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Recent developments in management of a child with Down Syndrome

[1]Amar Verma, [2]K. Sandhya, [3]Manika Verma, [4]Ravikant Narayan
[1]Department of Paediatrics and Neonatology & Genetic diseases Research department, RIMS, Ranchi, Jharkhand
[2]Department of Anatomy & Genetic diseases Research department, RIMS, Ranchi, Jharkhand
[3]Junior Resident, RIMS, Ranchi
[4]Junior Resident RIMS, Ranchi

Address for correspondence: Department of Paediatrics and Neonatology, Rajendra Institute of Medical Sciences, Ranchi, Jharkhand-834-001

Abstract: Down Syndrome (DS) is the commonest genetic cause of intellectual disability. Down syndrome (DS) is caused by trisomy of chromosome 21 (Hsa21) and is associated with a number of deleterious phenotypes, including learning disability, heart defects, early-onset Alzheimer's disease and childhood leukaemia.
First trimester screening was introduced as important screening tool but absence of its awareness may have contributed to steady increase of DS birth. There is need to educate medical professionals as well as people about recent management available in India and abroad.
Individuals with DS are affected by these phenotypes to a variable extent; understanding the cause of this variation is a key challenge. Large-scale studies of genotype–phenotype relationships in patients are likely to significantly contribute to the future understanding of DS.
This article also proposes an optimal guideline for follow up, keeping in mind the resource and laboratory constraints. Common preventive modalities on the horizon were also explored to understand their utility in a developing countries setting.
This article may be helpful to caring doctors and support groups both.
Key words: Down's syndrome, Trisomy, Counseling

I. INTRODUCTION

Down Syndrome continues to constitute the most common cause of genetic MR accounting for **1.7 per 1000 live births to currently 1 in 850 [unconfirmed data].** The prenatal screening test or commonly called CUB test (combined Ultra-Sonographic Biochemical test) has lead to a steady decline in DS births in developed world. Awareness about such modalities is needed in India or developing countries. The different clinical situations are encountered with DS in utero, or at birth and at times even in childhood. At times it becomes difficult to recognize phenotypic features clinically in abovementioned situations. Awareness among obstetricians, General practitioners or even pediatricians is needed urgently.

Down syndrome (DS) is caused by trisomy of human chromosome 21 (Hsa21). Approximately 0.45% of human conceptions are trisomic for Hsa21. The incidence of trisomy is influenced by maternal age and differs between populations (between 1 in 319 and 1 in 1000 live births are trisomic for Hsa21). Trisomic fetuses are at an elevated risk of miscarriage, and people with DS have an increased risk of developing several medical conditions . Recent advances in medical treatment and social inclusion have significantly increased the life expectancy of people with DS. In economically developed countries, the average life span of people who are trisomic for Hsa21 is now greater than 55 years.

Life expectancy of a child with DS was around 25 yrs in 1983. Currently due to increasing awareness and good medical care, it has increased to nearly 50-60 yrs in the west. Recent data reveal that more than 70 percent of infants with Down syndrome are born to women younger than 35 years. This may be due to the higher birth rate in women in this age group. Consanguinity does not predispose to Down syndrome.

The prenatal diagnostic tests both utilizing serum and ultrasound markers have lead to a steady decline in DS births in developed word. The earliest ultrasonic markers are absence of nasal bone, nuchal translucency thickness in 11-13 week scan. Clinician usually encounters DS in the diagnosis of the fetus beyond 20 weeks due to ultrasonic makers like short femoral length, pyelectasis, echogenic intracardiac fetus or a positive triple screen.

The first clinical situation is the diagnosis of the DS fetus suspected beyond 20 weeks was due to ultrasonic makers like short femur length. If detected early in the third trimester the parents should be provided moral support and offered linkage to existing DS support groups. This is likely to offer a positive outlook and impart knowledge about availability of similarly affected parents.

Post natal care:

In case the suspicion is after the birth of the neonate as is usually the case. Gestaltic evaluation is of permanent importance as the diagnosis may be challenging in preterm LBW neonates.

The diagnosis should be discussed if preterm neonate or in an unsure situation only after a FISH report or a Karyotype reports is available but may be feasible in situations where clinical genetics support exist. While evaluating the adaptation to extra uterine life it is important to identify life threatening malformations like GI tract obstruction which may need additional care.

Growth:

No growth chart specific for Indian subcontinent is available but are present in western countries such as USA & UK. However, in the absence of DS specific growth charts, an average DS child usually performs at the 2nd centile of the ethnic growth charts.

The postulated reasons for poor growth in infancy are difficulty in sucking and swallowing, accompanying organic diseases such as congenital heart disease, celiac disease, obstructive sleep apnea hypothyroidism and associated nutritional deficiencies. However during adolescence due to inadequate physical activity in the presence of good diet they tend to become overweight. Some children demonstrate an absence of pubertal growth spurt while some growth is observed during adolescence. Controversial literature exists regarding GH/IGF axis and from a developing country perspective GH supplementation should only be reserved for affording families with unequivocal evidence of GH deficiency.

Development:

Children with DS may show variable cognitive development, ranging from mild (50-70), moderate (35-50) to severe (20-30). Children with DS have a better social quotient which shows much better improvement with early intervention. DS children tend to behave more effectively in social situations than predicted on basis of cognition. Enrolment in child development centers should be encouraged in these children due to favorable outcome. Rashtriya Baal Suraksha Karyakram is a novel program where disability centered approach is advocated in children with delays and may prove vital in India. Some behavioral Issues may be present in these children.

Early intervention definitively improves outcome in children with DS. Motor development requires about double the time taken by an average child. Amongst other deficits in the pediatric age group epilepsy is seen in DS. West syndrome(WS) is the commonest pattern and seen in 0.6 – 18% of DS (representing 4.5 – 47% of seizures). It has been postulated that intra-neuronal accumulation of β-amyloid appears to trigger the cascade of neuropathological manifestations of the AZ phenotype.

Cardiac Complications constitute major co-morbidities. More than 50% of children have structural or functional defects. These constitute a major cause of morbidity in the 1st year of life. Routine cardiovascular systemic examination may fail to identify a defect and echocardiography is essential in all children with DS. This is important even if the fetal echo has been unremarkable. Pulmonary hypertension in isolation has been seen to develop before 6 weeks. One Indian study reported congenital heart disease in 63.4% of DS (256/404) with atrio-ventricular septal defect being the commonest (70%), VSD 28% & PDA 43%. Surgical correction was attempted in this session 40.6% with an excellent outcome in one study from India. Surgery in children with DS has been reported to have good outcomes.

Development of pulmonary arterial hypertension in absence of CHD exists in children with DS and may be related in term to airway and respiratory problems. Existing GERD may also worsen the PAH present in these children. While transiting to adolescence, one needs to be vigilant about mitral value prolapse and development of aortic regurgitation. These lesions may in turn, lead to atrial fibrillation and left ventricular hypertrophy further restricting activity.

Gastrointestinal problems are also seen in upto 12% of DS children. In the neonatal period duodenal and jejunal atresia need urgent treatment. Other associated problems are gastroesophaged reflux disease and constipation both of which significantly alter the quality of life.

Clinical clues to screening may be identified to direct targeted screening and optimal resource allocation. Clinical clues are (a) family H/o celiac disease (b) positivity for markers of other autoimmune disease like diabetes mellitus, autoimmune hepatitis and thyroditis (C) Chronic disease (d) failure to retain percentiles on DS charts (e) anemia (f) recurrent abdominal pain.

Respiratory problems are those which constitute an important cause of non cardiac morbidity. Commonly encountered respiratory problems include subplural cysts, tracheal bronchus and bronchiactasis. Recurrent and prolonged wheeze observed in this population could be due to malaria of the lower airway and hypotonia of intestinal muscles. This may amount to a proportion or nearly 36%. In the absence of respiratory

symptoms a mandated Chest Xray is not indicated. In children with recurrent wheeze the use of pentavalent vaccine, influenza and pneumococcal vaccine is advocated. Morbidity due to respiratory causes such as Respiratory syncytial virus(RSV) has also been observed in various series.RSV humanized IgG monoclonal antibody through advocated in developed countries in DS children with CCHD, PAH, BPD should be weighed carefully and costs discussed with parents prior to use.

ENDOCRINE PROBLEMS:

A variety of endocrine issues need to be addressed in DS children. Hypothyroidism is 28 times more common in children with DS compared to general population. One quarter of the DS children will develop or show evidences of hypothyroidism in the first year of life. Subclinical hypothyroidism may be transient in few children with DS. If the TSH is upto 10 mIU but values of T4 are normal one has to individually decide regarding treatment. In one large Indian series hypothyroidism was seen in 13.6% cases [239934063]. The frequency of monitoring of TSH should be at birth, 6 months, 1 year & then annually. Clinical pointers like lethargy, cognitive defects, impaired growth and dementia which are a routine spectrum of DS are usually not useful due to their innate presence in these children. Hyperthyroidism and diabetes mellitus may be seen occasionally and represent auto immune phenomenon.

Hematological issues:

Both thrombocytopenia and polycythemia may be seen in infants with DS. Upto two third of DS children may demonstrate macrocytosis which is thought to occur as a sequale of alteration in the erythrocyte membrane. This leads to difficulties in diagnosis of Iron deficiency anemia, lead toxicity and thalassemia based on MCV estimation.

Transient myeloproliferative disorder is an entity unique to DS and is seen to occur in 10% DS babies in the first three months of life. TMD is defined by presence of blasts in the peripheral smear in infants less than 3 months, usually seen in the 1st week of life.

Onclologic Issues:

The risk of malignancies in children with DS is increased with risk of ALL being 20 fold more common and AML 500 fold more common. Tumors like germ cell tumors are also 5 times more common.

Anesthesia Care:

Special precautions need to be observed in DS children undergoing anesthesia. Jacob et al conducted a study in which 71/518 patient with DS were diagnosed with airway obstruction. Out of these 71 enrolled patients, 39 had most severe symptoms and underwent operative endoscopy. Commonly encountered problems are tracheomalacia (59%) laryngomalacia (28%) macroglossia (28%) subglottic stenosis (23%) congenital tracheal stenos is (5%) were found in these patients . Multiple sites of obstruction were seen in 38% of these cases. (8797558)

Atlanto–axial instability is another co-morbidity that should be considered when a child with DS is being taken for surgery. Studies indicate that the incidence of AAI seen on radiography is 14-20%.

ENT problems:

Patients with DS have a range of ENT problem including secretory otitis media ,hearing loss, recurrent respiratory tract infections etc. Anatomic abnormalities like mid face hypoplasia, stenotic ear canals (40-50%) abnormal Eustachian tube ,short palate with relative macroglossia ,narrow oropharynx and nasopharynx, generalized hypotonia and physiologic abnormalities like defective immune system, ciliary dyskinesia predispose these children to these problems. 50-90% children with DS have hearing impairment.

Hearing loss in these children can be conductive or sensori-neural. Conductive hearing loss is usually due to recurrent serous otitis media because of the above said anatomic abnormalities causing under-aeration of the middle ears and also sometimes due to mastoid under-aeration and ossicular chain abnormalities. Recurrent grommet placements or surgery may be needed.

Obstructive Sleep Apnea:

OSAS in pediatric patient with DS has been estimated to be around 77-80%. whereas in general pediatric population it is seen in only 0.7-2%. Predisposing factors for OSAS in DS include mid face hypoplasia, smaller airways, relative macroglossia, hypotonia and obesity (22588039). OSAS leads to poorer neuro- development outcome and can cause pulmonary hypertension in DS children who are already predisposed for these.

Snoring points out to high likelihood for OSAS though it can be still present in children who do not snore. Other pointers can be disturbed sleep, abnormal sleep postures excessive day time somnolence and behavioral issues.

Vision problem:

More than half of DS children have ocular abnormalities.Vision disorders include refractive errors (43-70%), Strabismus (20-47%), nystagmus (11-29%), congenital cataract (4-7%), acquired cataract (3-15%), blepharitis (7-14%) and Glaucoma (<1%). Normally, most developing infants are hypermetropic, which decreases with age and they achieve emmetropia by 1 year of life. In children with DS there is a failure of this emmetropization (12601024) and early correction of refractive error and strabismus is important to prevent the risk of amblyopia. At birth, children with DS should be examined for congenital cataract by checking for red reflex. By first 6 months, it is recommended that, evaluation should be done by a pediatric ophthalmologist for strabismus, cataract and nystagmus.

Issues related self care in a baby with DS:

Apart from Medical Issues, equally challenging are the issues related to self care, schooling, job and career prospects and life expectancy. This part focuses on these issues.

Self care revolves around these areas a) daily activities, house chores, playing games, watching television or going to a cinema or theatre, b) refers to works done regularly like washing, preparing simple meals, going out alone and using bus or metro c) verbal communication with ability to make oneself understood, competence in writing, use of money and degree of autonomy and d) social and sibling relationships. These revolve around three crucial issues and include the DQ (deciding whether an individual is educable or trainable), the family and social support and in part on the phenotype.

Attempt should be made to make them enter mainstream schooling provided they are not severely and profoundly retarded. Ebesensen et al compared children staying in residential schools with those staying in schools for children with special needs. Those living in residential schools had significant gains in housekeeping and health related activities but decline in personal care and health. Despite this benefit, social isolation from parents and lack of regular health checkups resulted in more rapid functional decline.

LIFE EXPECTANCY:

After the age of 35 years in one study the annual mortality rate for DS adults doubled every 6.3 years compared to 9.6 years for adults with other classes of ID. The mortality rises sharply after 40 years due to dementia, loss of parents, decline in self help and communication and complication of co- morbidities.

GENETIC COUNSELING AND RISK OF RECURRENCE:

Counseling should be non-judgemental and directive to the involved couple. Due care should be taken about the timing of counseling as too early may be inappropriate considering the fact that they have yet not adjusted to the fact that a random mistake of fate has created this situation. At an appropriate time during the follow up period and after the genotype is available counseling is advised preferably in the presence of both partners. They should be made to understand the chromosomal nature of the disorder and the low recurrence risk above baseline in case it is a free trisomy.

Appropriate risk figures are needed in situations where one parent is a carrier of a balanced translocation. Here it is important to understand that 70% translocations are also denovo events. However depending upon the parent of origin different risks of recurrence exist. In a 21: 21 translocation the risk is 100% as a monosomic zygote is incompatible with life. In case of t(21:22) the risk is below 5% if one of the parent is a carrier and in case of D/G translocation if mother is a carrier the recurrence risk is below 10% and if father is a carrier the risk is below 5%. In a large study from India, of 1021 cases, 87.37% --pure trisomy, 4.5%--translocation and 8.13% demonstrated mosaicism. The Sex ratio of male to female was 1.4:1 and that of translocation was 1.1:1 and of the 46 cases of translocation, 5 were originated from the mother and 1 from the father. 26 were denovo in origin. Amongst groups the proportions were t(14;21) --(43.47%), t(21;21)--36.95%.
Counseling should also inform parents about prenatal screening strategies, meaning of risks and preventive actions. Prenatal risk assessment can be done from 3 factors- maternal age, serum markers, ultrasound and confirmation will be done by karyotyping/FISH/NIPT. In first trimester screening can be done using serum markers like beta-HCG, PAPPA or USG (nuchal translucency). Sensitivity of beta- HCG. PAPPA, nuchal translucency (3.5 mm or greater), serum (HCG+PAPPA), combined screening (age, serum markers, nuchal translucency) are 22-29%, 37-51%, 70%, 70%, 87% respectively at a false positive rate of 5%. Second trimester screening can be done by triple test (HCG+ AFP+ unconjugated estriol) or quad screen (triple test+ inhibin). Sensitivity of these tests are 69% and 80% respectively. Integrated screening (both first and second trimesters) using serum markers alone has sensitivity of 88% whereas serum markers+ USG+ maternal age has a sensitivity of 95% but false positivity rate is also high. Confirmation of trisomy 21 can be done using invasive modalities like chorionic villus sampling or amniocentesis. CVS can be done in 10-12 wks whereas amniocentesis in 15-18 weeks. Risk of fetal loss are 0.5-1.5% and 0.5-1% respectively.

Non Invasive Prenatal Testing (**NIPT)** is a new non invasive modality to look for the karyoytype of the fetus. It has been available since November 2011 in the United States & since 2013 in India. It analyzes cell-free fetal DNA circulating in maternal blood: (cffDNA) .Can be detected earliest at 9 weeks. It analyses the placental and fetal-derived cells. Currently it is widely practised for thalassemia and Rh-negative.

There is need for proper scheduling of follow up visits, needs for specialty consultations, frequency of laboratory consultations. The presence of DS support group, need for early intervention and participation in schooling programs are emphasized. Prenatal testing strategies also need to be strengthened as families bear the burden of the disease. IEC practices are needed across all specialties to cater to the specific needs of children.

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