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IAP Handbook of Developmental and Behavioral Pediatrics

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Contents

1. **A History of Developmental Behavioral Pediatrics: An Idea whose Time has Come 1**
   Samir H Dalwai
2. **Normal Development and Behavior 6**
   Kawaljit Singh Multani
3. **Theories of Normal Development and Behavior 13**
   Kawaljit Singh Multani
4. **Developmental Concerns in Pediatric Practice 21**
   YK Amdekar
5. **Developmental Surveillance and Screening 24**
   Leena Deshpande
6. **Approach to Global Developmental Delay 28**
   Leena Srivastava
7. **Developmentally Supportive Care 35**
   Naveen Jain
8. **Follow-up of the High-risk Newborn 40**
   Rhishikesh Thakre
9. **Genetics and Neurodevelopmental Disorders 48**
   Rashid Merchant, Snehal Mallakmir, Ami Shah
10. **Intellectual Disability 54**
    Samir H Dalwai, Aradhana Rohil
11. **Multiple Disabilities 59**
    Leena Deshpande
12. **Down Syndrome 62**
    A Somasundaram
13. **Turner Syndrome 70**
    Shambhavi Seth
14. **Noonan Syndrome 74**
    Kawaljit Singh Multani
15. **Fragile X Syndrome 81**
    MA Florita, B Yambao-Dela Cruz, Kaye M Napalinga, Randi J Hagerman

JAYPEE BROTHERS

16. Klinefelter Syndrome 85
Kawaljit Singh Multani

17. Prader-Labhart-Willi Syndrome 89
Manju George Elenjickal, Neethu Mary Mathew

18. Angelman Syndrome 92
Shabina Ahmed

19. Williams Syndrome 95
Jyoti Bhatia

20. Neurofibromatosis 99
Z Bassi

21. Tuberous Sclerosis 104
Z Bassi

22. Mucopolysaccharidosis: Developmental and Behavioral Outcomes 109
Shibani Kanungo, Neelkamal Soares

23. Rett Syndrome 115
Leena Srivastava

24. Sleep Disorders 120
Leena Srivastava, Kawaljit Singh Multani

25. Feeding Disorders 128
Leena Deshpande

26. Elimination Disorders 132
Kawaljit Singh Multani

27. Seizures and Epilepsy 137
Sarbani Raha, Vrajesh Udani

28. Cerebral Palsy 143
Anaita Udwadia-Hegde, Omkar Pradip Hajirnis

29. Movement Disorders in Children with Neurodevelopmental Disorders 147
Abhishek R Jain, Lokesh Lingappa

30. Neuroregressive Disorders 154
Shekhar Patil

31. Inborn Errors of Metabolism: Developmental and Behavioral Outcomes 158
Shibani Kanungo, Neelkamal Soares

JAYPEE BROTHERS

32. Traumatic Brain Injury 162
Prameela Joji

33. Neuromalignancies and Developmental Outcomes.....166
Vasudha N Rao, Samir H Dalwai

34. Attention Deficit Hyperactivity Disorder 170
Samir H Dalwai, Hilla Sukhadwala

35. Disruptive Behavior Disorders 175
Leena Deshpande

36. Anxiety.....180
Manoj Bhatawdekar

37. Depressive Disorders.....185
Kersi Chavda, Alka A Subramanyam

38. Tics.....190
Kawaljit Singh Multani

39. Hearing Abnormalities in Children: Assessment and Management.....195
Abraham K Paul

40. Visual Impairment 202
Neepa Thackar Dave

41. Balance Disorders and Dizziness in Children.....205
Waheeda Pagarkar

42. Developmental Coordination Disorder 211
Leena Deshpande

43. Sensory Processing Disorders: Developmental Aspects.....215
Leena Deshpande

44. Language and Speech Disorders.....220
Patricia Osbourn

45. Selective Mutism.....223
Samir H Dalwai

46. Medical Comorbidities in Autism Spectrum Disorder 227
Yamini Jagannath Howe, Ann M Neumeyer

47. Autism Spectrum Disorder 231
Samir H Dalwai

48. Scholastic Backwardness 239
SS Kamath, Kawaljit Singh Multani

JAYPEE BROTHERS

49. Development Behavioral Disorders in Adolescence 243
Dilip R Patel, Swati Y Bhave

50. Specific Learning Disability 248
Samir H Dalwai, Hilla Sukhadwala

51. Child Abuse 253
Shabina Ahmed

52. Role of Evaluation in Developmental Behavioral Pediatrics 256
Anjan Bhattacharya

53. Early Intervention 261
Zafar Mahmood Meenai

54. Therapies and Interventions 266
Lata Bhat

55. Principles of Pharmacotherapy in Developmental and Behavioral Pedaitrics 272
Jeeson C Unni

56. Counseling 276
Leena Deshpande, Lavanya Iyer

57. Electronic Media and Gadgets 281
Samir H Dalwai, Barkha Chawla

58. Technology in Practice 287
Kawaljit Singh Multani

59. Complementary and Alternative Medicine in Developmental Pediatrics 291
Shambhavi Seth

60. Medicolegal Issues in Developmental and Behavioral Pediatrics 294
Santhosh Rajagopal

Index 299

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Chapter 16

Klinefelter Syndrome

Kawaljit Singh Multani

"Children are not things to be molded, but are people to be unfolded."
Jess Lair

INTRODUCTION

"Klinefelter syndrome" (KS) is the most common genetic cause of male infertility and has an estimated frequency of 1 in 500–1 in 1,000 males. Harry Klinefelter, Fuller Albright, and EC Reifenstein reported a series of nine men with gynecomastia, small testes, and azoospermia in 1942 which was named as Klinefelter–Reifenstein–Albright syndrome. Later in 1959, it was demonstrated by Patricia Jacobs and John Anderson that such cases have an additional X chromosome resulting in a 47, XXY karyotype. This additional X chromosome results in disruption of many aspects of fetal development which results in characteristic phenotype of KS.

Most of the cases (80–90%) have the karyotype (47,XXY) while the rest (10–20%) either have mosaic pattern (47,XXY/46,XY), or additional X chromosomes (48,XXXY or 48,XXYY) or structurally abnormal X chromosomes (47,XiXqY). The condition is not inherited and the additional X chromosome results from nondisjunction of sex chromosomes during meiosis I in the gonads and is inherited from the father in 50% and the mother in 50% of the cases. The risk is increased with increased maternal age as chromosomal abnormalities tends to increase with age.

CLINICAL DIAGNOSIS

Most of the children born with KS are normal at birth and the initial few years. Few cases have cleft palate, clinodactyly, cardiac abnormalities, inguinal hernia, cryptorchidism, hypospadias, or micropenis and these are more frequently seen in cases with higher degree of chromosomal abnormalities. Children with KS are taller than others and have muscle weakness which becomes more pronounced with age. Motor delays (developmental

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coordination disorder), speech delays (poor expressive speech), and learning disabilities [reading problems and specific learning disability (SLD)] are also found in patients with KS. They also tend to have emotional issues, anxiety, depression, limited problem-solving skills, and poor social skills. 10% of the cases can have autism spectrum disorder (ASD).

More than 75% of the cases are diagnosed after puberty. At puberty, boys (>50% of cases) develop gynecomastia, have small testes (<4 mL testicular volume) and less facial and bodily hair. Eunuchoid body structure (tall, slim with long legs and arms, and arm span exceeding height by ≥5 cms) with gynecomastia and androgen insufficiency is the hallmark of a case of KS. In a large case series of 44 patients, it was seen that two-thirds of the cases were diagnosed after 18 years of age and dysmorphism, developmental delays, cardiac abnormalities, intellectual disabilities, and behavioral issues [depression and attention deficit hyperactivity disorder (ADHD)] were commonly seen in pediatric population as compared to adults. Due to the additional X chromosomes, these males are prone to autoimmune disorders, thromboembolic phenomenon and osteoporosis. Almost half of the cases develop a metabolic syndrome (increased belly fat, hypertension, elevated lipids, and type II diabetes mellitus). Persons with KS have a 20–50 folds increase in risk of breast cancer as compared to normal population.

Differential diagnosis of KS includes Fragile X syndrome, Kallman syndrome, and Marfan syndrome. Diagnosis of KS should be suspected in all male children with delayed puberty, tall stature, small testes, and gynecomastia. Diagnosis can be confirmed by karyotyping. They have low testosterone levels and elevated follicle-stimulating hormone/luteinizing hormone (FSH/LH) levels with FSH levels being much higher as compared to LH. Serum testosterone levels continue to fall with age. Semen examination may reveal azoospermia or low sperm count with poor motility. Fibrosis of seminiferous tubules is seen in testicular histology.

MANAGEMENT

As the condition is genetic, the management is mainly supportive once the diagnosis has been made. A developmental intervention program in cases with motor delay as well as specific case-based interventions can be of use in school going children who have school/socialization issues and dyspraxias.

Hormonal replacement therapy with testosterone can be used for improving masculinity (increase in muscle mass and hair growth) as well as reduce the chances of osteoporosis. Intramuscular injections of testosterone can be given every 3 weeks; initial doses are kept low and as puberty advances the dose is increased **(Fig. 1)**. Depot preparations of testosterone (once in 3 months) are also available. Gynecomastia may persist despite treatment with

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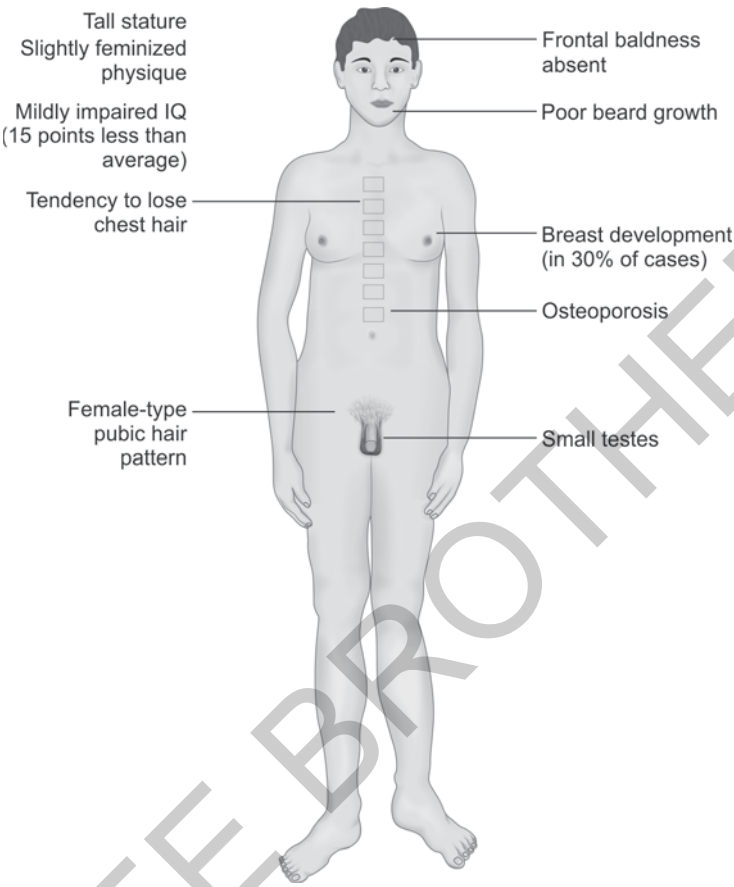

Fig. 1: Features of the Klinefelter's syndrome.

testosterone and require surgical resection. 3.1% of all males with infertility have KS. With the availability of intracytoplasmic sperm injection (ICSI) and testicular sperm extraction (TSE), it is now possible for men with KS to father children.

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Chapter 41

Balance Disorders and Dizziness in Children

Waheeda Pagarkar

INTRODUCTION

Balance disorders and dizziness are common in children, questionnaire studies worldwide estimating their prevalence between 5 and 18%. This may be an underestimate, as younger children may not have the language to report this symptom, and it often commands less medical attention than other somatic symptoms in a pediatric clinic.

Dizziness is a nonspecific term to denote a sense of unsteadiness or light-headedness whereas vertigo is an "illusion of movement" in the rotational or translational plane. Vertigo can be described as "spinning or tilting or moving" sensation of surroundings or of self. Whereas dizziness can be caused by a number of systemic and vestibular causes, vertigo implies a deficit in the vestibular system.

Balance is a complex multisensory function which depends on sensory input from the visual, proprioceptive, and vestibular systems. These inputs are integrated in the central nervous system and help to maintain posture through neural pathways such as the vestibulospinal tracts. The connections of these sensory pathways with the cerebral cortex are responsible for our spatial perception of posture and movement and, in disease states, for the sensation of dizziness. Conflict between these sensory inputs can lead to motion sickness, a common condition in children and adults.

The vestibular system serves two main functions, i.e., development of motor milestones and balance (through vestibulospinal pathways) and stabilizing the eyes during head movements, (through the vestibulo-ocular reflex), e.g., during reading and walking. This reflex is the reason why we do not see the world wobble, when we move our head! Vestibular dysfunction is more common in children with hearing loss affecting 30–60% of these children.

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CLINICAL DIAGNOSIS

Balance difficulties and dizziness in children can be due to vestibular, neurological, and other causes, which can vary from being innocuous (vasovagal) to being serious (intracranial tumors) **(Box 1)**. Children present to the pediatric clinic with delayed motor milestones, frequent falls, and clumsiness. Dizziness and vertigo can be described as "being on a merry-go-round", "walls falling", "being pushed", and "head feeling funny".

Box 1: Causes of balance disorders and dizziness in children.

- Vestibular migraine and benign paroxysmal vertigo (BPV; migraine variant)
- Neurological disorders:
  - Anatomical abnormalities: hydrocephalus, Arnold Chiari malformation
  - Space occupying lesions, e.g. medulloblastoma
  - Epilepsy causing "funny turns"
  - Neurodevelopmental disorders: Cerebral palsy and developmental coordination disorder
  - Neuromuscular diseases, e.g., Duchenne muscular dystrophy
  - Neurodegenerative disorders, e.g., Charcot Marie tooth, Friedrich's ataxia, mitochondrial disorders, and episodic ataxia
  - Genetic syndromes causing developmental delay: Down syndrome and 22q deletion
- Vestibular diseases:
  - Trauma: concussion, fracture temporal bone, fistula, and cochlear implant surgery
  - Ototoxicity: Gentamicin, streptomycin, and amikacin
  - Middle ear disease: Chronic suppurative otitis media, cholesteatoma, otitis media with effusion
  - Anatomical abnormality of vestibular organs: vestibular malformations, dilated vestibular aqueducts, and semicircular canal dehiscence
  - Infections/inflammation: Vestibular neuritis, labyrinthitis, bacterial meningitis, congenital CMV, and autoimmune inner ear disease
  - Vestibular hypofunction with deafness: Usher, Pendred, Alstron, auditory neuropathy, Jervell and Lange-Nielsen
  - Others: Meniere's disease, benign paroxysmal positional vertigo (BPPV; different from BPV), vestibular paroxysmia, motion sickness, autoimmune disorders, and Cogan's syndrome
- Cardiac:
  - Arrythmias
  - Postural hypotension/postural tachycardia syndrome (POTS)
  - Vasovagal syncope
- Metabolic:
  - Anemia, vitamin D deficiency, diabetes, thyroid dysfunction, and electrolyte imbalance
- Ocular:
  - Squint and uncorrected refractive errors
- *Skeletal disease*: Mucopolysaccharidosis scoliosis and rheumatoid arthritis
- Psychogenic:
  - Anxiety disorders and nonorganic symptom

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Migraine and benign paroxysmal vertigo (BPV) are the most common causes of vertigo in children and diagnosis is based on clinical history.

Vestibular Migraine

This is the most common cause of dizziness in children, accounting for 30–40%. It presents as sudden onset episodic dizziness lasting for hours, with or without headaches, photophobia, phonophobia, visual symptoms, nausea, and vomiting. There is often a trigger such as stress, infection, and diet (cheese, chocolate, and caffeine). A family history of migraine and motion sickness is often present.

Benign Positional Vertigo

This presents between 2 and 4 years of age, as sudden onset of paroxysmal, recurrent episodes of vertigo lasting for a few seconds to minutes, and rarely hours. The child appears frightened, sweaty, anxious, pale, imbalanced, or may stay immobile. Older children may complain of "spinning". Children may have nausea and vomiting; and spontaneous nystagmus may be seen. Differential diagnosis in this age group includes epilepsy and posterior fossa or cerebellopontine angle tumors. The diagnosis is clinical and one of exclusion and rests on the typical history and normal findings on examination. This is a migraine variant, which resolves as the child gets older, but may evolve into migraine headache.

Points to Remember

- Vestibular disorders are often overlooked in a general pediatric clinic and should be included in the differential diagnosis, particularly where hearing loss is present.
- Loss of consciousness should prompt neurological/cardiac investigations. It is not a feature of vestibular disease.
- Psychological causes are seen in children older than 7 years.
- Vestibular loss occurs in 40–80% of children with bacterial meningitis and is more common than deafness.

Key Points to Note in History

- Detailed milestones and evidence of regression
- Duration of vertigo, triggers, associated symptoms, relation to position
- Seizures, headaches, loss of consciousness, and focal neurological symptoms (neurological)
- Hearing and ear discharge (vestibular causes)
- Systemic symptoms: Palpitations and syncope (cardiac)

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- Vision
- Psychological history.

Key Points in Clinical Examination

- *General examination*: Anemia and dysmorphism
- *Full neurological examination*: Focal/generalized weakness
- *Eye movement examination*: For squint, smooth pursuit, saccades, and nystagmus
- Skeletal system examination including spine, feet, and joints
- Cardiac examination and blood pressure in lying and standing positions
- Ears, nose, throat (ENT) examination
- *Examination of neonatal reflexes*: Moro reflex, head righting reflex, and parachute reflex are mediated by vestibular inputs and their presence in a floppy infant indicates presence of vestibular function
- *Examination of the vestibular system:*
  - *Posture and gait tests*: Romberg test, standing on one leg, standing on foam, tandem gait, and Unterberger test. Children with neurological conditions and vestibular hypofunction will have difficulty doing these tests.
  - *Vestibulo-ocular reflex tests*: These tests are specific for vestibular pathology:
    - *Head thrust test*: The child is asked to focus on the examiner's nose. A rapid sudden head rotation in the yaw plane (like saying "no") to the right or left of approximately 30° is made. A "catch-up" saccade indicates hypofunction of the lateral semicircular canal on the side of the head thrust. This is the single most useful test in detection of vestibular hypofunction.
    - *Head shaking nystagmus/vibration-induced nystagmus*: These tests serve to bring out vestibular asymmetry by use of head shaking and vibration.
    - *Dynamic visual acuity*: A simple test that can be done in the clinic with use of a visual acuity chart. The child is asked to read a vision chart from a distance of 1.5 m with the head steady to obtain their baseline visual acuity. The child's head is then rotated horizontally (like saying "no") at 1–2 Hz. A loss of three lines or more of visual acuity may indicate vestibular hypofunction.
  - *Other tests*: Dix-Hallpike test [diagnostic of benign paroxysmal positional vertigo (BPPV)] and Tullio test (for semicircular canal dehiscence).

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Investigations

These are necessary only in selected children and are guided by history and examination. Blanket use of expensive tests is not useful.

- *Magnetic resonance imaging (MRI) scan*: Where hydrocephalus or a space occupying lesion is suspected, investigation of sensorineural hearing loss
- *Electroencephalography (EEG)*: For suspected seizures in "Funny turns"
- *Electrocardiogram (ECG)/Holter monitoring/cardiology referral*: If cardiac symptoms syncope
- *Blood tests*: Anemia, vitamin D, calcium
- *Microarray*: With undiagnosed dysmorphism
- *Relevant neurometabolic investigations*: With neuroregression.

Vestibular Function Tests

Their availability for children is limited, expensive, and involves a degree of cooperation that is not always forthcoming in children. They can be used for children with permanent hearing loss and suspected vestibular hypofunction and include:

- Video head impulse test
- Computerized rotational chair testing
- Bithermal caloric testing
- *Cervical/ocular vestibular evoked myogenic potentials (VEMPs)*: Can be done using special software on a brainstem evoked response audiometry (BERA) machine
- Computerized dynamic posturography
- Subjective visual vertical.

MANAGEMENT

This depends on management of the underlying cause. Migraine is amenable to prophylactic treatment with drugs such as propranolol, pizotifen and topiramate, if symptoms impact on quality of life. Management of otologic conditions with appropriate medication and surgery proves useful. Children with vestibular deficits often compensate using their residual vestibular function, visual, and proprioceptive information, due to the inherent plasticity of the nervous system, improving overtime. Children with bilateral vestibular hypofunction should use thin-soled shoes to optimize proprioception and well lit surroundings to provide visual input to maintain balance. They will need supervision during swimming as disorientation can occur when the head is underwater. Vestibular physiotherapists can advise on vestibular rehabilitation exercises to improve balance and vertigo in children with vestibular disorders.

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IAP Handbook of
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Salient Features

- A comprehensive textbook on development and behavioral pediatrics
- A desktop reference for pediatricians and students of neurodevelopmental pediatrics.

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