Consensus Statement of the Neurodevelopmental Pediatrics Chapter of Indian Academy of Pediatrics (IAP) on the Management of Children With Down Syndrome

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Justification: The diagnosis of Down syndrome (DS) is easily made clinically but the management is multi-disciplinary and life-long. There is no standard protocol available for its management in India. **Process**: A committee was formed under the Indian Academy of Pediatrics (IAP) chapter of Neuro developmental pediatrics consisting of 20 experts working in the related field. The various aspects of the condition were discussed and allotted to the concerned experts related for preparing the guidelines. The material received was collated to form a set of guidelines, which were reviewed by the committee, and a consensus statement made. The guidelines were then approved by the chapter, and by the IAP. **Objectives**: To define the condition and to look into the various aspects of antenatal and postnatal diagnosis. To explain briefly about the involvement of the various systems that are involved and formulate recommendations for management. To recommend early and sustained interventional therapies to enable children with DS lead an independent life. **Recommendations**: The stress on bio-psycho-social strategy for the management of children with DS is reiterated, and the need for a medical, social and rights model is recommended after each section. The age-wise recommendations are also highlighted in addition to the recommendations under each system.

Keywords: *Antenatal diagnosis*, *Comorbidities, Karyotyping, Outcome.*

Down syndrome (DS) is a genetic disorder caused by the presence of all or part of a third copy of chromosome 21. Majority of mothers of babies with DS in developing countries are in the 20s, as pregnancy above 35 years is comparatively less in these countries [1]. The management of DS has evolved from a purely medical model to a social, and now, a rights model. Regular and repeated counselling of parents is of utmost importance to ensure a sustained management program [2]. Awareness and educational programs for the public at large are important to create an inclusive society by which these children are able to lead an independent life.

PROCESS

A committee of experts was formed and the work was divided among the experts for collecting data in the allotted subject areas. All experts submitted the requisite information to the convener by email, who collated the same. The committee met physically on September 3, 2022, during the National Conference of the IAP Chapter of Neuro Developmental Pediatrics at Kolkata. Further discussions and interactions were done through e-mail. The final meeting was online on October 23, 2022, where the recommendations were discussed and approved. The final guidelines were cleared by the Executive Board of Indian Academy of Pediatrics.

OBJECTIVES

The objective of these guidelines is to detail briefly about the involvement of the various systems, and formulate recommendations for management. To provide a uniform structured guideline for the management of children with DS, that can be practiced across the country. To recommend early and sustained interventional therapies to enable children with DS lead a healthy and independent life.

RECOMMENDATIONS

The stress on bio-psychosocial strategy for the management of children with DS is reiterated, and the need for a medical, social and rights model is recommended after each section. Age-wise recommendations are also highlighted in addition to the recommendations under each system. Caregivers should be counselled and medical personnel sensitized and trained to provide appropriate management.

Prenatal Screening, Genetic Testing and Timing

Screening for DS should be offered to all pregnant women, irrespective of their age, family history or ethnic background. However, in low-and middle-income countries (LMICs), this is not usually practiced due to various reasons like financial constraints, lack of facilities available, and absence of a national protocol for screening [3]. First trimester combined screening is preferred, as it is done early in gestation and has a higher detection rate than when performed in the second trimester. The first and second trimester screening tests that are currently available for antenatal screening for DS, along with their reported diagnostic performance, are listed in **Table I** [4].

If the screen shows increased risk for trisomy 21, prenatal diagnostic testing by chorionic villus sampling [CVS] at 11 to 13 weeks of gestation or amniocentesis after 16 weeks of gestation is recommended. The risk of procedure-related pregnancy loss is around 0.11% for CVS and around 0.1-0.3% for amniocentesis [5].

Confirmatory testing by karyotyping or chromosomal microarray (CMA) should be done on the fetal sample. Karyotyping has a turnaround time of around 10-14 days and can detect chromosomal anomalies larger than 5-10 Mb in size. CMA is around two to three times more expensive than karyotyping but has a shorter turnaround time of around 7 days and a much higher resolution than karyotyping. Rapid aneuploidy detection techniques such as fluorescence in situ hybridization (FISH) or quantitative fluorescent polymerase chain reaction (QF-PCR) test, which have a shorter turnaround time of around 24 to 48 hours, are also usually performed.

Non-invasive prenatal testing (NIPT) or non-invasive prenatal screening (NIPS) is available for testing of common chromosomal aneuploidies including trisomy 21 [6]. It is based on testing of cell-free DNA (cfDNA) derived from the placenta through apoptosis of trophoblasts that can be extracted from the maternal plasma. NIPT is usually performed after 10 weeks of gestation, and has a detection rate and false-positive rate of around 99% and <0.1%, respectively for trisomy 21 [6]. Pre-test and post-test counselling are essential for all screening and diagnostic genetic tests.

Although, the diagnosis of DS is clinical, genetic testing using chromosomal analysis by conventional cytogenetics (karyotyping) is required after the child is born, which helps in providing disease-specific genetic counseling, and in guiding anticipatory management [7].

Table I Commonly Used Tests for Prenatal Screening of Down Syndrome

Screening test	*Detection rate*	*False positive rate*
First trimester screening (11-13 wk)		
Combined test: MA + NT + double marker test (serum free β-hCG and PAPP-A)	85-95%	5%
Combined test + ultrasound marker (nasal bone or tricuspid flow or ductus venosus flow)	93-96%	2.5%
Second trimester screening (15-22 wk)		
Triple marker test:		5%
MA + serum AFP, free β-hCG, uE3	65-70%	
MA + serum AFP, hCG, uE3	60-65%	
Quadruple marker test:		5%
MA + serum AFP, free β-hCG, uE3, inhibin A	70-75%	
MA + serum AFP, hCG, uE3, inhibin A	65-70%	

Strategies involving a combination of first and second trimester screening methods such as sequential screening, integrated screening, and contingent screening are used in some centers to improve the detection rate.

MA: maternal age; NT: nuchal translucency; β-hCG: β-human chorionic gonadotrophin; PAPP-A: pregnancy-associated plasma protein-A; AFP: alpha fetoprotein; uE3: unconjugated estriol.

Recurrence risk: Around 95% DS occur due to an extra chromosome 21 i.e., trisomy 21 due to non-disjunction during meiosis and recurrence risk in this is almost 0.5-0.7%. In case of parental Robertsonian translocations involving Group G/D (chromosomes 13,14,15 and 21,22) there are higher chances of recurrences depending on parental origin. In case of maternal carrier, the chances may be up to 15% and lesser in case of paternal carrier (<1%), possibly due to poor survival of sperms with an extra chromosome 21. In case of chromosome 21;21 translocation, there is 100% risk of recurrence, if not de novo [8].

Recommendations

i) All pregnant women irrespective of their age should be screened for DS preferably in the first trimester and prenatal diagnostic testing done, if needed.

ii) Karyotyping should be routinely done for confirmation, after the child is born.

Development and Growth Monitoring

Growth potential of children with DS is less compared to children with normal karyotype. Both height and head circumference are affected. Final height is less by 2-3 SD in comparison with that of individuals of same sex with normal karyotype. Head circumference is less by almost 2SD. Growth is more compromised in children with DS who have major congenital heart diseases or other systemic diseases.

DS specific growth charts are to be used for monitoring growth of children with DS and interpretation of growth faltering. Height/length, weight and head circumference must be documented at birth, during immunization visits at 6, 10 and 14 weeks, at 6 months, 1 year and 6 monthly thereafter.

Children with DS tend to become obese, especially during adolescence [9]. This has to be anticipated and measures should be taken for prevention. Likely determinants of obesity include increased leptin, decreased resting energy expenditure, comorbidities, depression, unfavorable diet and low physical activity. Obesity is associated with obstructive sleep apnea, dyslipidemia, hyperinsulinemia, and gait disorder [10].

Prevention and management of obesity is similar to that for all children, and includes appropriate exercise programs and dietary modification.

Recommendations

The height/length, weight and head circumference should be regularly monitored and plotted in a DS specific growth chart. Till we have an Indian Growth chart for children with DS, we can use any growth chart available. It is the growth pattern that is important and not the percentile shown in the chart as our children would be shorter. A widely used chart [11] is available at: *https://www.cdc.gov/ncbddd/birthdefects/downsyndrome/growth-charts.html*

Cardiac Lesions

The high prevalence of congenital heart disease (CHD) in DS (40-60%) [1,12], together with poor sensitivity and specificity of clinical examination, justifies routine echocardiographic screening at the earliest opportunity in these babies. The cardiac status should be established by 6 weeks of age.

Most cardiac lesions in DS are correctable through timely intervention and their management should be on the same lines as for children without DS. It is important not to delay correction in large shunt lesions such as atrioventricular septal defect (AVSD), ventricular septal defect (VSD), and patent ductus arteriosus (PDA), because of the propensity for rapid development of pulmonary vascular disease. The presence of DS does not significantly increase surgical risk for the common CHDs encountered. However, for complex defects such as unbalanced AVSD, and tetralogy of Fallot (TOF) with AVSD, management and outcome need to be carefully individualized.

Recommendations

i) Routine screening echocardiogram should be done at birth and cardiac status established by 6 weeks of age.

ii) There should be no delay in correction of large shunt lesions as it can lead onto pulmonary vascular disease.

Endocrine/Thyroid Status

Thyroid disorders are common in children with DS (24-50%). Both hypothyroidism and hyperthyroidism are described, but hypothyroidism is much more common and includes subclinical hypothyroidism (SCH), congenital hypothyroidism (CH), and autoimmune thyroid diseases (ATD). Detection of anti-thyroperoxidase antibodies are higher in DS compared to general population [13,14]. However, the presence of anti-thyroid antibodies is a better predictor for severity of hypothyroidism [15].

SCH, characterized by elevated serum thyroid stimulating hormone (TSH) and normal free thyroxine is the most common thyroid abnormality in children with DS. Almost 50% of children with SCH in DS have thyroid antibodies and half of these may progress to overt hypothyroidism.

Congenital hypothyroidism has been reported to be about 28-30 times more common in neonates with DS [16,17]. Most are due to thyroid hypoplasia. The TSH and T4 cutoffs used for screening CH in children with DS are the same as that for normal children [18,19]. Children with DS and ATD are more prone for other autoimmune

disorders. Reduced expression of the gene *autoimmune regulator* (AIRE) is noticed in DS, which may explain the higher incidence [20]. There are no clear recommendations for screening for autoimmune disorders in DS.

Children with DS have short stature; even though, there is no overt growth hormone (GH) deficiency. However, selective insulin like growth factor-1 (IGF) deficiency has been reported in children with DS older than 2 years [21]. No benefit in final adult height has been demons-trated with GH therapy. Pubertal children often show hypergonadotropic hypogonadism (high luteinizing hor-mone, LH; high follicle stimulating hormone, FSH), which is progressive from birth to adolescence [22]. Pubertal progression is also often delayed.

Low bone mineral density (BMD) is common and is due to low physical activity, less sun exposure, obesity, decreased muscle mass, associated illnesses (celiac disease) and drugs (anticonvulsants) [23].

Recommendations

i) CH is not always picked up in the newborn screening, hence repeat screening at 6 months is recommended. Screening has to be repeated at the age of one year, and every year thereafter.

ii) Current recommendation for SCH is to treat only when the TSH remains persistently above 10 mIU/mL, or if there are clinical symptoms of hypothyroidism or goiter, or if thyroid autoantibodies are present.

Hearing Issues

It is estimated that over 50% of people with DS have hearing impairment, which can range from mild to profound [24]. Otitis media with effusion causing conductive hearing loss is prevalent in children less than 5 years, whereas sensorineural loss occurs as age advances. Early hearing loss has a significant impact on speech and language development of children with DS, resulting in disproportionately severe speech delay.

Orofacial and craniofacial maldevelopment associated with DS contributes to inner, middle and outer ear problems. Large adenoids, small nasopharynx, impaired swallowing and narrow horizontal eustachian tubes are contributory factors [24]. There is also a higher incidence of chronic rhinosinusitis and adenoid hypertrophy in these children. Cochlear implant is reported to be successful in these children for the management of severe sensorineural hearing loss.

Recommendations

i) Neonatal screening is recommended followed by a full audiological assessment between 6 and 10 months; and intervention initiated if needed. An audiological review should be carried out at around 18 months in a manner appropriate for the cognitive level, which should be repeated at least yearly until age 5 and thereafter 2 yearly for life.

ii) Regular dewaxing is advised for wax accumulation.

iii) For otitis media with effusion - grommet insertion is advisable, with adenoidectomy in case of recurrent issues.

iv) Sleep studies or polysomnography may be done in the presence of suggestive symptoms, where available, as there is a high prevalence (50-70%) of obstructive sleep apnea (OSA).

Ophthalmic Problems

Ocular disorders have a high prevalence (60%) among people with DS [25]. Nasolacrimal duct obstruction is seen in 10-36% of infants, compared with 2-4% of infants with normal karyotype.

Refractive errors occur at an early age and are about 10 times more common. Around 54% of children with DS require prescription spectacles in preschool. Hyper-metropia, which often reduces spontaneously in other children, is likely to persist beyond infancy in these children. Around one third children with DS will have visual defects by 18 months to 2 years, and around 50% are likely to have refractive errors by the age of 4 years.

Blepharitis is seen in 30% of children with DS, the increased incidence is due to increased tendency to dry skin. Congenital cataract as well as developmental cataract, nystagmus, and congenital glaucoma are also more prevalent. Various studies have shown that difficulty in accommodation in DS can be corrected using bi-focal lenses.

Strabismus occurs in 25-30% children with DS, compared to 2-4% children without DS. Keratoconus is also seen in up to 15% children with DS, and regular monitoring is needed to avoid visual loss. Amblyopia is seen in up to 20%children with DS.

Recommendations

i) All newborns with DS should have an eye examination at 4-6 weeks to exclude congenital glaucoma, cataract and other eye abnormalities. Visual behavior needs to be monitored by a pediatrician before their first formal ophthalmological review.

ii) Between the age of 18 months and 2 years, all children should have an ophthalmological review, which is to be repeated at 4 years and thereafter every 2 years throughout life.

iii) Any child/adult with pain, and/or changing vision, or visual disturbances/red eye should be referred for urgent ophthalmological opinion.

Hematological Abnormalities

Transient abnormal myelopoiesis (TAM): Previously known as transient myeloproliferative disorder, it characteristically presents with hepatosplenomegaly, hepatopathy, skin rash, pericardial and pleural effusions, extreme leukocytosis and coagulopathy. Bone marrow examination is not useful for diagnosis since blast cells formed are from fetal liver. Moreover, bone marrow involvement does not correlate with severity [26,27].

TAM results in early death in 15-23% cases and among survivors, 20-23% of children will develop acute myeloid leukemia of Down syndrome (ML-DS). Predominant causes of death are progressive hepatopathy with cholestasis, leading to fulminant hepatic fibrosis, disseminated intravascular coagulation (DIC), malignant pericardial/pleural effusion, and multi organ failure. Overall event free survival rate is 63-68% [27].

Nutritional anemia: Many children with DS in developing countries do have anemia, which in turn can affect the cognitive status. Hence, yearly blood counts must be done at least till 5 years of age.

Recommendations

i) All newborns with DS should have a complete blood count (CBC) and peripheral smear examination (PBS), which should be repeated yearly till 5 years.

ii) All children with previous TL-DS should be monitored for progression to Myeloid Leukemia-Down Syndrome (ML-DS) with 3 monthly clinical review and CBC and PBS until the age of 2 years. If the CBC and PBS are normal and there are no clinical features of ML-DS, monitoring should continue 6-monthly till the age of 4 years.

Dermatological Manifestations

Seborrheic dermatitis, xerosis (dry skin) and palmoplantar keratoderma occur more frequently in individuals with DS. Dry skin predisposes individuals to irritant as well as allergic contact dermatitis. Acanthosis nigricans is also noted and is a marker of insulin resistance, and associated with obesity. Alopecia areata affects 6-10% of those with DS and is associated with autoimmune conditions such as vitiligo and hypothyroidism. Serum ferritin should be done in such cases as low iron reserves may affect hair regrowth.

Pustules, nodules and abscesses in the arm pits and groin are common. The response to treatment is often poor. Folliculitis due to malassezia, furunculosis and impetigo due to staphylococcus and infestations, especially crusted scabies, are noted.

Accelerated ageing is considered part of the DS phenotype and the signs include greying, thinning of hair, skin atrophy, early development of rhytids (wrinkles), and lentigines [28].

Recommendations

A thorough cutaneous examination, with particular attention to the commonly affected locations like scalp, axilla, groin, and feet should be done at all routine clinical visits.

Musculoskeletal Issues

Musculoskeletal problems in DS are due to central hypotonia, laxity of ligaments and excessive joint mobility [29]. Autoimmune conditions and endocrine issues like hypothyroidism and osteoporosis further add to these problems.

Foot, hip and spine are common areas involved in cases of DS, resulting in reduced mobility, lower bone density and high risk of injuries. Cervical spine instability due to issues with first and second cervical vertebrae result in neck pain, abnormal head/neck posture and motor symptoms in limbs. Upper cervical spine instability has the most potential for morbidity and, consequently, requires close monitoring. Rarely, spinal compression may lead to sudden death. Hip subluxation/dislocation, slipped upper femoral epiphysis, Perthe disease, pes planus, hallux valgus, congenital talipes equino varus (CTEV), patellar instability, scoliosis, kyphosis, inflammatory arthritis (JIA) and atlanto-axial dislocation are more common than in the general population. Plain radiographs do not predict well the increased risk of developing spine problems, hence routine radiologic evaluation of the cervical spine in asymptomatic children is not recommended. Any child who has significant neck pain, radicular pain, weakness, spasticity or change in tone, gait difficulties, hyperreflexia, change in bowel or bladder function, or other signs or symptoms of myelopathy must undergo plain cervical spine radiography in the neutral position, and referred, as required.

Recommendations

i) Hip and foot examination should be done in the first year of life.

ii) All children with DS and a limp should be evaluated with a hip *X*-ray.

iii) Routine screening of cervical spine is not recommended, unless they are engaged in contact sports,

have any symptom of atlanto-axial instability or as a part of pre-anesthesia checkup.

iv) Scoliosis screening should be considered in the presence of suggestive findings.

Oral Health Issues

Relatively large and fissured tongue with small oral cavity, malocclusion, mal-alignment, dental agenesis, enamel hypoplasia, delayed dentition, dental caries and periodontal disease are the common oral health issues encountered [30]. The first tooth eruption is usually at the age of 12 to 14 months and may be completed only by 4 to 5 years of age. Permanent teeth eruption may also be delayed. Orthodontics (braces) may improve some of the issues associated with the mal-alignment, but it could interfere with speech and many find it difficult to tolerate.

Recommendations

i) First dental visit should be within 6 months of the first tooth eruption or by 1 year of age; and thereafter yearly till 5 years of age.

ii) Brushing should be done twice daily with a soft toothbrush and fluoride toothpaste.

iii) Preferably floss daily, even if there is gum bleed, as brushing and flossing help to keep the gums clean and minimize inflammation.

iv) Limit the amount and frequency of sugar and refined foods.

Gastrointestinal Manifestations

Structural and functional disorders of gastrointestinal tract seen in DS include esophageal atresia/tracheoesophageal fistula, duodenal/jejunal atresia or stenosis, annular pancreas, anorectal anomaly and Hirschsprung disease. Feeding difficulty (due to poor oromotor function), gastroesophageal reflux, constipation, toddler diarrhoea, and gall stones are other disorders noted [31,32]. Celiac disease is seen in 5% of those with DS.

Recommendations

i) Complete physical examination of the infant including inspection of the perineum for anal patency.

ii) Enquire about passage of meconium

iii) Growth monitoring using DS growth charts as a screen for malabsorption; consider testing for coeliac disease, if symptomatic

Renal and Genitourinary Involvement

Congenital anomalies of kidney and urinary tract (CAKUT) group covering glomerulonephritis, renal agenesis, microcysts, ectopic kidneys, abnormalities of the urinary tract with hydronephrosis, hydroureter, posterior urethral valve, obstruction of anterior urethra, undescended testes, hypospadias and epispadias are noted in DS [33]. With increased survival, a large number of these patients present with chronic renal failure. Glomerular disease usually appears between the 2nd and 3rd decades of life with immunoglobulin A (IgA) nephropathy and focal segmental glomerular sclerosis being the most frequent pathologies.

Immune dysfunction associated with DS may predispose children to post infectious glomerulonephritis (PIGN). Urodynamic involvement is seen in 30% of children and 8.7% of adults. Children with DS take longer to develop sphincter control (4-5 years) and there may be incontinence to a greater extent (12-16%). In individuals with DS, the risk of testicular tumors is 6- 50 times higher than in the general population (0.3 to 0.7%).

Recommendations

i) A thorough physical examination to identify anomalies such as hypospadias, cryptorchidism, testicular cancer, and kidney malformations should be done. However, routine screening for renal and urological problems is not recommended.

ii) Postnatal follow up need to be done to rule out any renal problems, if anomaly scan had showed any abnormality.

iii) Yearly testicular examination should be done.

Puberty, Sexuality and Management of Menstrual Cycles

Various studies have shown that adults with DS have hypergonadotropic hypogonadism (higher levels of FSH and/or LH). This is due to Sertoli and Leydig cell dysfunction. Despite the gonadal dysfunction, puberty occurs on time and progresses at a typical rate as in other children. This emphasizes the need to counsel the caregivers to prepare children for upcoming pubertal changes [34].

Sexuality: In the past, sexuality was not considered an issue for young people with DS because of the inaccurate belief that intellectual impairment was equivalent to a state of permanent childhood. In fact, all individuals with DS do have intimacy needs and sexual feelings as in other children and should be counselled accordingly. It is important to recognize these for planning education, housing and other programs.

Fertility: Men with DS have lower fertility, but 70% of women with DS are fertile. However, there is an increased

chance of miscarriage. There is a 50% chance of having a child with DS, and a higher chance of having other congenital anomalies. Contraceptive advice should be provided by professionals with skills to support people with DS [35].

Management of menstrual cycles: Girls should be educated about menstruation in advance, so that they know whom to approach and what needs to be done. Most girls will be able to cope independently with their periods but they initially may need some support. Simple measures to treat dysmenorrhea should be taught to the caregivers. They may also experience premenstrual symptoms, but may not be able to report these symptoms. Hence, parents/ caregivers should be aware of mood changes and measures to be taken if needed.

Recommendations

i) Care givers should be counselled to prepare the children for pubertal changes.

ii) Menstrual hygiene should be taught to the children at the appropriate time.

Language, Communication and Social Development

Children with DS have a characteristic behavioral phenotype where language is the most impaired domain of functioning. This forms the greatest barrier to independent meaningful inclusion in the society. Children with Mosaic DS are noted to have better outcomes for language and cognitive abilities.

The DS phenotype is usually characterized by relative strengths in nonverbal communication skills like imitation and gestures, while verbal processing is slow compared to typical developing children of same mental age. They are often reported to progress; though delayed, through stages and sequences of prelinguistic early communication and later language development in a pattern similar to typically developing children. The general profile of language difficulties in children are in expressive language, compared to language comprehension [36,37]. These problems arise from the anatomical differences of the facial structure and due to the prevalence of hearing loss from frequent middle ear infections, which has a high incidence in the first year.

Social knowledge is the ability to analyze and reason social situations in relation to social rules necessary for social skill and social behavior development. Studies have shown that social functioning is good, but social understanding is poor compared to their normal peers. Poor vocabulary and low-requesting behavior are important predictors of social problems in these children. It is more useful to look at the sequence of development achieved, rather than the age at which it is reached.

Recommendations

i) Functional language and social assessment to be done from the age of one year onwards.

ii) Instructions should be short and clear. Teach children to hear and imitate, find their capability in sound discrimination.

iii) Concrete visual representation of language concepts to be presented.

iv) Parent-mediated intervention plans are encouraged, supporting an everyday bidirectional interaction in naturalistic settings.

v) Social skills training in understanding social situations is beneficial.

Interventional Programs, Educational and Vocational Aspects

Physical therapy with speech stimulation is to be started at birth or at least by 3 months of age [24]. Developmental therapy, occupational therapy, behavior therapy and cognitive therapy along with physical therapy and speech therapy should be initiated at the appropriate time. Psychological evaluation and support should be given as the child grows older. Management of attention deficit hyperactivity disorder (ADHD) (49%) and autistic disorders (16%) can manifest as early as 2 or 3 years of age and they should be addressed at the appropriate time. Psychiatric support, especially during adolescent age, is not to be ignored as they can have issues related to sexuality, anxiety and depression, as in any other adolescent. Support of the family, including siblings, should not be neglected, especially in the initial years of life.

Inclusive education is recommended, with special education facility at early school age, as needed. They should be enrolled in the first standard of a normal school by 7-8 years of age, based on their intellectual status. Many of the children have pursued vocational courses and some of them have become graduates. These children are highly trainable, and based on their aptitude; vocational training should be started by about 15 to 17 years (after completion of school). A suitable independent vocation should be encouraged and is preferred to group vocational activities, which should be reserved for children with moderate to severe intellectual challenges.

Recommendations

i) Early interventional programs should be started at least by three months of age.

ii) ADHD and autistic behavior should be looked for,

early, and managed.

iii) Psychiatric support should be given for the adolescent with DS and their parents.

iv) Inclusive education in a normal school should be advocated.

v) Vocational training to be initiated based on their aptitude.

Counselling

Communication with the family should start as soon as the diagnosis is suspected, preferably at birth itself. Confirmation can be made by FISH, which takes a shorter time; but karyotyping is essential to find out the type of DS and for genetic counselling. All the necessary age-appropriate tests and multi-disciplinary consultations should be completed in the shortest possible time and final counselling undertaken. Ample time should be made available to detail the child's status and to answer all the doubts raised. Both parents should ideally be present along with a support person who is acceptable to the family.

Start the counselling on a positive note providing accurate information in a balanced manner. Refer to DS as a condition and not as a disease; give importance to the person and not the condition when counselling. The associated conditions should be detailed, and the need for regular follow up should be reinforced. The absence of any disease affecting other systems can be highlighted in a positive manner, especially those systems where a high incidence is noted compared to babies who do not have DS. The possibility of other systemic involvement subsequently (e.g., hypothyroidism) should also be mentioned and the need for regular checkup should be emphasized.

The need for early interventional programs should be highlighted. Interventions should be regular and continued till advised. It should be stressed that the mainstay of treatment is the continued therapies as advised, and that there is no medicine that can modify the chromosomal status. Medicines prescribed for the systemic illnesses, if any, should be continued with regular follow up. The social issues should be discussed and their rights should be explained. The basis of management should be a bio-psycho-social strategy, together known as heath care counselling. We should take into account the biological aspect of the high incidence of physical health conditions, the psychological impact on the family and the children themselves, and social aspects such as financial support [38].

Connect them to a Down syndrome support group in the locality which will be of immense help in the months and years to follow. A designated person from the support group can act as a lay counsellor to support the family from the beginning, which will complement the efforts of the doctor.

Recommendations

i) Counselling should be initiated as soon as the diagnosis is suspected and after confirmation and full workup.

ii) A follow up chart should be provided to the parents.

iii) A bio-psycho-social strategy should be the basis of management and the need to continue interventional programs should be stressed.

iv) Connect them to a local DS support group where available.

Age-wise Recommendations

It is important to understand and empathize with the parents and find time to respond to all their queries. A proper counselling is mandatory so that they understand the need for a long-term regular follow up with stress on social and rights issues. Age wise follow-up of important medical issues till 18 years are given in **Table II** and detailed here.

At birth: Karyotyping and genetic counseling, CBC, thyroid function test (TFT), electrocardiogram (ECG), echocardiogram, systemic examination. Record head circumference (HC), weight and length. If antenatal ultrasonogram showed any abnormality, screen postnatally. Eye examination at 4-6 weeks should be done to exclude congenital glaucoma, cataract and other eye abnormalities.

6 months: TFT, full audiological review, record HC, weight and length; plot in DS specific growth charts

1 year: CBC, TFT (Free T4 and TSH once in 3 months, if hypothyroid), dental opinion, hip and foot evaluation in the first year of life. Monitor growth and development.

2 years: CBC, TFT, full ophthalmologic examination, audiology review if not done at 18 months, dental review, testicular examination, monitor growth and development.

3 years: CBC, TFT, audiology review, dental review, testicular examination, growth and development,

4 years: CBC, TFT, ophthalmology, audiology and dental review, testicular examination, growth and development,

5 years: CBC, TFT, audiology and dental review, testicular examination, growth and development.

6-9 years: TFT yearly, 2 yearly audiology and ophthalmology review, annual dental examination, testicular

Table II Follow-up of Important Medical Issues in Children With Down Syndrome Till 18 Years of Age

	At birth	*6 mo*	*1 y*	*2 y*	*3 y*	*4 y*	*5 y*	*6-9 y*	*10-18 y*
Karyotyping and genetic counselling	✓	-	-	-	-	-	-	-	-
Echocardiography	✓	-	-	-	-	-	-	-	-
Thyroid function tests	✓	✓	✓	✓	✓	✓	✓	✓[a]	✓[a]
CBC and PBS	✓	-	✓	✓	✓	✓	✓	-	-
Audiology / hearing	✓	✓	-	✓[c]	✓	✓	✓	✓[b]	✓[b]
Ophthalmology	✓	-	-	✓	-	✓	-	✓[b]	✓[b]
Dental	-	-	✓	✓	✓	✓	✓	✓[a]	✓[a]
Testicular examination	-	-	-	✓	✓	✓	✓	✓[a]	✓[a]
Growth / development	✓	✓	✓	✓	✓	✓	✓	✓[a]	✓[a]

✓: *indicates evaluation to be done; - indicates evaluation not to be done, unless clinically indicated.* [a]*Every year;* [b]*once in 2 years;* [c]*at 2 years if not done at 18 months. Routine vaccinations should not be skipped; and the need for pneumococcal conjugate/ polysaccharide vaccine, influenza and varicella vaccines should be stressed. Evaluation and investigations to be done more frequently, if warranted.*

examination, growth and development. Life skills programs with special focus on inter-personal relationships to be initiated.

10-18 years: Continue as in 6-9 years. In puberty: discuss physical and psychological changes, need for gynecologic care in pubescent females.

Interventional programs: Developmental therapy, physical therapy, occupational therapy, speech stimulation/ therapy, behavior therapy, cognitive therapy, psychological support for child and family. Early interventional programs should be started at least by 3 months of age.

CONCLUSIONS

Persons with DS have only mild to moderate intellectual disability and have high potential to develop skills in various fields. Early interventional programmes along with early detection and management of associated systemic issues can help these persons lead a disease free independent life. The care-givers should be counselled about the condition and the need for sustained interventional therapy as advised; the medical personnel should be sensitized and trained to provide the right management using a uniform country specific protocol.

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REFERENCES

1. John ST, Gayathri K, Sahasranam K. Cytogenetic patterns, congenital heart disease and thyroid dysfunction in children with Down syndrome. J Pediatr. 2022;245:196-200.
2. Nair MKC, Leena ML, Ajithkumar K. Concept of Health Care Counseling for Pediatricians. Indian Pediatr. 2016;53:961-3.
3. John ST, Gayathri K. Screening of mothers to detect Down syndrome: a practical approach in a resource limited setting. Int J Contemp Pediatr. 2022;9:566-70.
4. Nicolaides KH. Screening for fetal aneuploidies at 11 to 13 weeks. Prenat Diagn. 2011;31:7-15.
5. Akolekar R, Beta J, Picciarelli G, et al. Procedure-related risk of miscarriage following amniocentesis and chorionic villus sampling: A systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2015;45:16-26.
6. Gil MM, Akolekar R, Quezada MS, Bregant B, Nicolaides KH. Analysis of cell-free DNA in maternal blood in screening for aneuploidies: Meta-analysis. Fetal Diagn Ther. 2014;35:156-73.
7. Gardner, RJM, Sutherland, GR. Chromosome abnormalities and genetic counseling.5 th ed. Oxford University Press. 2018.
8. Cuckle HS. Primary prevention of Down's syndrome. Int J Med Sci. 2005;2:93-9.
9. Kaur H, Bhalla AK, Panigrahi I. Percentile Charts for Body Mass Index of Indian down syndrome children. J Pediatr Genet. 2021;11:261-6.
10. Bertapelli F, Pitetti K, Agiovlasitis S,et al. Overweight and obesity in children and adolescents with Down syndrome-prevalence, determinants, consequences, and interventions: A literature review. Res Dev Disabil. 2016;57:181-92.
11. Centre for Disease Control and Prevention. Birth Defects. Growth Charts for Children with Down Syndrome. Dec 2022. Accessed on Jan 10, 2023. Available from: *https://www.cdc.gov/ncbddd/birthdefects/downsyndrome/growthcharts.html*
12. Narayanan DL, Yesodharan D, Kappanayil M, et al. Cardiac spectrum, cytogenetic analysis and thyroid profile of 418 children with Down syndrome from South India: A cross-sectional study. Indian J Pediatr. 2014;81:547-51.
13. Whooten R, Schmitt J, Schwartz A. Endocrine manifestations of Down syndrome. Curr Opin Endocrinol Diabetes Obes. 2018;25:61-6.

14. Bull MJ, Trotter T, Santoro SL, et al. Health supervision for children and adolescents with Down syndrome. Pediatrics. 2022:149:e2022057010.
15. Iughetti L, Predieri B, Bruzzi P, et al. Ten-year longitudinal study of thyroid function in children with Down's syndrome. Horm Res Paediatr. 2014;82:113-21.
16. Karlsson B, Gustafsson J, Hedov G, et al. Thyroid dysfunction in Down's syndrome: relation to age and thyroid autoimmunity. Arch Dis Childhood. 1998;79:242-5.
17. Purdy IB, Singh N, Brown WL, et al. Revisiting early hypothyroidism screening in infants with Down syndrome. J Perinatol. 2014;34:936-40.
18. Pierce MJ, LaFranchi SH, Pinter JD. Characterization of thyroid abnormalities in a large cohort of children with Down syndrome. Horm Res Paediatr. 2017;87:170-8.
19. Rivkees S, Bauer AJ. Thyroid disorders in children and adole-scents. *In*: Sperling MA, Majzoub JA, Ram K, Menon RK, Stratakis CA (eds). Sperling Pediatric Endocrinology, 5th ed. Elsevier, 2021.
20. Skogberg G, Lundberg V, Lindgren S, et al. Altered expression of autoimmune regulator in infant down syndrome thymus, a possible contributor to an autoimmune phenotype. J Immunol. 2014 2014;193:2187-95.
21. Annerén G, Gustavson KH, Sara VR, Tuvemo T. Growth retardation in Down syndrome in relation to insulin-like growth factors and growth hormone. Am J Med Genet Suppl. 1990;7:59-62.
22. Hsiang YH, Berkovitz GD, Bland GL, et al. Gonadal function in patients with Down syndrome. Am J Med Genet. 1987;27:449-58.
23. García-Hoyos M, Riancho JA, Valero C. Bone health in Down syndrome. Med Clin (Barc). 2017 Jul 21;149:78-82.
24. Roche E, Hoey H M C V, Murphy J. Hearing impairment. Medical management of children and adolescents with Down syndrome in Ireland. 2015; :18-19.
25. Charleton P, Woodhouse M. Vision and eye disorders. *In*: Newton RW, Puri S, Marder L, eds. Down syndrome: Current perspectives. 2015;77-87
26. Tunstall O, Bhatnagar N, James B, et al. Guidelines for the Investigation and Management of Transient Leukaemia of Down Syndrome. Br J Haematol. 2018;182:200-11.
27. Webb D, Roberts I, Vyas P. Haematology of Down syndrome. Arch Dis Child Fetal Neonatal Ed. 2007;92: F503-7.
28. Ryan C, Vellody K, Belazarian L, Rork JF. Dermatologic conditions in Down syndrome. Pediatr Dermatol. 2021;38: 49-57.
29. Selby KA, Newton RW, Gupta S, Hunt L. Clinical predictors and radiological reliability of atlantoaxial subluxation in Down syndrome. Arch Dis Child. 1991;66: 876-78.
30. Marder L, Nunn J. Oral and Dental health. *In*: Newton RW, Puri S, Marder L, eds. Down syndrome: Current perspectives. 2015;229-237.
31. Holmes G. Gastrointestinal disorders in Down syndrome. Gastroenterol Hepatol Bed Bench. 2014;7:6-8. 32.
32. Jackson PD, Gillet P, Almond S. Gastrointestinal disorders. In: Newton RW, Puri S , Marder L, eds. Down syndrome: Current perspectives. 2015;165-80.
33. Mora-Bautista VM. Congenital anomalies of the kidney and the urinary tract in Down syndrome children. Internet. Rev Colomb Nefrol. . 2018];5:54-60.
34. McCall C, Straw F. Puberty adolescence and sexual health. Health series. Down syndrome Association Publication. 2018:1-19.
35. Schwab W. Sexuality in Down syndrome brochure. Clinical information series. National Down Syndrome Society. 2005. Accessed on Jan 10, 2023. Available from: *https://www.ndss.org/resources/relationships-sexuality*
36. Howell, P. Speech control in children with Down Syndrome. Down Syndrome Research and Practice. 2010;12: 98-102.
37. Roberts J E, Price J, Malkin C. Language and communication development in Down syndrome. Ment Retard Dev Disabil Res Rev. 2007;13:26-35.
38. Harvey B. Down's syndrome: a biopsychosocial perspective. Nursing Standard. 2004;18:43-5.

ANNEXURE I

Expert Committee

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