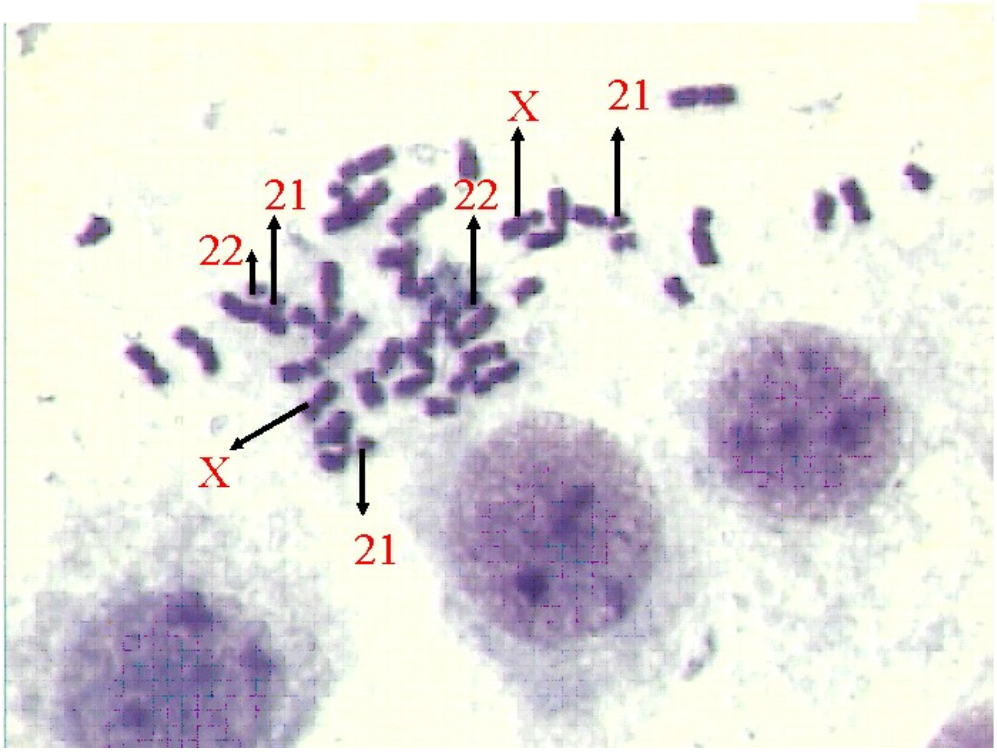
☐ ASD ☐ VSD ☐ PDA ☐ TOF with PDA ☐ Endocardial cushion defects

Karyotyping



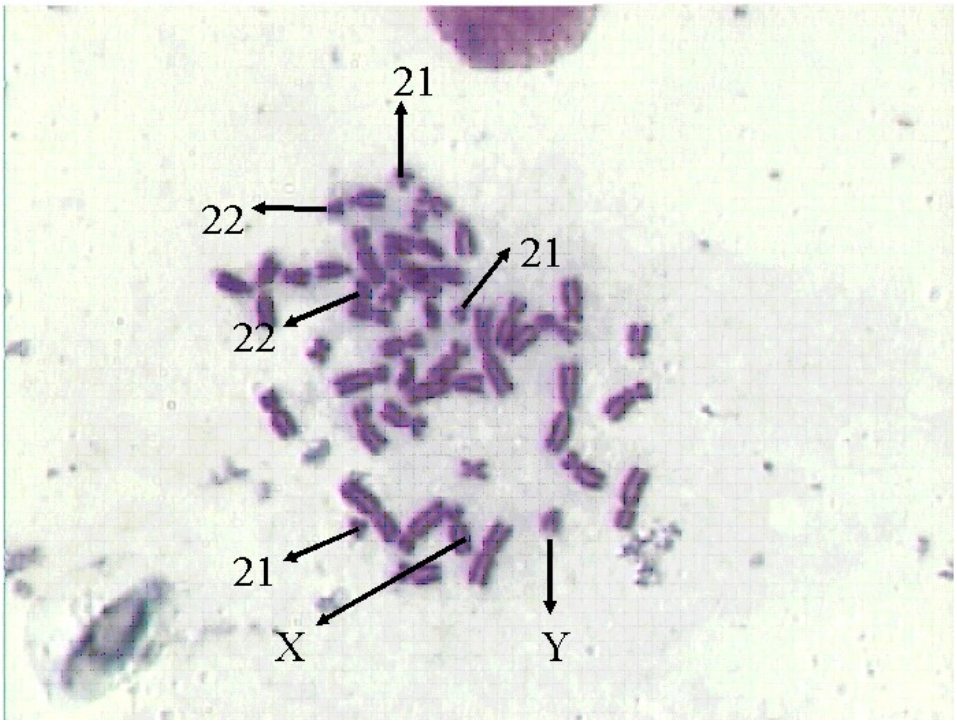
47, XX, +21 46, / XX (Mosaic)

70% 30%



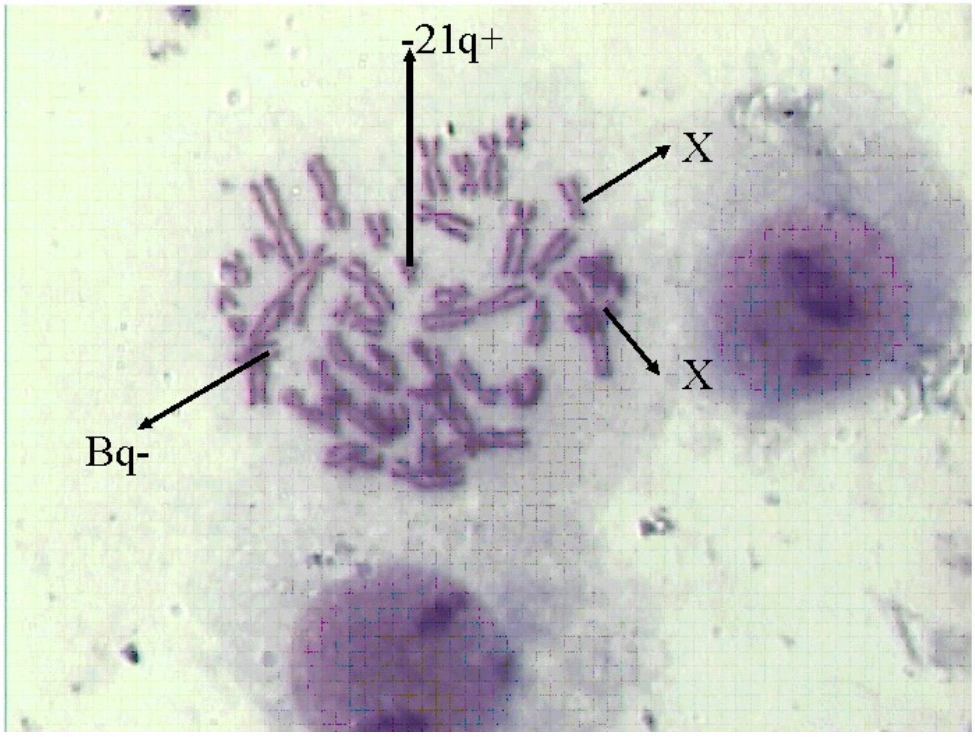
46, XX / 47, XY, +21 (mosaic)

55% 45%



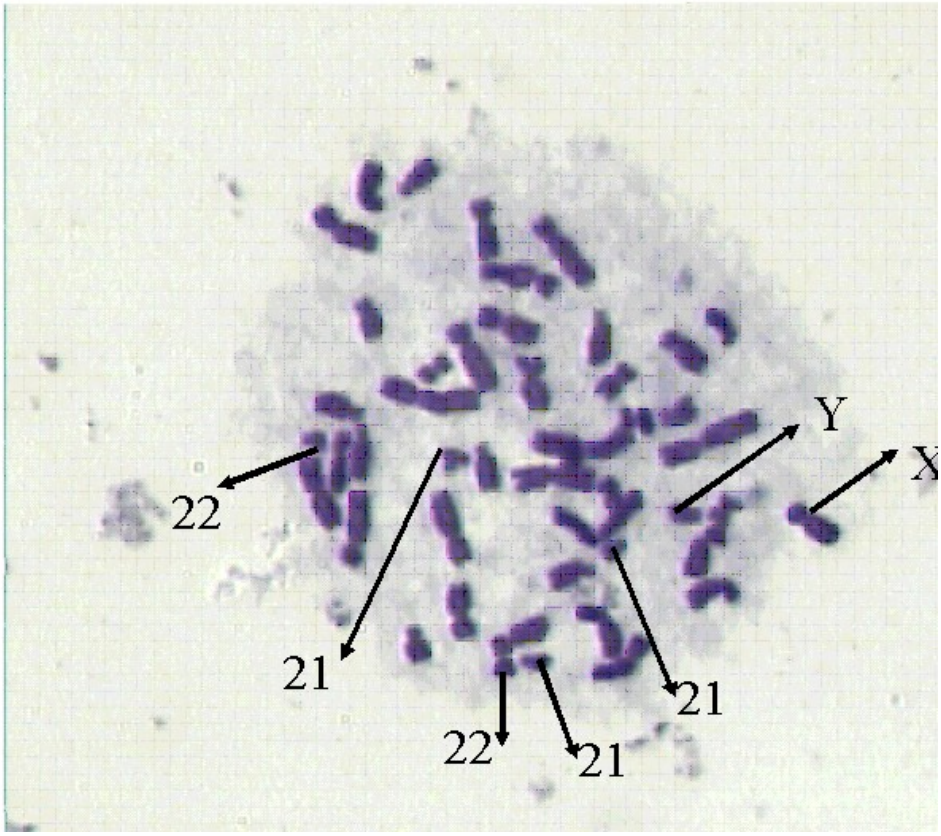
- 46, XX / 46, XX, t (13q-; 21q+)

40% 60% (mosaic)

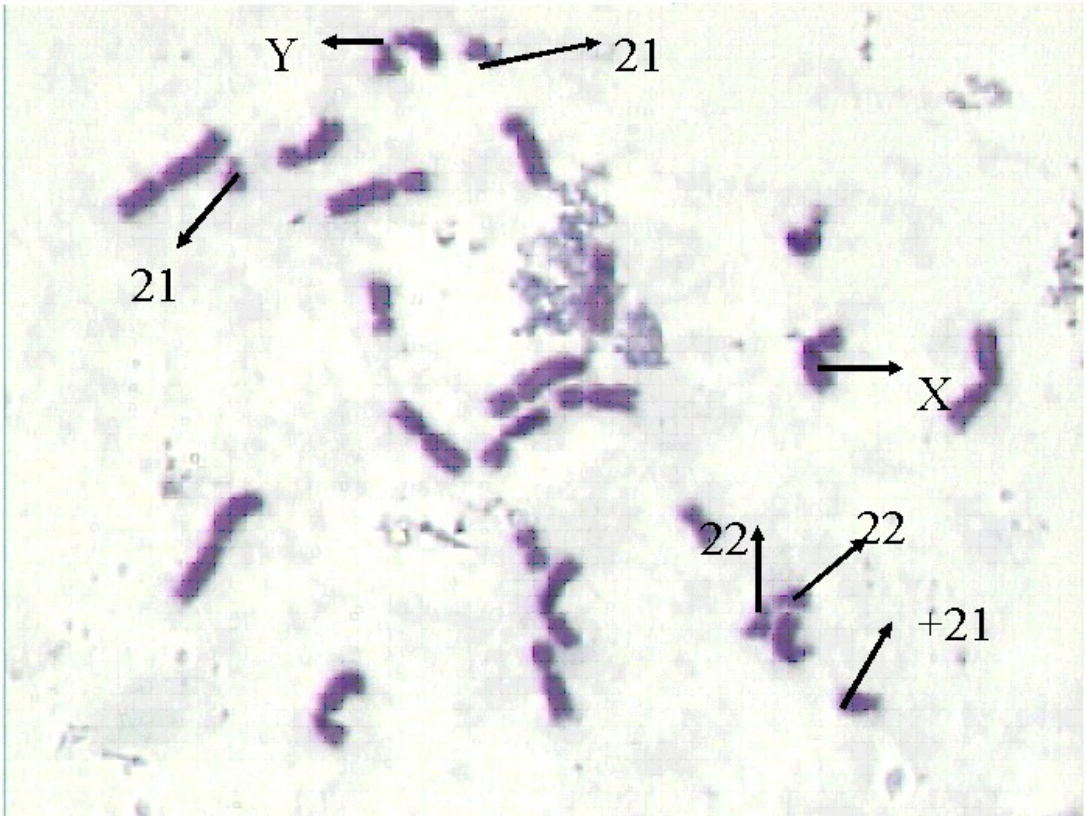


46, XY / 47, XY, +21 (Mosaic)

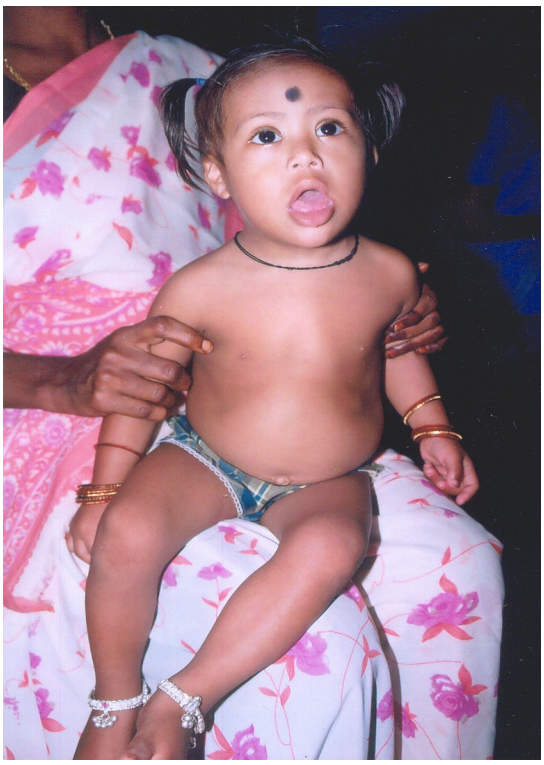
30% 70%



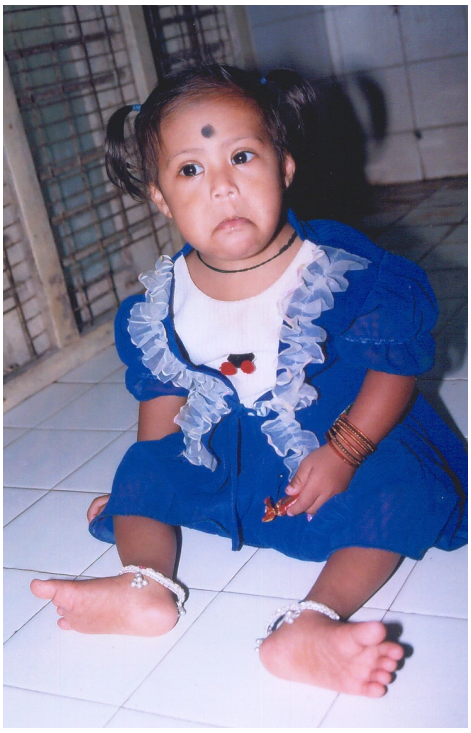
– 47, XY, +21



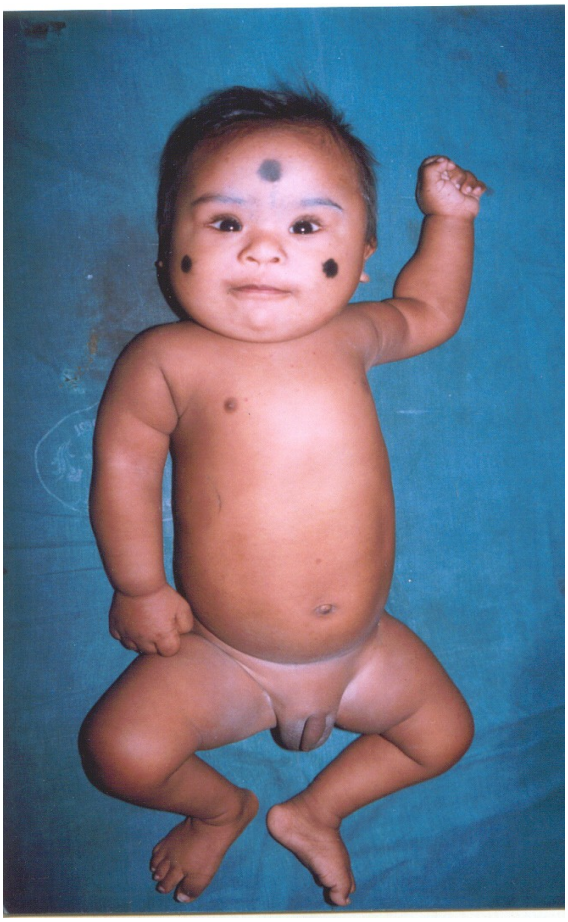
Down syndrome child with protruded tongue and abdomen



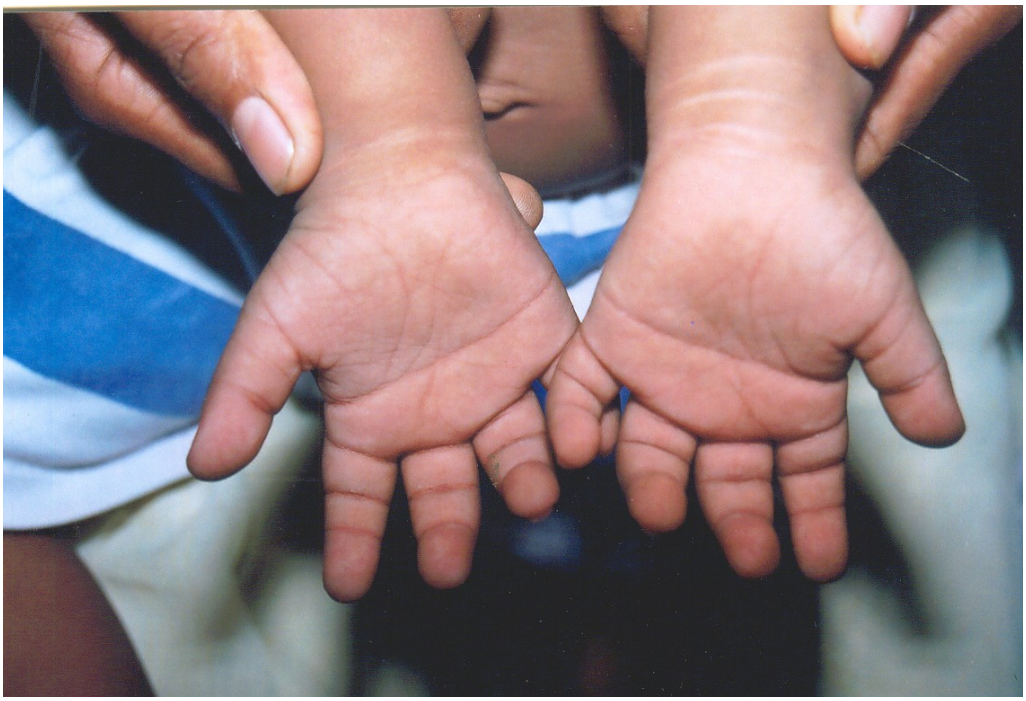
Down syndrome child with epicanthic folds and low set ears



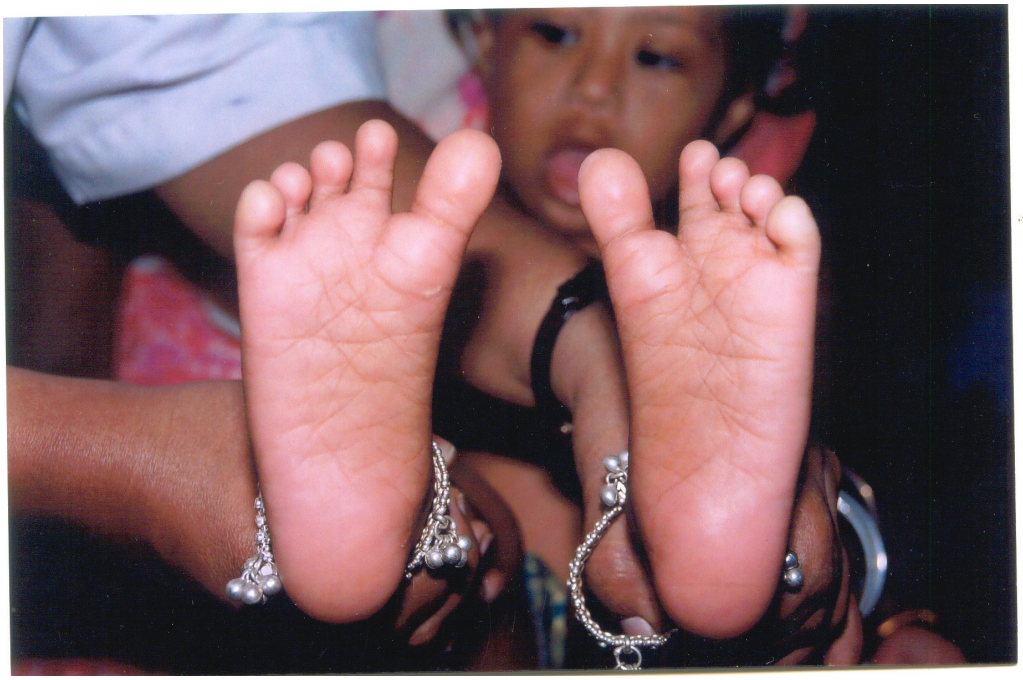
Down syndrome infant with hypertelorism, depressed nasal bridge



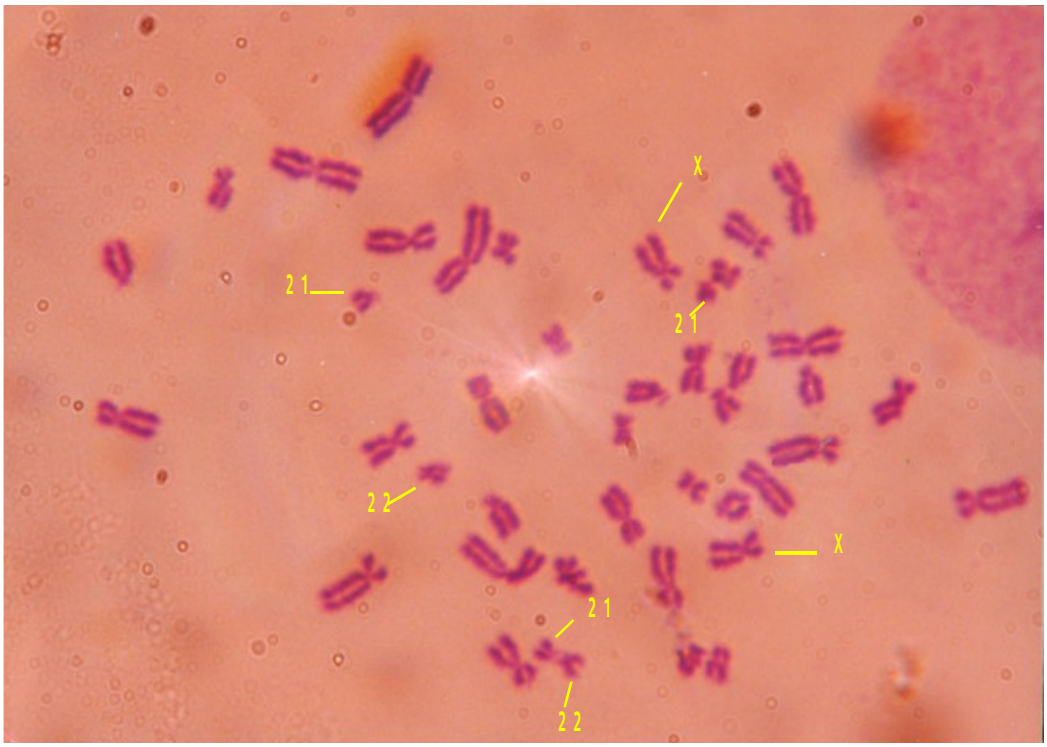
SIMIAN CREASE



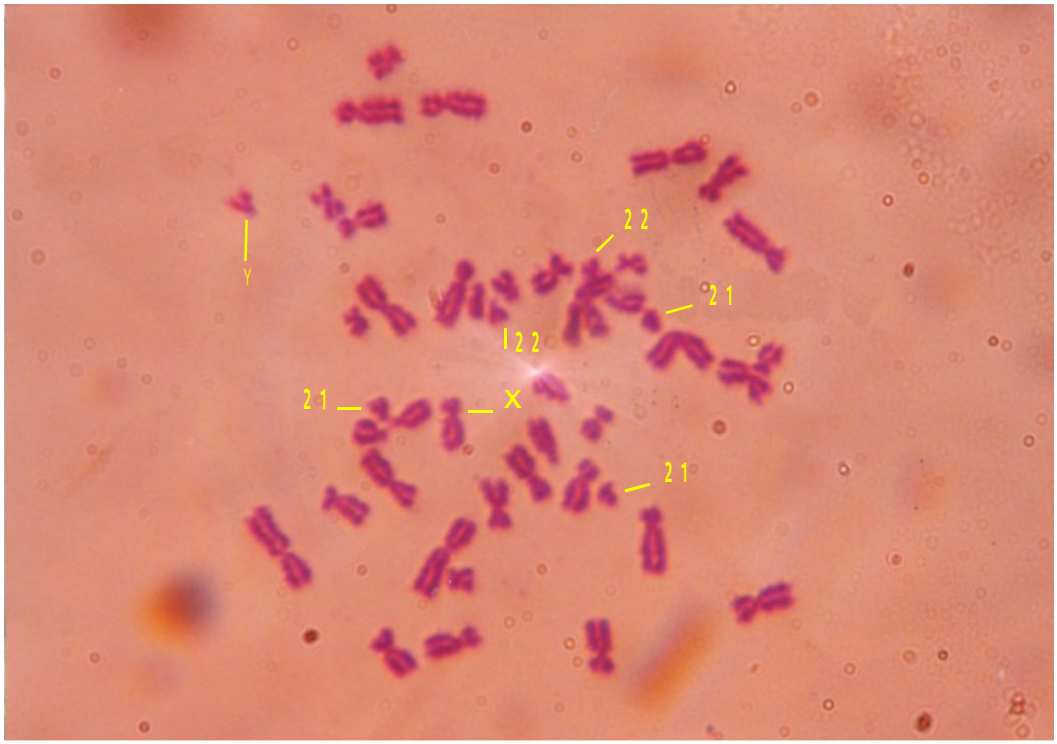
Sandalgap with deep plantar crease



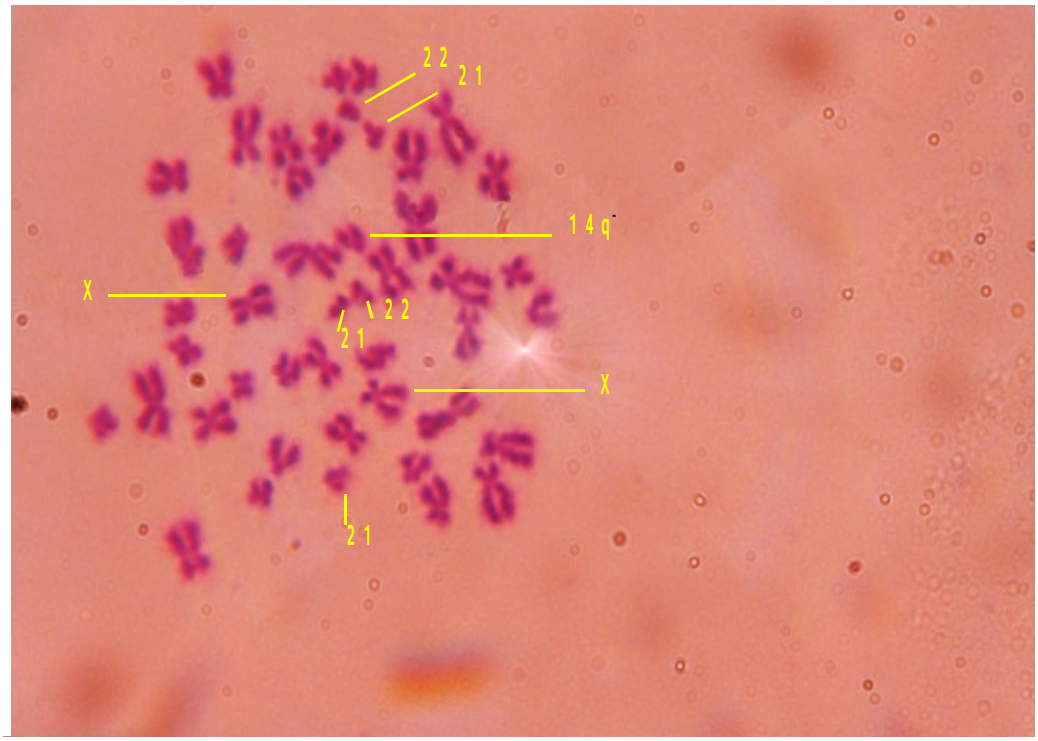
47,xx,+21/46,xx Mosaic



47,xy, +21;22S+ / 46, xy Mosaic



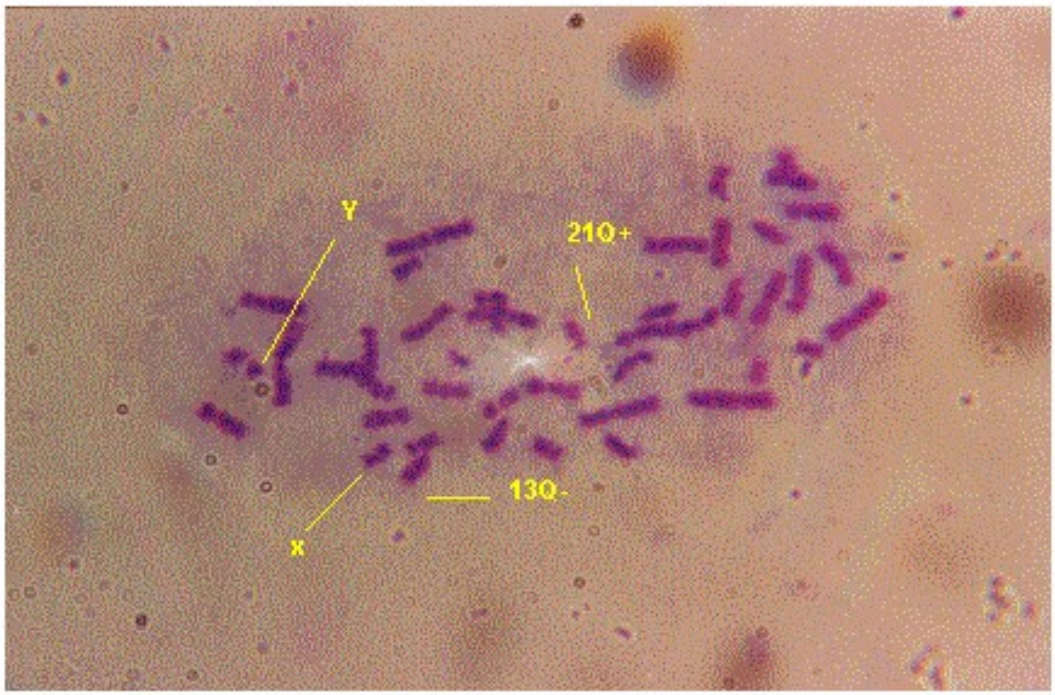
47, xx, +21; del(14q-) Mosaic



46xy,t(13q;21q+) Mosaic

47,xx,+21;del(9q-)/46xy Mosaic

46xy,t (13q ; 21q +) Mosaic



47, xx, +21 ; del (9q-) / 46 xy Mosaic