CHAPTER 16

GENETICS

16.1 DOWN SYNDROME: RISING UP

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INTRODUCTION

Down syndrome (DS) has a long history and it may not be wrong to state that the specialty of medical genetics began with the disorder named as DS. It is the most common cause of intellectual disability. The characteristic phenotype makes the clinical diagnosis easy. The British clinician, Langdon Down, described it as a Mongolian idiocy in 1862 and the disorder got the name, DS. With development of karyotyping techniques in 1956, Lejeune identified trisomy of chromosome 21 as the cause of DS.[1]

A lot of developments in genetics and technology got reflected in the understanding of trisomy 21. It led to improved investigations for not only the diagnosis, but also population-based screening for trisomy 21. The developments in diagnosis and management of trisomy 21 parallel the genetic approach to other chromosomal and monogenic disorders, especially those with intellectual disability.

Not only there were developments in genetic technologies over last few decades, the societal change in the perspective toward and facilities for children with special needs changed the scenario for the families with DS children. Now, individuals with DS or other neurodevelopmental disabilities have opportunities to get incorporated in the society and contribute to it by living a fruitful and happy life **(Fig. 16.1.1)**. The words like "mental retardation" and "intellectual disability" are getting replaced by special children or individuals

Fig. 16.1.1: Facial features of children of various ages with trisomy 21.

Table 16.1.1: Possibility of giving birth to a child with Down syndrome with increasing maternal age.

Age of the mother (in years)	*Possibility of a child with Down syndrome*
20	1:1,925
25	1:1,205
30	1:885
35	1:365
40	1:110
45	1:32

with special needs and abilities. This is a major step in opening the arms of society to take these "special individuals" in its folds. This chapter in the 21st century plans to present the positive aspects of children with DS along with clinical features, diagnostic tests, genetic counseling issues, and population-based prevention.

EPIDEMIOLOGY

The birth prevalence of DS is reported to be 1 in 700 worldwide[2] and 1 in 1,200 in India.[3] The difference is likely to be due to the average age of women at childbirth as the possibility of birth of a child with trisomy 21 increases as the mother's age increases **(Table 16.1.1)**. In India, most of the children with trisomy 21 are born to young mothers. As DS is the most common genetic disorder, all pediatricians and neonatologists need to be well-conversant with diagnosis, management, and genetic counseling for this disorder.

ETIOLOGY

Extra copy of chromosome 21 is the etiology of DS. In around 95% of cases, the extra chromosome 21 is free **(Fig. 16.1.2)** and the total number of chromosomes is 47 (47, XX, +21 or 47, XY, +21). In about 4% cases of DS, the extra chromosome 21 is attached to another chromosome **(Figs. 16.1.3A to C)**, usually some acrocentric chromosome (21, 22, or 14). In such cases with translocation, karyotyping of the parents is necessary for giving risk of recurrence in the next child as some cases might have received the translocated chromosome from one of the parents who is a balanced carrier of the translocation. Remaining 1% cases are mosaic with trisomy 21 in some cells and some cells with normal cell line with 46 chromosomes.

Percentage of normal cell line is not the only factor to predict the outcome regarding cognitive function and presence of mosaicism does not always predict better intelligence quotient (IQ). Though the definite clinical

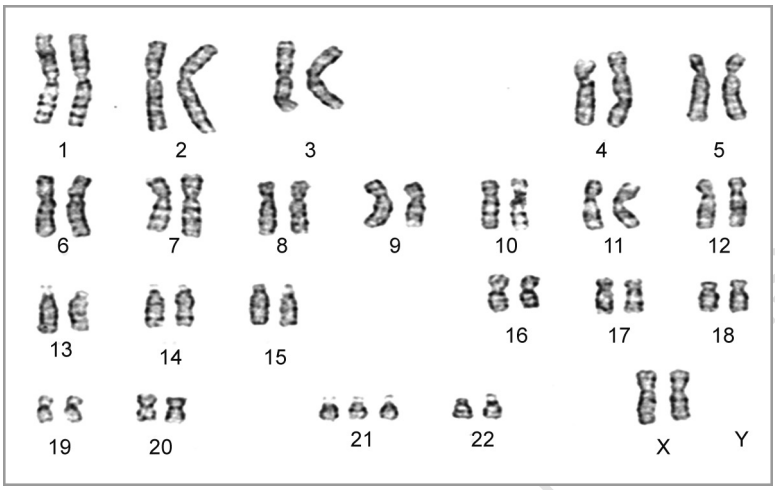
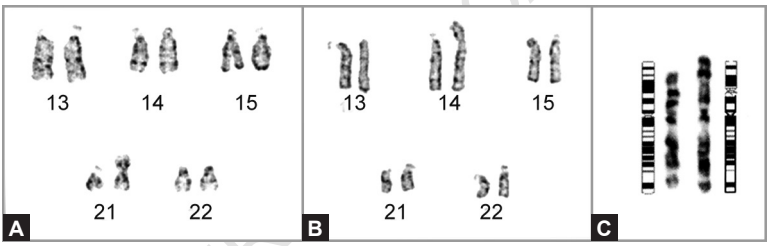


Fig. 16.1.2: 47, XX, +21. Karyotype of a girl with Down syndrome with free trisomy 21.



Figs. 16.1.3A to C: Partial karyotypes showing translocation of chromosome 21 to other chromosome. (A) Translocation between chromosome 21 and chromosome 21; (B) Translocation between chromosome 14 and chromosome 21; and (C) Chromosome 21 is attached to chromosome 11.

diagnosis is possible in most of the children with DS, karyotyping is essential as the risk of recurrence in the siblings and other relatives will depend on the chromosomal abnormality. Chromosomal analysis of parents of a child with free trisomy 21 (47, +21) is not indicated. Rarely, the child with DS is not alive and, in such situation, karyotyping of parents can provide useful information for genetic counseling.

PATHOGENESIS

Presence of extra copy of chromosome 21 (trisomy instead of normal disomy) leads to presence of three copies of genes on chromosome 21 and attempts have been made to find out the critical region of chromosome 21 for the features of DS. Study of genotype-phenotype correlation in cases with partial trisomy of a small part of chromosome 21 suggested region from 21q21 to 21q22.3 to be the critical region for manifestations of DS. However, study of these cases suggested that it was not possible to attribute all features to one critical

region on chromosome 21. There are at least 300 genes on chromosome 21 and studies have shown that 22% of them are expressed 1.5 times of the normal and may be responsible for the features of DS. Contribution of genes important for specific features has been discussed.[2] Premature aging and decreased function of the immune system may be caused by the overexpression of superoxide dismutase 1 (*SOD1*) gene (OMIM 147450). Neuropathological changes of Alzheimer disease are seen in all individuals with DS more than 40 years old. Association of amyloid beta A4 precursor protein (*APP*) gene on chromosome 21 with Alzheimer disease is being investigated. Better understanding of effects of various genes may be useful in planning novel therapeutic strategies.

AUTOIMMUNE DISORDERS IN CHILDREN WITH DOWN SYNDROME

Increased risk of autoimmune disorders and leukemia in children with DS is well-known. Celiac disease has a prevalence of 4.5–7%, autoimmune thyroiditis is diagnosed in 5–54% of DS subjects, and type 1 diabetes (T1D) is present in 1% of these individuals. Increased risk of infections and autoimmune diseases suggests abnormalities of immune function in DS, though the exact mechanisms of pathogenesis are not understood. Though organ-specific autoimmune diseases are common in DS patients, systemic autoimmune diseases like systemic lupus erythematosus are not more common than the general population. Natural T regulatory cells play an important role in autoimmunity by suppressing the autoreactive T cells that escape the thymic negative selection in circulation. It has been shown that in DS patients, the circulating T regulatory cells are increased in number compared to the healthy control, whereas their function is impaired.[4]

Other factor thought to be implicated in autoimmune disorders in DS is autoimmune regulator (AIRE) protein, a transcription factor located on chromosome 21 that plays a crucial role in autoimmunity by regulating promiscuous gene expression.[5] *AIRE* gene is located on chromosome 21 and is a transcription factor for many genes that encode for peripheral tissue-restricted antigens. The role of this gene was evaluated because the spectrum of autoimmune diseases in DS subjects is similar to that seen in the rare autosomal recessive disease namely autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome, also called autoimmune polyendocrine syndrome type 1 which is caused by mutations in *AIRE* gene. In spite of being located on chromosome 21, the gene expression is reduced to half of the normal in thymuses of DS individuals rather than being increased to 1.5 times. It was confirmed that all three copies of the gene were expressing but significantly fewer AIRE-positive cells were found in the thymic medulla of DS patients compared with those in the control group. This suggests that reduced AIRE expression may be playing a role in change in immune tolerance in DS.

LEUKEMIA IN CHILDREN WITH DOWN SYNDROME

Children with DS have a significantly increased risk of childhood leukemia. Acute megakaryoblastic leukemia (AMKL) and DS-acute lymphoblastic leukemia (DS-ALL) are 500 times and 20 times, respectively, more common in DS than normal children. A preleukemia, called transient myeloproliferative disorder (TMD), characterized by a GATA-binding protein 1 (*GATA1*) mutation, affects up to 30% of newborns with DS. Though spontaneous regression is common, life-threatening issues and progression to AMKL or myelodysplastic syndrome (MDS) are seen in one-fourth of the cases. Other than *GATA1* gene, genetic variations and epigenetic changes in other genes are implicated in the progression to leukemia which is a multistage process. DS-ALL is a high-risk leukemia and mutations in the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway are frequently observed. JAK inhibitors may improve outcome for this type of leukemia. Key candidate genes in leukemogenesis on chromosome 21 include *ERG*, *ETS2*, *RUNX1*, *GABPA*, *BACH1,* and *DYRK1A*. Mateos et al.[6] have provided an extensive review of leukemia and MDS in DS.

CLINICAL FEATURES

The clinical features of patients with DS are shown in **Box 16.1.1**. Intellectual disability is the most serious manifestation. The clinical diagnosis is possible based on the characteristic facial phenotype due to the combination of variations of eyes, nose, and ears **(*see* Fig. 16.1.1)**. The IQ of children with the disease is usually between 40 and 60 but may be higher in many, like variability of cognitive function among normal children. Most of the affected children walk, talk in simple language and can be trained in self-care and a vocation that requires simple and repetitive tasks.

Major malformations associated with trisomy 21 are cardiac malformations especially atrioventricular canal defects, duodenal atresia, tracheoesophageal fistula, congenital cataract, and Hirschsprung disease. Other important problems are epilepsy, hypothyroidism, deafness, atlantoaxial instability, and increased risk of leukemia. Other than hypothyroidism, the risk for other autoimmune disorders like celiac disease, alopecia areata, and vitiligo is increased. When serious malformations are present and are untreated, death may occur during infancy but otherwise life expectancy is not markedly reduced. In adults with DS, there is increased prevalence of dementia and neuropathological changes like those seen in Alzheimer disease.

Small teeth, missing teeth, and increased risk of periodontal disease need special mention. Large tongue and small jaw are other contributory factors to the dental problems which can be looked for and prevented by training and supervising dental care.

Box 16.1.1: Clinical features of patients with trisomy 21.

- Brachycephaly
- Flattened facial features
- Flat occiput
- Epicanthic folds
- Oblique palpebral fissures
- Hypertelorism
- Brushfield spots
- Dysplastic ears
- Low-set ears
- Small nose
- Depressed nasal bridge
- Excess skin at the nape of the neck
- Short and broad neck
- Open mouth
- Protruding tongue
- Furrowed tongue
- Narrow and high-arched palate
- Dental abnormalities
- Broad hand and short fingers
- Short fifth middle phalanx
- Clinodactyly of the fifth finger
- Short limbs
- Transverse palmar crease
- Increased gap between the first and second toes
- Hyperextensibility of the joints
- Rough skin on the dorsum of the hands
- Hypotonia
- Intellectual disability
- Congenital heart disease
- Duodenal atresia
- Hirschsprung disease

NEONATAL PRESENTATION

Down syndrome is usually detected at neonatal stage. It is sometimes a surprise to the obstetrician, pediatrician, and the family who is expecting a normal healthy child. Most of the babies with trisomy 21 do not have any obvious external anomalies and the parents and family members do not have any clue to the existence of a major chromosomal abnormality in the baby. To break the news that the child has a serious birth defect which is associated with subnormal intelligence is a challenging task for the clinician and hence, it must be handled carefully by the senior obstetrician or pediatrician.[7] The diagnosis should be declared as early as possible to the family. This is important not only for the family but also for the neonate who needs to be evaluated for serious internal malformations, which may require urgent attention. Preferably, both the parents should be present and if appropriate

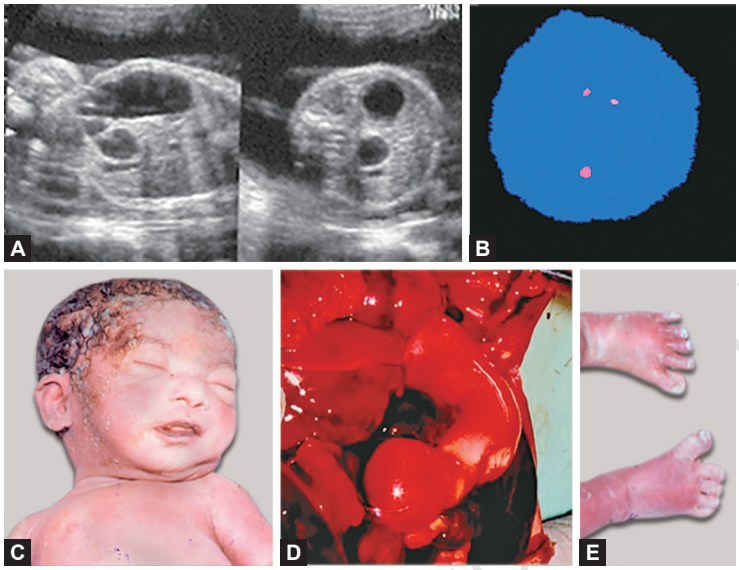
elder or other family members may be involved in the session. There is no correct way to provide the news of existence of a problem with long-term implications, but an attempt may be made to reduce the emotional trauma to the family. Positive but realistic information about outcome and ways to help the baby by providing supportive care need to be provided. Rare complications should not be mentioned in the beginning. The diagnosis should be confirmed by chromosomal analysis in each case, though usually clinical diagnosis is correct. In some neonates, especially premature babies, the phenotype may be subtle, and the clinician may like to wait for the report before disclosing the diagnosis.

In current era of population-based screening for DS, rarely a child with DS may be born to a family who had low risk of trisomy 21 on biochemical screening done on maternal blood during first or second trimester. Counseling such a family is a difficult task and needs a lot of empathy, understanding of principle of screening test, and their detection rates.

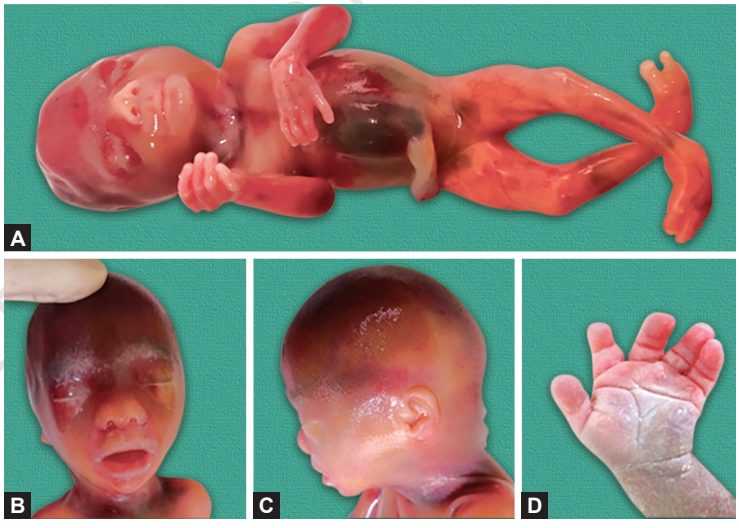
ANTENATAL PRESENTATION

Detection of duodenal atresia or cardiac malformation or other ultrasonographic markers like increased nuchal translucency during prenatal ultrasonography may suggest the possibility of DS in the fetus. 30% of prenatally detected fetuses with duodenal atresia have trisomy 21 **(Figs. 16.1.4A to E)**. Amniocentesis and chromosomal analysis by rapid test namely—fluorescence in situ hybridization (FISH) or quantitative fluorescent polymerase chain reaction (QF-PCR) for common trisomies (chromosomes 21, 13, and 18)—are indicated to plan the further management. A pediatrician may be required to be a part of counseling team.

Prenatal diagnosis of trisomy 21 is also done by fetal chromosomal analysis done by chorionic villus sampling or amniocentesis done due to detection of increased risk of trisomy 21 by biochemical screening [first trimester double marker test or second trimester quadruple test or noninvasive prenatal screening (NIPS) on free fetal DNA (ffDNA) in maternal plasma] or identification of ultrasonographic markers for trisomy 21 like increased nuchal thickening and absent nasal bone. Mother's plasma contains ffDNA shade from broken down trophoblastic cells of placenta. New technology of next generation sequencing (NGS) can identify the chromosomal aneuploidies in fetus by testing ffDNA and the test is known as NIPS. NIPS can detect almost all fetuses with trisomy 21, but rarely false-positive and false-negative results are reported. Thus, this costly test which is a technological marvel continues to remain a screening test with high sensitivity. If NIPS shows high risk of trisomy 21, it is essential to do confirmation on fetal sample collected by invasive method like amniocentesis before taking irreversible decision like termination of pregnancy. In such situations, most of the families may



Figs. 16.1.4A to E: Prenatally detected duodenal atresia in a fetus with Down syndrome. (A) Double bubble appearance on antenatal USG; (B) Interphase FISH showing three signals for chromosome 21 probes; (C) Subtle facial phenotype of Down syndrome; (D) Distended duodenal bulb; and (E) Increased gap between first and second toes. (FISH: fluorescence in situ hybridization; USG: ultrasonography)



Figs. 16.1.5A to D: Fetus with trisomy 21.

opt for termination of pregnancy within the legal limits allowed by medical termination of pregnancy act. Pediatrician may be involved to examine the fetus after termination.[8] It should be noted that most of the fetuses with trisomy 21 do not have external malformations and characteristic facial phenotype is not obvious till later part of pregnancy **(Figs. 16.1.5A to D)**.

STILLBIRTHS

More than 50% of conceptuses with trisomy 21 are lost before birth. Most of them are spontaneously aborted and chromosomal analysis of products of conception may identify trisomy 21. Chromosomal abnormalities are seen in 5% of stillbirths. Though the chromosomal analysis of products of conception from each spontaneous abortion is not indicated, fetal autopsy and chromosomal analysis of stillborn baby is essential to provide genetic counseling. Pediatrician can play an important role in explaining the importance of fetal autopsy for providing risk of recurrence and also in examining fetuses for dysmorphic features and helping in diagnosis.

INFANCY AND CHILDHOOD

Many families are not told about the diagnosis of DS during neonatal period or infancy. The parents note developmental delay in the later part of infancy or childhood and then the child may be given the diagnosis of DS. Indian experience showed that parents of only 27% of children with DS were communicated about the diagnosis during infancy and most of them were not aware about the association of intellectual disability and lack of curative treatment for that.[9] At whatever age, a child with DS is seen by a sensitive pediatrician who must assess the knowledge of the family about the condition and attitude toward the disorder and their child with DS. Based on the assessment, appropriate counseling and accurate but positive information should be provided. Acceptance of the disorder in the child is the first and most important step toward the direction of evaluation and starting therapies.

INVESTIGATIONS

As mentioned above, every child with clinically diagnosed or suspected DS should be evaluated by karyotyping. Karyotype, in addition to confirming the diagnosis, gives the specific chromosomal abnormality, which is essential for genetic counseling. Rarely, extra chromosome may be attached to a chromosome other than G or D group of chromosomes **(*see* Fig. 16.1.3C)**. Karyotype report is available usually within 2–3 weeks. In babies with serious malformation and the need to confirm the diagnosis at the earliest, molecular techniques like FISH (which can be done on interphase nuclei) or QF-PCR can be done. The reporting time for these tests is 3–4 days. The other advantage of QF-PCR is that it does not need live cells and hence sample [1–2 mL of blood in ethylenediaminetetraacetic acid (EDTA) vial or a small part of umbilical cord] from stillborn baby or dead neonate can be collected and stored for long time and the test done as per the family's convenience.

It is important to remember that the phenotypes of other disorders like Zellweger syndrome, other chromosomal abnormalities like duplication of

part of q arm of chromosome 10 or p arm of chromosome 9 are similar to DS and need to be suspected if trisomy 21 is not detected.

Investigations to look for associated anomalies and disorders are discussed in the management section.

MANAGEMENT

Management of DS has multiple components including lifelong surveillance for complications, surgical management of malformations, supportive therapies, special education, employment opportunities, and efforts to incorporate them in the society in fruitful and fulfilling ways. Pediatricians should not only give the diagnosis, but has to become the central pillar to coordinate various modalities of evaluation and treatment. The surgical management of major malformations, occupational and physical therapies, and timely diagnosis of associated illnesses like hypothyroidism, celiac disease, and anemia has improved life expectancy of individuals with DS and hence, parents, pediatricians, and society have to make the best efforts to help the special individuals with one extra chromosome to lead happy, healthy, and useful life. Guidelines for health supervision of children with DS are available[10] and the pediatricians must take up the responsibility of management of these children. This is especially important, as there are hardly any special clinics for DS in India though the need for such special clinics at medical college level is strongly felt. Pediatricians also have responsibility to transfer the adolescent to adult care facilities and ensure that the transition is smooth. Providing emotional support and maintain positivity are very important to develop correct attitude in the parents who play a major role in deciding outcome of the child **(Box 16.1.2).**

Box 16.1.2: Achievements of son shared by proud parents of a young man (Fig. 16.1.6) with Down syndrome.

- Special Olympics Bharat National Games (December 2005) in New Delhi—Gold medal in softball throw
- Special Olympics Asia-Pacific Regional Games (December 2013) at Newcastle, Australia—Silver medal in Aquatics
- Young Achiever's Award by Lucknow Management Association (LMA) in December 2014 in recognition of his exemplary bold and indomitable spirit—the first intellectually disabled person to receive such an award
- UP State Award for "Outstanding Role Model" in mental disability by "Viklang Jan Vikas Vibhag" of the Uttar Pradesh Government in 2014
- First District Yogasana Championship (September 2015) in Lucknow—second position among normally abled
- National Basketball Championship organized by SOB at Chennai in August 2016—fourth position
- Qualified Senior Secondary School Examination (12th class) of the National Institute of Open Schooling (NIOS) in April 2019
- National Floor Hockey Championship in November 2018—Gold medal for UP team

Fig. 16.1.6: Achiever who makes his parents feel proud of him.

TREATMENT OF MALFORMATIONS

Cardiac anomalies are present in 40–50% of children with DS and need urgent attention after birth. Immediately after birth, evaluation for life-threatening anomalies like tracheoesophageal anomalies, cardiac anomalies, gastrointestinal anomalies including anal atresia, etc. need to be looked for. If clinically stable, cardiac evaluation by echocardiogram and electrocardiogram can be done within first week to first month after birth. Even if there are no clinical findings suggestive of cardiac anomaly, each child should be evaluated by echocardiography. Surgical interventions are curative for the cardiac anomalies, gastrointestinal tract anomalies, and craniovertebral junction anomalies. They have a good outcome on the functioning of the organ. However, the family should be informed that the developmental delay and intellectual disability associated with DS does not have curative treatment. Surgical treatment of cardiac and other system anomalies is lifesaving and is very important to avoid sufferings of the child in later life. These include cleft lip, gastrointestinal malformations, and Hirschsprung disease.

NEURODEVELOPMENTAL PROBLEMS

During neonatal period and early infancy, it is difficult to understand the severity of intellectual disability in the figures of IQ. The realistic description about the outcome in simple understandable form is essential. Most of the children with DS learn to walk, talk, take care of self, and express and feel love and emotions. These children are mostly pleasant with happy demeanor, trainable, and can work and live under partially supervised setups. Better upbringing and training have shown that grown-up individuals with DS do

very well in special Olympics, hospitality industry and make their parents feel proud of them **(*see* Fig. 16.1.6 and Box 16.1.2)**. Evidence suggests that by late teenage years and early adulthood individuals with DS achieve an adequate level of autonomy in daily personal care and improve their independence skills outside the home.[11]

Evaluation for deafness during neonatal period and then at regular intervals is essential as untreated deafness will affect the development of speech as well as other fields. Hearing evaluation should be yearly as the children with DS are at increased risk of otitis media which may affect hearing. Same is true for congenital and later onset hypothyroidism and presymptomatic diagnosis and treatment are essential for good outcome. **Table 16.1.2** shows the simplified protocol for evaluation.[10] Frequent evaluation for behavioral problems, sleep apnea, swallowing study, etc. can be done as the need arises.

Table 16.1.2: Evaluation essential for a child with Down syndrome since birth.

Evaluation	*Age*	*Remark*
Evaluation for tracheoesophageal fistula, duodenal atresia, anal atresia, and cardiac anomaly	Day 1	Need urgent management
Karyotype and explaining the diagnosis	Birth to 1 month	As early as possible
Electrocardiogram (ECG) and echocardiography	Birth to 1 month	Immediate if clinical symptoms suggest the need
Eye examination for cataract	Birth to 1 month	–
Hearing evaluation	Birth to 1 month	After 6 months and then every 2 years
Congenital hypothyroidism	Days 3–7 along with other tests done for newborn screening	6 monthly in first year and then yearly
Ophthalmological evaluation for squint, refractive errors, etc.	6 months and then every 2 years	
Clinical evaluation for dentition, anemia, symptoms of celiac disease*, behavioral problems, gait abnormality, muscle weakness, upper motor neuron signs, and neck pain	Yearly	If signs and symptoms indicate, imaging for atlantoaxial dislocation needs to be done
Behavioral assessment, speech problems	Yearly	Evaluation and management by specialist may be needed

*Symptoms of celiac disease like constipation, nausea, diarrhea, and behavioral problems are seen in many, but biopsy proved celiac disease is seen in 1–6% of children.[12]

SURVEILLANCE FOR COMPLICATIONS

Table 16.1.2 shows the timeline for surveillance. Feeding difficulties, gastroesophageal reflux, and hypotonia may need special attention during infancy. Rare associations like atlantoaxial dislocation and risk of leukemia need not be mentioned to the parents. As evaluation by plain radiograph for atlantoaxial joint is not reliable, careful evaluation by history and examination should be done to look for spinal cord compression during every follow-up visit. Detailed neuroimaging may be needed, if there are any signs or symptoms or the child has to take part in contact sports and special Olympics. Dentition may be delayed, and parents can be assured for the concern. Risk of leukemia is 1%, but transient MDS is found in 10% of newborns. It usually resolves by 3 months, but can be fatal or preleukemic. Evaluation for hematological malignancies and *GATA1* mutations is not advised for all neonates and children with DS. Hypothyroidism is reported in 4–10% of cases. There is increased prevalence of other autoimmune disorders like alopecia areata and vitiligo. Hirschsprung disease is a known association and needs to be picked based on symptoms. Behavioral problems, speech problems, bowel habits, and dribbling of saliva may need guidance by a pediatric psychologist or a developmental pediatrician. As the child grows, anticipatory guidance about puberty, vocational education, and employment needs to be initiated.

SUPPORTIVE THERAPY

For special issues, each child may need management. Hypotonia is very common during infancy and developmental delay is universal. Social milestones are usually not markedly delayed and often the parents refuse to accept the delay during infancy as the child keeps on gaining milestones and delay may not be appreciable to the laypersons, especially those in stages of denial. Parents should be encouraged to enroll the child in early intervention program. It is useful to the child and also gives a meaning to the life to parents who wish from their heart to do contribute to the development of the child. The gain of milestones during physiotherapy gives positivity to the parents. Normal vaccination, admission to preschool with normal children, and encouragement to parents to treat the child like a normal child help to change the attitude of the family to the child. Supportive therapy includes assessment of the emotional status of parents and intrafamilial relationships. The continued involvement of the pediatrician comfortable with DS goes long way in family's acceptance and emotional adjustments. Discussions about the differently abled child and what to tell the family and friends should be initiated and the siblings and grandparents should be involved in that.

EDUCATION AND OCCUPATION

Like normal population, there is a great variability in the cognitive function of the children with trisomy 21. Presence of mosaicism does not mean that the IQ will be better. Continued follow-up of development and IQ estimation during childhood give some idea about the functional outcome during adulthood. Availability of special educators, opportunity to mix with other children, and changing attitude of parents and society in this era are reducing the gap between the lives of individual with DS and those without them. The right to education is fundamental as per our constitution and employment of teachers for students with special needs will go a long way in providing opportunities to children with DS and other neurodevelopmental disorders and appreciating their contribution to the society. Such school atmosphere is also good for the emotional growth and development of sense of responsibility for future citizens of the country. Schooling with normal children prepares the children with DS to integrate in the society as adults.

EXPERIMENTAL THERAPIES

Available options of occupational therapy, behavioral therapy, and special education are not curative. Though they bypass some components and train using available strengths, the disability cannot be completely eliminated. Trials using megavitamin therapy, piracetam, cholinesterase inhibitors, stem cell therapy, etc. have not provided evidence of their efficacy on improving cognitive function.[13] The counseling sessions should initiate the topic and scientifically correct and up-to-date information will satisfy the parents.

GENETIC COUNSELING

Counseling begins as soon as a neonate is seen with the face suggestive of DS. Extreme sensitivity, good communication, and positive and careful use of words are the requisite for the pediatrician to break the news. Emotional care of the parents is as essential as the parents who were expecting a perfectly normal baby and are seeing one. The laypersons cannot appreciate the facial phenotype and do not feel that anything is unusual about the child, if there are no structural malformations. For a pediatrician to be able to give positive but realistic scenario, he or she has to be aware of the improved facilities for training and the satisfactory outcome of the children with intellectual disabilities including DS. All parents go through the various stages of coping and acceptance, but many parents never forget the day and the way the diagnosis of DS was disclosed to them. Diagnosis of DS is easy, but disclosing it to the parents is difficult. Pediatrician needs to provide follow-up for medical care and helps in organization of supportive care facilities including

connecting to the DS care facilities, medical genetics center, and parents' support group. The continued involvement of the pediatrician is an important aspect of the management. For a newborn or infant with DS after preliminary counseling, ordering chromosomal analysis and evaluation for associated treatable malformations and illnesses need immediate attention. Special mention needs for the babies with major malformation or serious life-threatening neonatal illness. A photograph and urgent chromosomal analysis are essential. If the neonate dies, the accurate diagnosis will be useful for genetic counseling regarding the risk of recurrence. If there is no access to karyotyping facilities, 1 or 2 mL of blood in EDTA vial stored at 4°C can be used later for confirming the diagnosis by QF-PCR.

The next part of genetic counseling is providing information regarding risk of recurrence during next pregnancy. It should be a part of initial counseling session even if the family may not think of next pregnancy now. The risk of recurrence is given in **Table 16.1.3.** It should be noted that the risk of recurrence in siblings in most of the cases is only 1%, but indicates the need of prenatal diagnosis. If one of the parents is a carrier of a balanced translocation, the risk of recurrence increases and depends on the carrier parent. Balanced translocation between both copies of chromosome 21 is a rare situation and will need other reproductive options like gamete donation to prevent a child with trisomy 21.

Table 16.1.3: Down syndrome due to translocation: Types, relative prevalence, and risk of Down syndrome in the offspring of the carriers of translocation.

Chromosomes involved in the translocation	*Relative frequency among the cases with Down syndrome due to translocation*	*Prevalence of de novo* translocation*	*Prevalence of inherited translocation*	*Risk of Down syndrome in the offspring of a translocation carrier*	
				Carrier mother	*Carrier father*
Dq21q [t(14;21) or others]	54.2%	55%	45%	10–15%	1–5%
21qGq t(21;21) t(21;22)	40.9%	96%	4%	– 100% 5–10%	– 100% 1–5%
21 with chromosomes other than G and D groups	4.9%	Few	Most	10–15%	1–5%

*The risk of recurrence of Down syndrome in the siblings of a case with *de novo* translocation or mosaic trisomy 21 is 1%.

Note: D—D group of chromosomes, i.e. 13, 14, or 15; G—Group of chromosomes, i.e. 21 or 22.

PRENATAL DIAGNOSIS AND POPULATION-BASED SCREENING

Prenatal diagnosis and population-based screening are the domains of the obstetricians and clinical geneticists. But being a part of genetic counseling and population-based screening being offered to all pregnant women, pediatricians can help in providing information required for the family to make informed decision. Prenatal diagnosis with the objective of terminating the pregnancy if the fetus has trisomy 21 and proactive management to help a child with DS may appear superficially contradictory to each other unless one appreciates different perspectives of the two entirely different situations. Every family wants a healthy normal child and option of prenatal diagnosis and termination of pregnancy, if the fetus has a serious disorder, is acceptable to most of the families and is legally possible before 20 weeks of gestation in India. The families who love their child and are taking the best care of the child with DS may opt for prenatal diagnosis and they need not feel guilty about it.

The other important scientific aspect about DS is an important part of history of medical genetics and that is population-based screening. Association of advanced maternal age with increased risk of a child with trisomy 21 was identified and prenatal screening based on maternal age using cutoff of 35 years was introduced in 1980s. This could detect 30% of fetuses with trisomy. Later, various biochemical markers were identified and currently first trimester double marker [free beta human chorionic gonadotropin (hCG) and pregnancy-associated plasma protein A (PAPP-A)] in maternal blood combined with ultrasonography for nuchal thickening (ultrasonographically measured subcutaneous thickness behind the neck of the fetus) or second trimester quadruple test identifies about 90% of fetuses with trisomy 21. The cut-off used for screen positivity is 1 in 250 and the false-positive rates are 5%. Quadruple test includes testing for alpha-fetoprotein (AFP), a protein made by the fetus, hCG, a hormone made by the placenta, estriol, a hormone made by the placenta and the baby's liver, and inhibin A, another hormone made by the placenta. This test using four biochemical markers done around 16 weeks of gestation is the cost-effective method and it includes AFP, which screens for neural tube defects which is five times more common than trisomy 21.

NONINVASIVE PRENATAL SCREENING

The latest development is detection of fetal aneuploidy by studying cell-free fetal DNA (cffDNA) in maternal plasma. This test has detection rate of 99% and minimizes the need of invasive testing for fetal karyotyping. Though the sensitivity of testing on cffDNA is very high, occasionally false-positive and false-negative results are reported. Hence, the test continues to be a screening test. At present, very high cost of test on cffDNA does not justify its use for

population-based screening and its use needs to be limited to the high-risk pregnancies or the families wish to avoid for invasive testing.

The availability of various screening tests of different costs and with various detection rates makes choice of test difficult. Guidelines for screening test for DS in Indian setup are needed to make the protocol-based testing and this is discussed in Indian Journal of Medical Genetics.[14] An uptake of screening test, invasive test, and termination of fetus with trisomy 21 are personal decisions for the family and depend on many factors like the previous obstetric history, family history, and personal views and values. Therefore, appropriate pretest and posttest counseling in nondirective fashion is essential for the success of population-based screening program for trisomy 21. Equally important is to stress cost-effectiveness of such a program and needs to remember that many other genetic disorders of severe nature and disability need attention. Medical fraternity in India and all over world is trying to increase the detection rates for DS by screening methods at all costs; may be with the objective of eradicating the disorder. One has to ponder about it and there will be many people and doctor who do not feel it justified. Also, need to remind everyone that prevention of DS is an option and not a compulsion.

Taking a three-generation pedigree is the most important screening test to prevent birth of children with many other disabilities and disorders with poor outcome.

With facilities for management of medical issues in children with DS and opportunities to integrate in the society, individuals with DS are contributing to the society by leading happy and meaningful life **(Fig. 16.1.7)**. A small study on the coping strategies of parents of children with DS from India showed that

Fig. 16.1.7: Star performers, photographer, and the audience on a special children's day: Dreams come true.

both mother and father have good acceptance for the situation and have used refocus on planning.[15] It is the time that pediatricians feel positive about the outcome of children with DS and take care of the different issues proactively. There is great variability in IQ and capabilities of so-called "normal" people and the artificially created boundaries between "normal" and those with intellectual disability need to be wiped out. Efforts to integrate everyone in the society are needed. Pediatricians caring children with DS will play a major role by organizing the comprehensive care of these children with beautiful faces and minds, thus changing the views of society toward DS.

PEEPING INTO THE FUTURE

Shutting the function of genes on the extra copy of chromosome 21 can be the curative treatment of DS. Though far from clinical application, a study has provided proof of this concept in cell lines of trisomy 21.[16] Jiang et al. inserted a single gene, X-inactive specific transcript (*XIST*) (the X-inactivation gene), in chromosome 21 of a pluripotent stem cells derived from DS patient. *XIST* gene is normally present on X chromosome and is responsible for silencing of genes from one X chromosome in females. The XIST noncoding RNA coated chromosome 21 and triggered stable heterochromatin modifications, chromosome-wide transcriptional silencing, and DNA methylation to form a "chromosome 21 Barr body". The cells with one "lyonized" chromosome 21 showed that the expression of the genes on chromosome 21 (which are expressed 1.5 times in patients with trisomy 21) returned to normal level. When these stem cells were transformed to neurons, the rate of proliferation of the neurons was normal as compared to slow growing neurons with all three copies of chromosome 21 functioning. Successful trisomy silencing *in vitro* also surmounts the major first step toward potential development of "chromosome therapy".

CONCLUSION

Down syndrome being the commonest cause of intellectual disability, the pediatricians need to be conversant with the management of the children with DS and their families. In addition to scientific aspects of diagnosis and management an extra allowance of empathy, communication skills and positivity is needed in pediatricians taking care of children with DS. The involvement of pediatrician starts from the day of birth and sometimes on prenatal diagnosis of DS. There is a need of special clinics for DS children and adults at medical college and tertiary care hospitals to provide comprehensive care for DS. Pediatricians can be the in-charge coordinating supportive care facilities and providing regular surveillance as per protocol. As the facilities and approach of the society, government and schools towards individuals

with different abilities and special needs are getting incorporated in the society and leading healthy, happy and fruitful lives. Pediatricians need to play a proactive role for children with DS. Everyone working with DS realises that the attempts to help the children with DS and their families brings peace to the mind and soul.

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