Issue 1 | Volume 35 | July-September 2020

Print ISSN 0975-5152

Karnataka Pediatric Journal

Official Publication of IAP Karnataka State Branch

IAP Karnataka State Branch
www.iap-kpj.org

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Karnataka Pediatric Journal (KPJ) is an open-access peer-reviewed journal committed to publishing high-quality articles in the field of Pediatrics. The journal is owned by the Indian Academy of Pediatrics Karnataka State Branch and published by the Scientific Scholar. Journal follows a double-blind review process with quarterly frequency.

Information for Author

Karnataka Pediatric Journal does not charge any processing fees to the authors for submission or on acceptance. All manuscripts must be submitted online at: https://editorialassist.com/kpj

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Printed and Published by

Pritesh Sheth on behalf of the owners Indian Academy of Pediatrics Karnataka State Branch **Printed at** Dhote Offset Technokrafts Pvt Ltd., 2nd Floor, Paramount P, Plot No 5A, Above Book ER, Off Aarey Road, Near Pravasi Ind Est, Opposite Gambhir Ind Est, Goregaon (E), Mumbai, Maharashtra. India and **Published at** Scientific Scholar Pvt Ltd., 301, Annex Dimple Arcade, Asha Nagar, Behind Sai Dham Temple, Thakur Complex, Kandivali East-400101, Mumbai, Maharashtra, India. **Editor:** Dr. Bhaskar Shenoy.

Karnataka Pediatric Journal

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Karnataka Pediatric Journal

Editorial

Genesis - Karnataka Pediatric Journal

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Received : 13 August 2020
Accepted : 13 August 2020
Published :

DOI
10.25259/KPJ_17_2020

Quick Response Code:

I am immensely proud to pen few words on the genesis of Karnataka Pediatric Journal of our State Branch of Indian Academy of Pediatrics over three and a half decades ago.

Indian Academy of Pediatric Karnataka state branch in its executive committee meeting held at Mysore, decided to publish a Karnataka pediatrics journal to encourage young pediatricians to publish their work quickly. It is a felt need for budding pediatricians of then. The Karnataka Pediatrics Journal's first issue is released in the VIth Karnataka State pediatric conference held at Mangalore on August 22, 1987, under the editorship of Dr. B Sanjeev Rai.

He continued as an editor till 2019.

Dr. Varadaraj Shenoy was the Editor for a year in 1994–1995, during the Presidentship period of Dr. Sanjeev Rai.

Dr. Sudharshan Shetty was elected as an Editor, and Sanjeev Rai continued as Editor-in-Chief from 2013 onwards.

Dr. Bhaskar Shenoy was elected as the Editor-in-chief from 2020.

The cost of the journal printing, overcome by contributions from the members, and the proceedings of the State/National Pediatric Conference held in Karnataka's contributions.

KPJ was published for over three decades without any financial contributions from the pharmaceutical industries as per the wishes of pediatric colleagues.

I sincerely thank all my editorial members from time to time and all our pediatric colleagues who have contributed to the journal printing cost.

My special thanks to pediatric colleagues of KMC and Father Muller Medical College for their unstinted support and contributions for bringing out KPJ issues year after year. I also thank the organizers of the State and National Pediatric Conference of Karnataka, who reimbursed printing the conference issue of the KPJ.

Last but not least, our research article contributors that made the journal running.

I am also indebted to the successive presidents and the executive board members for supporting the additional costs of printing from the inception of this journal.

Dr. Bhaskar Shenoy was elected as a new editor in chief from 2020 onwards.

We, members of the KPJ editorial board, wish team KPJ all the best.

I am sure that under dynamic editorship and experience of Dr. Bhaskar Shenoy and his team, our journal will reach the international standards with high-impact factors.

I wish him and his team all the best.

How to cite this article: Rai BS. Genesis write-up. Karnataka Pediatr J 2020;35(1):1.

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Karnataka Pediatric Journal

Editorial

From the desk of Editor in Chief

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Received : 27 August 2020
Accepted : 27 August 2020
Published :

DOI
10.25259/KPJ_18_2020

Quick Response Code:

Dear IAPians,

At the outset, I would like to express my sincere gratitude to IAP Karnataka for selecting me as editor-in-chief of this prestigious journal. I should place on record the services rendered by Dr. Sanjeev Rai as editor-in-chief of this journal for nearly 20 years. The responsibility on me is huge, I am happy to present the first issue of the journal July–September 2020. Although the first issue was supposed to be published from January 2020, due to unforeseen circumstances and prevailing pandemic, we could not do that. The most important goal would be to publish high-quality articles and to get the journal indexed. This process needs support and guidance from you all, especially if you could contribute original articles, review articles, and case reports to make the journal go strong.

The present issue contains very interesting and relevant articles. The article on cerebral palsy is a complete review incorporating recent advances in management of cerebral palsy.

In the article on "clinicians dilemma in the management of acute flare up of wheeze and asthma," the author has discussed the current management guidelines. Asthma is an earliest onset non communicable respiratory disease with significant psycho-socioeconomic burden. In the diagnosis of allergic disorders in children, the emphasis is still on a good clinical history and examination, demonstration of IgE-mediated reaction with correlated ingested foods either with skin prick test or *in vitro* testing, patient education about avoidance of causative foods, and treatment of allergic reactions.

The original article on pulmonary function tests in children with beta-thalassemia major is a very interesting study of lung function in children with beta-thalassemia. Lung dysfunction is among the least studied complication in thalassemic child. Antimicrobial resistance is a global problem and is particularly pressing in developing countries where the infectious disease burden is very high. In developing countries, where relatively easy availability and higher consumption of medicines have led to disproportionately higher incidence of inappropriate use of antibiotics and greater levels of resistance. The current article is an attempt to provide a set of key principles to guide the efforts to improve responsible and rational antibiotic use.

Asthma is the most common chronic respiratory illness affecting children. Inhaled corticosteroids (ICSs) form the main treatment modality in asthma. Anticipating the impact of steroids on bone metabolism and monitoring for it is essential. Annual monitoring of Vitamin-D levels and BMD in children on chronic therapy is beneficial for the early detection and management of steroid-induced osteopenia. Judicious ICSs use at the lowest effective dose should be tailor-made for every individual. These issues are discussed in the article "Vitamin D status and bone mineral density in children on long-term inhaled corticosteroids." In addition, an interesting case of

Senior Loken syndrome has been included. We have a regular section on journal bits.

I thank the managing editor Dr. Vinod Ratageri who has been the backbone of this journal, all the editorial board members, authors, reviewers, Dr. Sanjeen Rai, and Dr. Santosh Soans for guiding me in every stage in making this issue get published. I thank the publishers Scientific Scholars for the excellent support in the publication process. I thank Microlabs for the generous contribution for this academic endeavor, without whose support, publication of this journal would not have been possible. I would like to express my gratitude to Dr. Shantaraj (President IAP Karnataka 2020) and Dr. Natesh (Secretary, IAP Karnataka 2020) for their unstinted support and guidance in bringing out this journal.

Stay safe Stay healthy

JAI IAP

How to cite this article: Shenoy B. Editorial. Karnataka Pediatr J 2020;35(1):2-3.

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Karnataka Pediatric Journal

Review Article

Recent advances in cerebral palsy

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Received : 02 June 2020
Accepted : 07 June 2020
Published :

DOI
10.25259/KPJ_1_2020

Quick Response Code:

ABSTRACT

The words unpreventable, incurable, and untreatable are still synonymous with cerebral palsy (CP). However, research and evidence coming from the fields of neuroplasticity, neuroregeneration, and neuroprotection provide considerable cause for optimism for children with CP. There are now at least 64 different interventions for CP seeking 131 outcomes. A search of the Cochrane Library, PubMed, and Google Scholar was made using the keywords: CP, static encephalopathy, birth asphyxia, perinatal insult, hypoxic-ischemic encephalopathy, and neonatal encephalopathy. We found evidence to suggest that following interventions: Anticonvulsant drugs, ankle casting, botulinum toxin for focal spasticity, bisphosphonates, diazepam, hip surveillance, and dorsal rhizotomy are effective. The following interventions improve function: Bimanual training, constraint-induced movement therapy, context focused therapy, goal-directed/functional training, home programs, and occupational therapy. These interventions are effective if started early in life. Therapies such as hyperbaric oxygen, hip bracing, and neurodevelopmental therapy when child contractures are already developed are ineffective. In the last decade, the evidence on CP has rapidly expanded, providing clinicians and families with the possibility of newer, safer, and more effective interventions. In this update, the author reviews the current evidence of the management of CP and provides a comprehensive evaluation and multidisciplinary management.

Keywords: Cerebral palsy, Birth asphyxia, Hypoxic-ischemic encephalopathy, Early intervention, Multidisciplinary management, Early intervention requires early identification, Of infants with possible cerebral palsy

INTRODUCTION

Cerebral palsy (CP) is a well-recognized neurodevelopmental condition beginning in early childhood and persisting through the lifespan. Originally reported by Little in 1861 and originally called "cerebral paresis."[1] The incidence of CP is 2–2.5/1000 live births[2] and the resulting disability varies from mild to total dependence. "The definition of CP describes a group of disorders of the development of movement and posture, causing activity limitation that is attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of CP are often accompanied by disturbances of sensation, cognition, communication, perception, and/or behavior, and/or by a seizure disorder."

ETIOLOGY OF CP

W. J. Little in the 1840s, assertion that nearly all cases of CP what he called spastic rigidity of newborns resulted from preterm birth or asphyxia at birth has left an enduring mark on subsequent thinking about the etiology. Later Sigmund Freud cautioned against assuming these two factors as fully causal, but only in the latter half of the 20th century did research begin to illustrate the complex nature of this disease and associated etiological factors. Present-day evidence suggests

that about 80% of CP is caused by an in-utero brain injury; only 10% occurs around the time of birth and 10% occurs in early childhood.[3] In a recent systematic review, ten risk factors have been reported to be significantly associated with CP and these are placental abnormalities, major and minor birth defects, low birth weight, meconium aspiration, emergency cesarean section, birth asphyxia, neonatal seizures, respiratory distress syndrome, hypoglycemia, and neonatal infections.[4] Various other risk factors are shown in [Table 1]. In India, still, perinatal risk factors are a major cause of CP. A study done by Gowda *et al*. showed that birth asphyxia is the main risk factor in 45% of children with CP.[5]

NEUROPATHOLOGICAL ASPECTS OF PERINATALLY ACQUIRED CP IN PRETERM AND FULL TERM

For better conceptualization of topic, pathology can be divided into three parts: Encephalopathy of prematurity, ischemic injury in term infant, and perinatal stroke. Major neuropathological varieties of neonatal hypoxic-ischemic encephalopathy are selective neuronal necrosis, parasagittal cerebral injury, periventricular leukomalacia (PVL), and focal (and multifocal) ischemic brain necrosis-stroke

SELECTIVE NEURONAL NECROSIS: PATTERNS OF INJURY

Selective neuronal necrosis is the most common variety of injuries observed in neonatal hypoxic-ischemic encephalopathy. Three basic patterns derived from clinical and brain imaging are diffuse- very severe and very prolonged, cortex with deep nuclear (putamen, thalamus) – moderate to severe and prolonged and deep nuclear with brain stem-severe and abrupt. Two other patterns, pontosubicular neuronal injury and cerebellar injury, occur, particularly in premature infants. The development of CP can be considered the result of a remarkable series of events that occur in the brain during its development. Understanding etiological factors and pathways involved in its pathogenesis is utmost importance for treatment and exploring newer therapeutic options. [Table 2] shows the clinicopathological correlation and neurological outcome of CP.

TYPES AND CLASSIFICATIONS OF CP

It is understandable that in such a diverse collection of disorders, many attempts at classification should be of limited value. [Table 3] shows the various classification of CP.

Classification of CP subtypes based on Surveillance for CP in Europe (SCPE) shown in [Figure 1]. Adapted from SCPE plenary meeting, held in Oxford, 1999.[6]

The classification of subtypes of CP is based on clinical features and predominant neurological findings. It identifies three main groups: Spastic, dyskinetic, and ataxic CP. All subtypes of CP have an abnormal pattern of movement and posture. Additional features include:

1. Spastic CP
   a. Unilateral spastic CP – earlier called hemiplegic CP
   b. Bilateral spastic CP – it can be a diplegic or quadriplegic type.
2. Dyskinetic CP
   a. Dystonic CP is dominated by decreased movements with increased tone
   b. Choreathetotic CP dominated by increased movements with decreased tone.

   The same child can have both spasticity and dystonia in mixed CP. The dominating features should determine subtype classifications and can be labeled as mixed CP dyskinetic with spastic when dystonia more than spasticity vice versa.
3. Ataxic CP is characterized by – loss of orderly muscular coordination.

Table 1: Risk factors for cerebral palsy.

Pre-natal (Maternal/fetal/placental)	Perinatal	Post-natal
Iodine deficiency, iron deficiency, and poor nutrition	1.Birth asphyxia	Neuroinfections
Intrauterine infections (TORCH), high fever, UTI	2.Prematurity	Viral encephalitis
Chorioamnionitis	3.Intrauterine growth retardation	Tubercular meningitis
Hypertension	4.Hyperbilirubinemia	Pyogenic meningitis
Maternal diseases, for example, diabetes, hypertension, hyperthyroidism	5.Intraventricular and intracerebral bleeds	Head injuries
	6.Hypoglycemia, dyselectrolytemias	Anoxia
Teratogens – drugs, radiation, smoking, alcohol, and environmental toxins	7.Sepsis, pneumonia, and meningitis	Suffocation
	8.Premature separation of placenta	Electrocution
Fertility problems, for example, advanced age at conception, history of infertility, recurrent fetal wastage		Post-operative cardiac arrest
		Post-epileptic
Poor antenatal care		Cerebrovascular accidents/strokes
Poor socioeconomic status		Gastroenteritis and dehydration

*Often etiology may be multifactorial

Table 2: Clinical-pathological-etiological and outcome correlate in cerebral palsy.

CP subtype	Pathology	Underlying etiology	Neurological outcome
Spastic diplegia	Periventricular leukomalacia	Prematurity	Visual impairment, hyperactivity
Spastic quadriplegia	Multicystic encephalopathy cerebral malformation	Perinatal/intrauterine hypoxic-ischemic events	Decreased IQ seizures bulbar weakness
Spastic hemiplegia	Cerebral injury (infarction, necrosis)	Pre-natal events like hypoperfusion, hemorrhage, Genetic	Seizures, learning problems
Dyskinetic	Basal ganglion – status marmoratus due to bilirubin deposition	Perinatal asphyxia bilirubin-induced neurological dysfunction – BIND (kernicterus)	Hearing impairment
Ataxic	Cerebellar lesions	Pre-natal (genetic)	Motor delay

BIND: Bilirubin-induced neurologic dysfunction

Table 3: Classification of cerebral palsy.

Physiologic	Topographic	Functional – GMFCS/walking	Etiological
Spastic	Diplegia	Class I: Walks without limitations	Pre-natal
Dyskinetic	Hemiplegia	Class II: Walks with limitations	natal
1. Dystonic	Quadriplegia	Class III: Walks using a hand-held mobility device	post-natal
2. Choreoathetotic	Monoplegia	Class IV: Self-mobility with limitations; may use powered mobility	
Ataxic	Triplegia	Grade V – Transported in a manual wheelchair	
Mixed	Double hemiplegia		

GMFCS: Gross motor function classification system

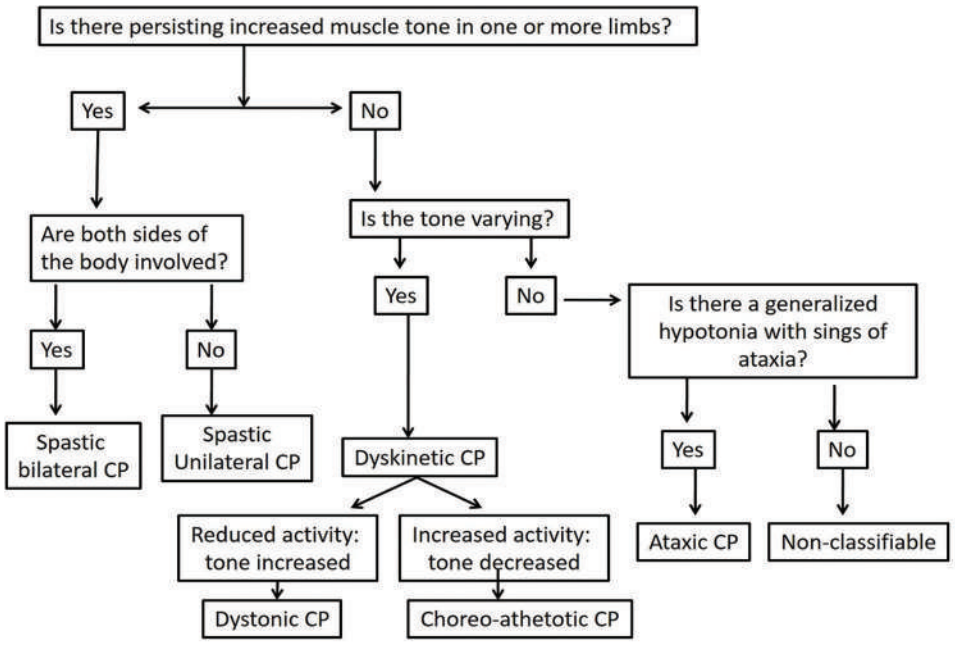

Figure 1: Flow diagram showing Surveillance for Cerebral Palsy in Europe (SCPE) classification of cerebral palsy. Hierarchical classification tree of sub-types (adapted from DMCN2000).

CP MIMICS

All children with features of CP should be carefully evaluated for an underlying cause, particularly in the presence of red flag features shown in [Table 4].[7,8] CP mimics can be grouped on the basis of age of presentation or clinical examination and history. They can be grouped into a subtype of CP, as shown in [Table 5].[7-9] Ataxic and dyskinetic syndromes are particularly liable to cause confusion. This important distinction between a progressive and non-progressive

Table 4: Red-flags symptoms and signs for cerebral palsy to consider other causes.

History	Examination	Neuroimaging
Positive family history of similar disease	Dysmorphic facies	Normal MRI of brain
History of consanguinity	Neurocutaneous markers	Isolated abnormal signals from globus pallidus.
Absence of sentinel events	Isolated muscular hypotonia	Imaging features are not suggestive of cerebral palsy
No risk factors for CP	Paraparesis	Cerebellar atrophy
Neurodevelopmental stagnation or regression	Peripheral nervous system involvement (pes cavus)	Demyelination
Episodic decomposition	Optic atrophy/retinopathy	
Fluctuation in motor functions	Systemic signs	

MRI: Magnetic resonance imaging

Table 5: Differential diagnosis/cerebral palsy mimics for various types of cerebral palsy.

S. No.	Condition/disease
Conditions presenting with true muscle weakness	
1	Duchenne muscular dystrophy, hereditary motor sensory neuropathy, myopathies
2	Infantile neuroaxonal dystrophy – INAD
3	Mitochondrial cytopathies
4	Cerebral white matter diseases – hypomyelinating leukodystrophies
Conditions with significant dystonia or involuntary movements	
1	DOPA responsive dystonia
2	PKAN – pantothenate kinase-associated neurodegeneration
3	Pyruvate dehydrogenase deficiency, Leigh syndrome, and other mitochondrial disorders
4	Glutaric aciduria type I and other organic acidurias
5	Juvenile neuronal ceroid lipofuscinoses
6	Rett syndrome
7	Pelizaeus-Merzbacher disease
8	Lesch-Nyhan syndrome
Conditions with predominant spastic diplegia or quadriplegia	
1	Adrenoleukodystrophy – ALD
2	Arginase deficiency
3	Metachromatic leukodystrophy
4	Hereditary progressive spastic paraplegia
5	Holocarboxylase synthetase deficiency
6	Pre-natal iodine deficiency (“neurological cretinism”)
7	TORCH infections
Conditions with ataxia (ataxic CP is rare)	
1	Angelman syndrome
2	Niemann-Pick disease type C
3	Ataxia-telangiectasia
4	Pontocerebellar hypoplasia or atrophy
5	Chronic/adult GM2 gangliosidosis
6	Mitochondrial cytopathy (NARP mutation)
7	Posterior fossa tumors
8	Joubert’s syndrome
Conditions with significant bulbar and oral-motor dysfunction- Worster-drought syndrome/ perisylvian/ opercular syndrome	
1	Polymicrogyria
2	Zellweger syndrome

disorder is made on clinical grounds and appropriate investigations when indicated.

EARLY PREDICTORS IN CP

Early diagnosis is very important for early intervention and thus determines the outcome. It also helps in counseling worried parents appropriately. Early markers of CP can be identified based on neurological examination and evolution of signs in CP, general movement assessment, and neuroimaging studies. The great advantage of detecting an increased risk of CP at such an early stage consists of the possibility of intervention long before the emergence of obvious pathological features of CP.

Some of the commonly used neurological examination tools in the high-risk clinic are the Hammersmith Infant Neurological Examination (HINE), the Amiel-Tison scale, The Bayley Scales of Infant and Toddler Development, and Dubowitz neonatal neurological examination.

HINE

It is a well-studied neurological exam in healthy or high-risk infants. The HNE is easy to perform. It is relatively brief and standardized. It is a scorable clinical neurological examination. It is an application to in the age group of 2 months–24 months. It is easily accessible to all clinicians. It has good inter-observer reliability, even in less experienced staff. It has no associated costs such as lengthy certifications or proprietary forms. The use of the HINE optimality score and cutoff scores provides prognostic information on the severity of the motor outcome. The HINE can further help to identify those infants needing specific rehabilitation programs. It includes 26 items assessing cranial nerve function, posture, quality and quantity of movements, muscle tone, and reflexes and reactions. Each item is scored individually such as 0, 1, 2, or 3. The sum score of all individual items ranges from 0 to 78. A questionnaire with instructions and diagrams is included on the scoring sheet, similar to the Dubowitz neonatal neurological examination. HINE score allows the

identification of early signs of CP and other neuromotor disorders if apply sequentially. Individual items predict motor outcomes. For example, in preterm infants assessed between 6 and 15 months corrected age, scores above 64 predict independent walking with a walked sensitivity of 98% and specificity of 85%. Conversely, scores below 52 were highly predictive of CP and severe motor impairments.[10]

COMPREHENSIVE EVALUATION OF CHILDREN WITH CP

The comprehensive evaluation and care of a child with CP can be simplified into the following five steps: Confirming the diagnosis and determining the cause, assembling "the team," assessing functional abilities, determining goals of care, and comprehensive care initiation

Step 1: Confirming the diagnosis and determining the cause

This step includes a detailed history taking and examination followed by necessary investigations such as computed tomography (CT) or magnetic resonance imaging (MRI) of brain and ancillary investigations such as electroencephalography (EEG), metabolic, genetic, and coagulopathy testing. American Academy of Neurology (AAN) recommendations on neuroimaging:[11] Neuroimaging is recommended in the evaluation of a child with CP if the etiology has not been established. MRI is better than CT scanning as the yield of MRI is higher and helps in the identification of timing of insult (Level A, Class I-III evidence).

Step 2: Assembling the team

This will include a coordinated approach between various branches of medicine in providing complete care to a child with CP.

Step 3: The complete assessment

This step includes a comprehensive and extensive evaluation of the functional abilities, comorbidities, and the support system of children with CP. It can be further subdivided into the following steps:

1. Mobility and motor impairment evaluation
2. Associative conditions assessment
3. Activities of daily living evaluation
4. Family dynamics and socioeconomic status assessment
5. Educational assessment.
   A. Muscle tone: Modified Ashworth Scale is used for tone assessment, as shown in [Table 6].
   B. Associative conditions assessment: AAN recommendation on additional testing for comorbidities:[11] Due to the high incidence of associated conditions, children with CP should be screened for "intellectual disability, ophthalmologic and hearing impairments, and speech and language disorders" (Level A, Class I and II evidence). Monitoring should be done for nutrition, growth, and swallowing dysfunction. If screening tests are suggestive of impairments, it should be confirmed by other diagnostic tests.
   C. Activities of daily living evaluation: The following points are to be noted to give appropriate assistance as per the impairment, bathing, dressing and undressing, eating, food preparation, grooming, housekeeping, leisure, and play; recreation, personal hygiene, mobility, self-care, shopping, transferring (bed, chair, toiletry, etc.), and work

Table 6: Modified Ashworth scoring system.

Grade 0	No increase in muscle tone
Grade 1	Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part(s) is moved in flexion or extension
Grade 1+	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM
Grade 3	More marked increase in muscle tone through most of the ROM, but affected part(s) easily moved
Grade 3	Considerable increase in muscle tone, passive movement difficult
Grade 4	Affected part(s) rigid in flexion or extension

Step 5: Coordinated, comprehensive care plan implementation

After a detailed evaluation, multidisciplinary care is implemented with the help of the team gathered so as to achieve the goals set. Ashwal *et al.*[11] have provided a practice parameter for diagnostic assessment and evaluation of a child with CP, which provides a comprehensive flow chart for evaluation.[11]

COMORBIDITIES IN CHILDREN WITH CP

CP is often accompanied by disturbances of sensation, perception, cognition, communication, behavior, epilepsy, and secondary musculoskeletal problems. This definition has led not only to an increase in awareness of the occurrence of comorbidities in individuals with CP but also the need for interdisciplinary management of these comorbidities to improve the life span and quality of life of children with CP. Brown *et al.* defined comorbidity as any disorder associated with CP, but which can also occur as a stand-alone disorder

in individuals without CP.[12] Comorbidities occurring in Children with CP are shown in [Table 7]. They categorized types of comorbidities in individual with CP:

1. Comorbid/co-occurring: Disorders not caused by the injury to the developing brain, nor are complications of the main CP condition
2. Co-casual: Disorders caused by the same injury to the developing brain that caused CP (i.e., epilepsy and cognitive impairment)
3. Complications: Disorders that are complications of the main CP condition (i.e., scoliosis and hip dislocation)

SEIZURES IN CP

Seizures are frequently encountered in children with CP. The frequency of seizures in children with CP is 40 times higher than the general population. Epilepsy in CP modifies the course of CP, it complicates rehabilitation, and it also influences motor and intellectual function. It can be life-threatening also. Various studies show, on an average, 43% (range 35–62%) of children with CP have epilepsy.

RISK FACTORS FOR EPILEPSY IN CP[13]

1. The presence of neonatal seizures
2. Low Apgar score (≤4 points)
3. Extremely preterm infants (≤31 weeks of gestation)
4. Neonatal resuscitation
5. Family history of epilepsy
6. CP caused by pre-natal factors, especially cerebral dysgenesis
7. Intrauterine infection (especially herpes encephalitis).
8. Hemiplegic and tetraplegic forms of CP
9. Severe intellectual disability
10. The presence of epileptiform discharges on the EEG.

CHARACTERISTICS OF EPILEPSY IN CP

Despite the wide polymorphism of clinical cases, epilepsy in combination with CP has a number of common characteristics. They can be expressed as the following features.

1. In the majority of cases (up 74.2%), epilepsy in children with CP occurs within the 1st year of life
2. Children with CP have a broad spectrum of epilepsies – varying from favorable combinations with benign forms to extremely severe epileptic encephalopathies (Ohtahara, West, Lennox-Gastaut syndromes, etc.)
3. Seizures often need polytherapy
4. There is increased risk of seizures going into status epilepticus
5. Increased risk of recurrence of epilepsy in children with CP after antiepileptic drugs (AED) are discontinued
6. Seizure free period of 1 year is achieved in children with normal intelligence, children on monotherapy, spastic diplegia subtypes, and children having single seizure type.

Table 7: Comorbidities in children with cerebral palsy.

S. no.	Neurologic disorders	Medical disorder	Psychiatric disorders
1.	Seizure/ Epilepsy	Nutrition and growth	ADHD
2.	Intellectual disability	Gastrointestinal 1.Feeding problems 2.Dysphagia 3.GERD 4.Constipation	Autism spectrum disorder
3.	Speech	Respiratory 1.Obstructive sleep apnea 2.Parenchymal lung disease due to aspiration 3.Restrictive lung disease due to severe kyphoscoliosis 4.Insufficient coughing	Behavioral disorders
4.	Sleep disorders	Genitourinary 1.Urinary incontinence 2.Detrusor hyperactivity 3.Recurrent UTI 4.Detrusor sphincter dyssynergia	Depression
5.	Spasticity	Orthopaedic 1.Contracture 2.Subluxations 3.Bony deformities 4.Osteopenia	Learning problems
6.	Dystonia	Hearing impairment and visual impairment	Anxiety

CP is the most common cause for West syndrome in India, the history of spasms should be asked as most of the time, epileptic spasms are missed and if not treated early, the long-term outcome of CP is poor.

CHALLENGES IN IDENTIFYING SEIZURES IN CP

1. Epileptic seizures may be difficult to distinguish from other involuntary movements, particularly in dystonic/dyskinetic or ataxic CP
2. Children with CP may have breath-holding spells, reflex anoxic attacks, vasovagal syncope, and other types of non-epileptic paroxysmal disorders
3. Gastroesophageal-reflux disease (GERD-Sandifer syndrome) is commonly seen in CP
4. Consider seizures in the differential diagnosis of any unexplained worsening of the motor disorder in CP, sudden falls, a cognitive decline or a decrease in alertness
5. CP and intellectual disability: Unable to describe the epileptic events themselves, parents may not recognize subtle seizure manifestations.

Diagnostic delay is associated with a 7.4-point drop in Vineland Scales of Adaptive Behavior motor score, 8.4-point drop in processing speed on Wechsler Intelligence Scale for Children (WISC) and 14.5-point drop-in full-scale intellectual quotient (IQ) on WISC.

ROLE OF EEG

Consider when history or examination is suggestive of epilepsy or epilepsy syndrome. Not useful in predicting the development of seizures in a child with CP. When there is difficulty in differentiating seizures from dyskinetic movements and there is a history of doubtful myoclonic jerks, EEG has to be done. EEG is useful for diagnosis of seizure type, identification of epilepsy syndrome, prediction of long-term outcome, severity, and monitoring.

TREATMENT

The principles of drug therapy in children with CP and epilepsy are the same as those for children with epilepsy in general. The type of seizure, epilepsy syndrome, age, gender, cost, the side effect profile of the medicine being considered, interactions with other possible medications, and associated comorbidities guide the selection of AEDs. In general, the drugs of the first choice for focal seizures are oxcarbazepine and carbamazepine should be avoided in CP as they can aggravate myoclonic jerks. In the case of infantile spasms, injectable or oral steroids and vigabatrin should be considered.

NEUROIMAGING IN CP

Neuroimaging should be done in all cases of CP of unknown origin. Although the diagnosis of CP is clinical, neuroimaging helps in establishing etiology and timing of insult and identifying malformations which have genetic underpinnings.[11]

Identifying etiology is important especially for,

1. Genetic counseling (recurrence risk and pre-natal diagnosis in genetic etiology)
2. Avoids further unnecessary testing
3. Medicolegal cases.

Neuroimaging-which one to choose?

1. Cranial ultrasonography-perinatal period
2. CT scan of brain, yield is 77%. Poor for dyskinetic CP, good for hemiparetic CP. Picks up TORCH infection and identifies surgically treatable cause in ~5% of children like hydrocephalus
3. MRI of brain, yield is 89%. Helps in assessing the timing of insult such as pre-natal, perinatal, or post-natal. Good for prematurity associated CP/PVL. Better for dyskinetic CP to look for basal ganglia and thalamus and also malformation of brain.

Lesions and type of CP

1. PVL: Spastic diplegia
2. Basal ganglia-dyskinetic CP
3. Focal lesions – e.g., porencephalic cyst – spastic hemiplegia.

Multidisciplinary management of CP

CP rehabilitation is a complex process aiming at ensuring children and their families the best possible quality of life. A child with CP should be managed within an integrated multidisciplinary team with appropriate expertise [Figure 2].[14]

Evidence based management of CP

In the last decade, the CP evidence base has rapidly expanded, providing clinicians and families with the possibility of newer, safer, and more effective interventions. In 2013, Novak *et al.*[15,16] conducted a systematic review of interventions for children with CP and color-coded the evidence using Evidence Alert Traffic Light Grading System. Where green = go (high-quality evidence indicates effectiveness); red = stop (high-quality evidence indicates ineffectiveness); and yellow = measure individual outcomes (evidence is conflicting).

CP and comorbidities

As already discussed, all commodities should be recognized, and specific treatments [Table 8] for these problems should be managed. This can substantially improve the child's outcome and quality of life, even though CP itself cannot be treated.

[Figure 3a] shows child with diplegic cerebral palsy, [Figure 3b] shows MRI of brain with periventricular leukomalacia commonly seen in diplegic cerebral palsy. [Figure 3c] clinical photo showing microcephaly in a child with quadriplegic CP with multicystic encephalomalacia with subdural effusion on MRI of brain [Figure 3d]. [Figures 4a and b] shows child with dyskinetic cerebral palsy with MRI (4b) brain T2 axial showing hyperintensities in bilateral posterior putamen and thalami suggestive of acute hypoxic insult. [Figures 4c and d] shows child with dyskinetic cerebral palsy with dystonic posturing and arching of neck due to dystonia and MRI brain (4d) T2 axial showing bilateral symmetrical hyperintensities in globus pallidus due to bilirubin induced neurologic dysfunction. [Figures 5a and b] shows child with dystonic cerebral palsy with severe arching of back and neck due to dystonia and computed tomography (b) brain showing bilateral thalamic calcifications with cerebral atrophy with enlarged ventricles suggestive of hypoxic insult. [Figures 5c and d] shows child with hemiplegic cerebral palsy with magnetic resonance imaging (d) of brain showing porencephalic cyst. [Figures 6a-c] perisylvian syndrome-type of cerebral palsy showing drooling, MRI of brain (6b,

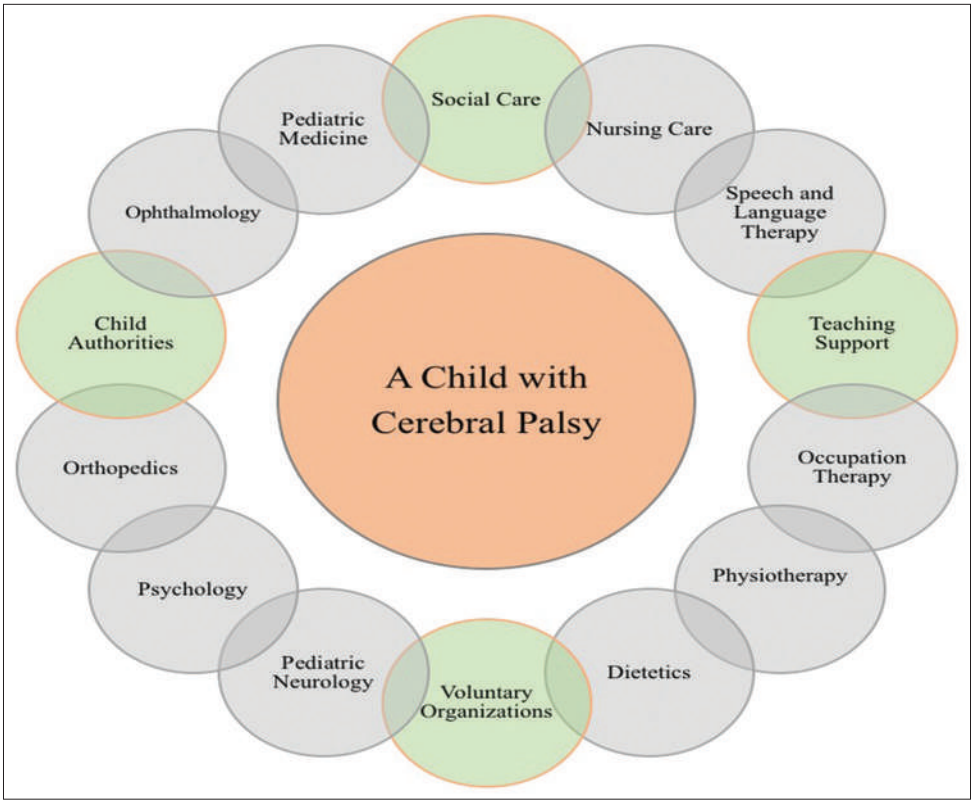

Figure 2: Multidisciplinary team for the child with cerebral palsy. Adapted from NICE guidelines.

Table 8: The comorbidities of cerebral palsy assessment and evidence-based management.

Comorbidity	Incidence (%)	Evidence-based intervention/prognosis
Pain	75	Treat to prevent sleep and behavioral disorders
Intellectual disability	50	Poorer for ambulation, continence, academics
Non-ambulant	33	Independent sitting at 2 years predicts walking
Hip dislocation	33	6–12 monthly X-ray of pelvis
Non-verbal	25	Augment speech therapy
Epilepsy	25	Antiseizure medications
Behavior disorder	25	Detect early and should be managed
Bladder incontinence	25	Investigate and allow time
Sleep disorder	20	Investigate and manage early
Blindness	10	Assess early and vision therapy
Non-oral feeding	7	Allow swallow safety and monitor growth
Deafness	4	Assess early and hearing aid

c) showing gliosis in the perisylvian region. [Figures 6d-f] neonatal hypoglycemic brain injury: Clinical photo (6d) showing strabismus and MRI of brain: DWI (6e) and ADC (6f) showing restricted diffusion and low ADC in the bilateral parieto-occipital region.

Medical management of CP

Wide assortments of medications are used in CP to reduce symptoms and address complications and treat comorbidities. Children who experience spasticity and unwanted or uncontrolled involuntary movements such as dystonia, chorea, and athetosis are often prescribed drugs to minimize the movements, relax muscles, increase comfort, and facilitate better posture and functionality. Drug therapy is also used to treat seizures, behavioral issues, pain, bowel movements, and manage other comorbidities and improve quality of life.

Spasticity management

Spasticity treatment may include one or more of the following options:

1. Oral medications
2. Chemical blockage: Botulinum toxin and/or phenol
3. Intrathecal baclofen pump
4. Surgical management
5. Physical measures such as physiotherapy, occupational therapy, orthosis, and plaster caster use.

The most commonly used drugs and dosages are:

1. Baclofen – dose 0.12–1 mg/kg/day
2. Tizanidine – 0.3 mg–0.5 mg/kg/day
3. Benzodiazepines (e.g., diazepam – 0.12–0.8 mg/kg/day and clonazepam – 0.01–005 mg/kg/day)
4. Dantrolene sodium: 3–12 mg/kg/day.

FEW TIPS TO SELECT DRUGS FOR SPASTICITY

1. Intractable seizures AND seizure tendency – avoid baclofen
2. Spasticity AND dystonia – baclofen
3. Sleep problems – bedtime diazepam/tizanidine
4. Myoclonus – clonazepam
5. Liver problems – avoid tizanidine, dantrolene.

MANAGEMENT OF MOVEMENT DISORDERS IN CP

Medications used for dystonia are:

1. Trihexyphenidyl – Anticholinergic. Starting dose of 0.1–0.2 mg/kg/day, increase once in 3 days to the maximum dose of 1 mg/kg/day (total-max dose <10 kg–30 mg/day and more than 10 kg–60 mg/day. can be tried with monitoring adverse effects). The main side effects are dry eyes and mouth, gastrointestinal disturbances, urinary retention, and behavioral disturbances
2. Tetrabenazine – dose 0.5 mg–4 mg/kg/day. In 2 or 3 divided doses, increase once in 3 days. Side effects include drowsiness, parkinsonism, depression, insomnia, nervousness, anxiety, and akathisia
3. Baclofen (in high doses 1 mg/kg /day reduces dystonia)
4. Levodopa (Syndopa) – start at 0.5 mg/kg/day up to 10–20 mg/kg/day)
5. Benzodiazepines (e.g., diazepam – 0.12–0.8 mg/kg/day and clonazepam – 0.01–005 mg/kg/day)
6. Deep brain stimulation.

REHABILITATION: PHYSIOTHERAPY AND OCCUPATIONAL THERAPY

Therapy program

1. Infant-stimulating advanced postural equilibrium and balance reactions to provide head and trunk control
2. Toddler and preschool-stretching the spastic muscles strengthening the weak ones and promoting mobility
3. Adolescent-improving cardiovascular status.

Therapy methods

1. Bobath neurodevelopmental therapy. This is the most commonly used therapy method in CP world-wide. The aims of this therapy are to normalize muscle tone,

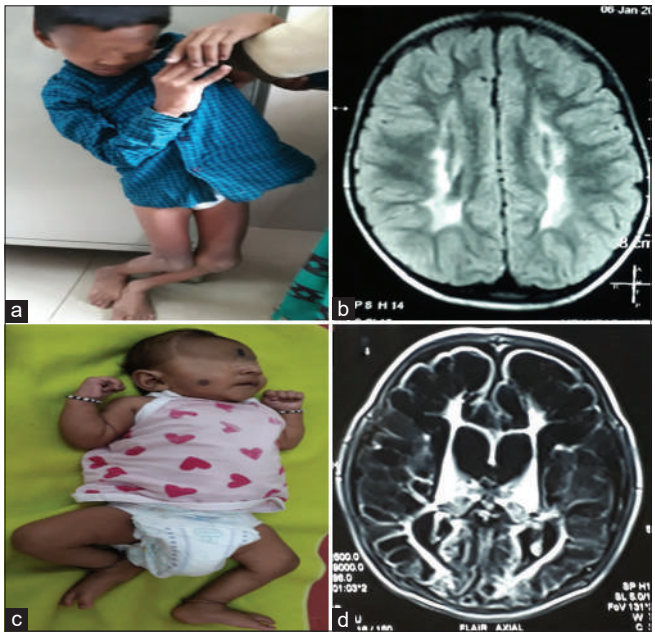

Figure 3: (a) Bilateral spastic cerebral palsy – spastic diplegic type with scissoring of both lower limbs with deformity. (b) Magnetic resonance imaging (MRI) of brain T2 axial sections showing periventricular hyperintensities suggestive of periventricular leukomalacia. (c) Clinical photo showing microcephaly in a child with bilateral spastic cerebral palsy of quadriplegic type with multicystic encephalomalacia with subdural effusion on MRI of brain (d).

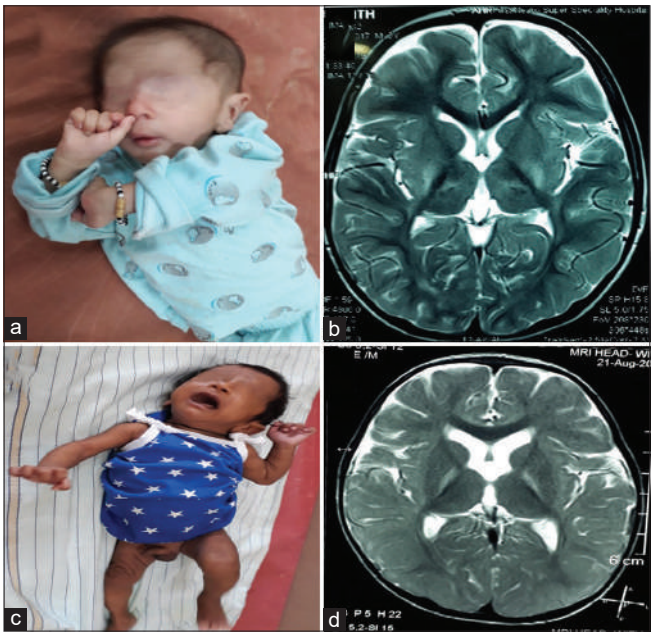

Figure 4: (a and b) Child with dyskinetic cerebral palsy with magnetic resonance imaging (MRI) (b) brain T2 axial showing hyperintensities in bilateral posterior putamen and thalami suggestive of acute hypoxic insult. (c and d): Child with dyskinetic cerebral palsy with dystonic posturing and arching of neck due to dystonia and MRI brain (d) T2 axial showing bilateral symmetrical hyperintensities in globus pallidus due to bilirubin-induced neurologic dysfunction.

stimulate normal movements, and inhibit abnormal primitive reflexes. It uses reflex inhibitory positions to decrease tone and promote the development of advanced postural reactions by stimulating key points of control.

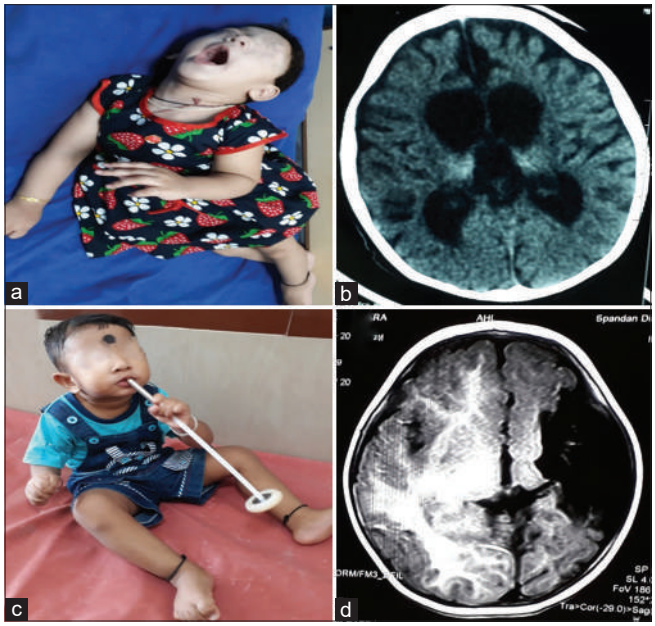

Figure 5: (a and b) Child with dystonic cerebral palsy with severe arching of back and neck due to dystonia and computed tomography (b) brain showing bilateral thalamic calcifications with cerebral atrophy with enlarged ventricles suggestive of hypoxic insult. (c and d): Child with hemiplegic cerebral palsy with magnetic resonance imaging (d) of brain showing porencephalic cyst.

2. Hand-arm bimanual intensive training (HABIT) for hemiplegic CP where the child is trained to use both hands together through repetitive tasks such as drumming, pushing a rolling pin, and pulling apart construction toys (Legos).
3. Constraint-induced movement therapy (CIMT) involves restraint of the unaffected limb to encourage the use of affected limb during the therapeutic tasks. The restraint may be by the use of casting or physically restraining by holding the normal hand.
4. Context-focused therapy involves changing the environment rather than the child's approach.
5. Goal-directed functional training lays emphasis on activities based on goals set by the child using a motor learning approach.

OCCUPATIONAL THERAPY IN CP

As CP can affect children in very different ways, the occupational therapist will start with a full assessment. The focus of the assessment will be as much about understanding the child's abilities as understanding what they are finding difficult and why. During the assessment, the occupational therapist will also want to gain an understanding of the child's own goals as well as the goals of their parents, carers, or school. The occupational therapist will provide tailored advice once information obtained during assessment. Below

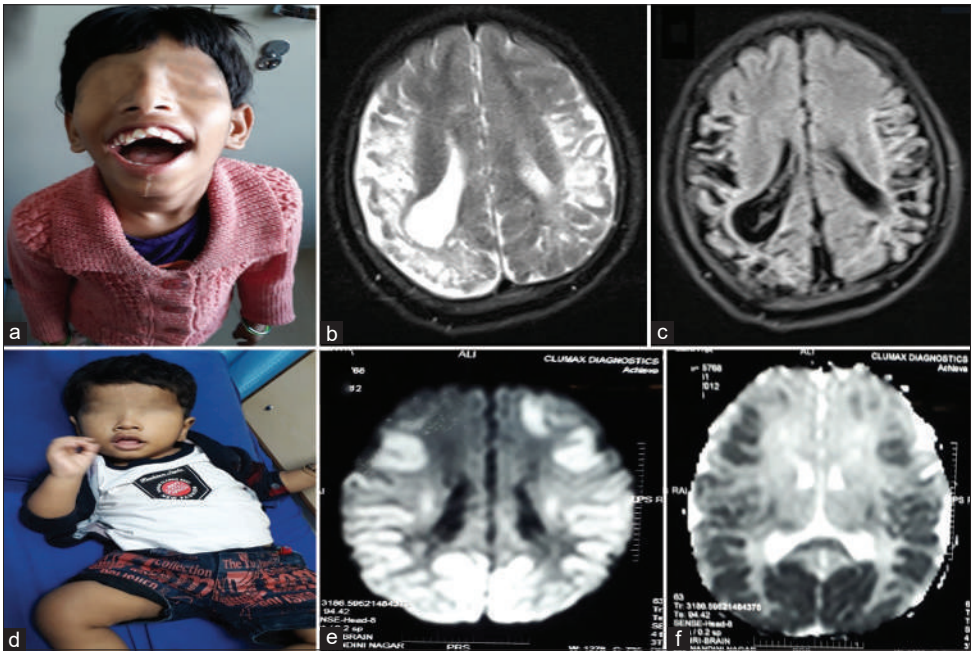

Figure 6: (a-c) Perisylvian syndrome – type of cerebral palsy showing drooling, magnetic resonance imaging (MRI) of brain (b and c) showing gliosis in the perisylvian region. (d-f): Neonatal hypoglycemic brain injury: Clinical photo (d) showing strabismus and MRI of brain: DWI (e) and ADC (f) showing restricted diffusion and low ADC in the bilateral parieto-occipital region.

are some examples of how an occupational therapist can assist:

- Improve the child's skills by adapting tasks, teaching, and training or advise on appropriate assistive technology to maximize independence and increase participation
- Provides structural building changes and/or equipment in home and schools to facilitate safe access
- Facilitate access to the school curriculum and support school staff in understanding how to best support the child's education
- Provides advice on equipment and techniques to maintain postural alignment, to reduce the risk of fixed postural changes such as splinting, supportive seating, and positioning while sleeping.

EXERCISES USED IN OCCUPATIONAL THERAPY

Occupational therapy involves using functional activities to progressively improve functional performance. Occupational therapy exercises focus on the following skill areas:

- Fine motor control – improves hand dexterity by working on hand muscle strength, finger isolations, in-hand manipulations, arching the palm of the hand, thumb opposition, and pincer grasp. Activities include squeezing a clothespin, playing with water squirt toys, and pushing coins into the slot of a piggy bank
- HABIT: Bilateral coordination
- Upper body strength and stability – play focuses on strengthening and stabilizing the trunk (core), shoulder and wrist muscles through exercises such as crawling and lying on the prone position while reading
- Crossing the midline – these activities such as making figure eights with streamers and throwing balls at a target to the right or left of center, teach the child to reach across the middle of their body with their arms and legs to the opposite side
- To improve visual motor skills, activities that improve hand-eye coordination such as drawing, stringing beads, catching, and throwing a ball
- For visual perception – activities include alphabet puzzles, playing with different shapes, and matching games
- For self-care, activities such as brushing their teeth, getting dressed, and self-feeding are useful.

VARIOUS TECHNIQUES TO REACH THEIR GOALS ARE

- Pediatric CIMT – ask the child to use weaker limb while restraining normal limb
- Sensory integration therapy – here advise activities that stimulate various sensations such as the skin by providing different texture experiences; sand, water, dough, and finger painting.

ROLE OF BOTULINUM TOXIN AND ORTHOPEDIC INTERVENTION IN CP[17-19]

Quick orthopedic examination includes

1. Gait and gross motor function classification system (GMFCS) grading
2. Analysis of range of motion and joint contractures of various joints
3. Motor strength assessment
4. Assessment of torsional deformity
5. Upper limb and spine examination.

PATIENT SELECTION FOR BOTULINUM TOXIN

1. Favorable factors
   a. Focal goals with specific anticipated functional benefits
   b. Increased dynamic muscle stiffness
   c. Muscular hypertonia with a functional goal.
2. Negative factors
   a. Severe fixed contractures
   b. Bony torsion and joint instability
   c. Bleeding disorders
   d. Too many target muscles – consider other treatment options, or prioritize.

TIMING OF TREATMENT FOR BOTULINUM TOXIN

- For the lower extremity, early treatment is preferable: 1–6 years of age
- For the upper extremity: More than 4 years of age
- Treatment during the dynamic phase of motor development maximizes the chance of permanent modification of the disease
- Early treatment may allow postponement, simplification or even, occasionally, avoidance of surgery
- Later treatment can still be valuable in terms of pain relief, ease of care, and functional goals such as sitting or standing.

RECOMMENDED SAFE DOSE OF BOTULINUM TOXIN

1. Range (U/Kg body wt.): 1–20 U
2. Maximum total dose (U): 400 U
3. Range maximum dose/site (U): 10–50 U.

We did study Koushik *et al.*[20] there is no difference in outcome with the administration of injection botulinum toxin manual versus ultrasound-guided for lower limb muscle spasticity.

ORTHOPEDIC SURGERIES IN CP

Various surgeries done

1. To improve muscular problems
   - Tendon lengthening: Tendoachilles lengthening and hamstring lengthening
   - Intramuscular/fractional lengthening: Gastrocnemius/hamstring fractional lengthening
   - Muscle release: Hamstring, iliopsoas brim release, and adductor tenotomy
   - Tendon transfer: Pronator rerouting, split posterior tibial/tibialis anterior transfers, and semitendinosus transfer
   - Neurectomy: Obturator neurectomy.
2. To improve static problems
   - Reduce subluxated or dislocated joints: Hip varus derotation osteotomy, acetabular surgeries for coverage (shelf osteotomy), and excisional arthroplasty
   - Correction of bony abnormalities and rotational problems: Femoral shortening/extension/derotation osteotomy, tibial corrective osteotomy, and foot lateral column lengthening surgery
   - Fuse joints to provide stability: Triple arthrodesis of foot, etc.
3. Spine deformity correction surgery

We reported earlier, Gowda *et al.*,[21] that hip dysplasia is not uncommon in Indian children with CP.

CEREBRAL VISUAL IMPAIRMENT (CVI)

CVI is defined as visual loss resulting from damage to the retrochiasmatic visual pathways and cerebral structures. The eye and anterior pathways (optic nerve and chiasma) are essentially normal and do not contribute to the visual impairment. The term "Cerebral" is used as there is the involvement of the sub-cortical structures, white matter of the brain, and visual processing areas also in this process, in addition to the visual cortex. It should be differentiated from autism spectrum disorder, severe intellectual disability, and delayed visual maturation in infants.

ENVIRONMENTAL MODIFICATION FOR TREATMENT OF CVI

1. Reducing clutter – minimize the number of objects in the working space/play area to avoid visual confusion
2. Increasing lighting and contrast – use dark pencils, outline pictures, add a table lamp, etc.
3. Presenting tasks in the preferred field of gaze
4. Encouraging auditory learning
5. Using touch to identify objects
6. Marking the edges of steps and pathways in contrasting colors to delineate the path clearly.

PERISYLVIAN SYNDROME AND MANAGEMENT OF DROOLING IN CP

Perisylvian syndrome, also called Worster Drought Syndrome or Congenital Bilateral Perisylvian syndrome, is quite a common but under-recognized and sub-optimally managed entity. It falls within the spectrum of CP and usually has a predominantly motor component, but it can also have cognitive, behavioral issues, and epilepsy as comorbid conditions. All these complaints can be localized to the involvement of Perisylvian area. The specialty of this entity is that the motor impairment is only pseudobulbar paresis with mild spastic quadriplegia, thus making the patient have a good GMFCS score. However, the speech and feeding problems are severe and if they are not addressed, they lead to various complications which will hamper the quality of life of the patient. All we have to understand is that these children have a specific phenotype which when recognized early, can make a significant difference in management and prognosis.

MANAGEMENT OF DROOLING[9]

It is a challenging condition and requires the coordinated services of Pediatrician, Pediatric Neurologist, Speech therapist, ENT Surgeon, and Occupational Therapist. There are two main approaches:

1. Non-invasive – oral motor therapy and pharmacological therapy
2. Invasive – Surgery – rarely used.

NON-INVASIVE MODALITIES

Positioning

When seated, a child should be fully supported and comfortable. Good posture with proper trunk and head control with appropriate seating devices facilitates better control of drooling and swallowing.

Feeding skills

Poor feeding skills can exaggerate drooling. Care should be taken to ensure lip closure, tongue movements, and swallowing properly. Avoidance of acidic fruits is worthwhile.

Oral facial facilitation

Most widely used and first line of therapy. This improves oromotor control, sensory awareness, and frequency of swallowing, done by a speech therapist. It is easy to do with no side effects, but may only have a short-term benefit.

1. Icing, effect lasts for 5–30 min, improves tone, swallow reflex
2. Brushing, effect lasts for 20–30 min, to be done before meals

3. Vibration improves tone in high tone muscles
4. Manipulation such as tapping, stroking, and patting, firm pressure directly to muscles using fingertips improves oral awareness
5. Oral motor sensory exercise, lip and tongue exercises.

Oral prosthetic devices such as chin cup, dental appliances for mandibular stability, better lip closure, tongue position, and swallowing.

Pharmacological is the second line of management. Anticholinergic drugs such as atropine, benztropine, glycopyrrolate, scopolamine, and benzhexol hydrochloride work by anticholinergic blockade of muscarinic receptor sites to reduce parasympathetic stimulation of salivary glands. However, they also act on muscarinic receptors elsewhere too causing side effects. They are quite effective, but owing to these side effects, they are not considered very ideal. However, these effects are reversible after the stoppage.

In conclusion, mild drooling can be managed by behavioral strategies, hands-on therapies, and proper positioning. In persistent problematic drooling, medications may be tried, but if they still do not respond, surgical interventions may be tried. Finally, a coordinated interdisciplinary approach may alleviate this complex issue.

FEEDING PROBLEMS IN CP

Recent systemic review and meta-analyses by Speyer *et al*. showed that pooled prevalence of 44% for drooling, 50% for swallowing problems, and 54% for feeding problems in children with CP.[22] The feeding problems are very common in children with CP. A thorough nutritional assessment should be done, and nutritional support should be started with dietary advice and modification of oral feeding, if safe and acceptable. In the presence of unsafe swallowing and inadequate oral intake, enteral nutrition should be initiated, and early gastrostomy placement should be evaluated and discussed with parents/caregivers. Gastrointestinal problems in CP children are frequent, should be actively detected and appropriately managed to prevent nutritionals status of child.[23] Various gastrointestinal problems are oromotor dysfunction, GERD, and constipation.[23]

PROGNOSIS OF CP

Prognosis regarding walking

A common question asked by parents of children with CP is whether the child will be able to walk independently?

1. In general, children have an enhanced capacity for brain plasticity, resulting in a capacity to recover and improve from brain insults.[24]
2. The prognosis depends on the type and extent of brain injury. The more severe the child's physical, functional, or cognitive impairment, the greater the possibility of difficulties with walking.[14]
   A. The ability to sit independently and rollover at 2 years of age is predictive of future ambulation[25]
   B. If a child can sit at 2 years of age, it is likely, but not certain, that they will be able to walk unaided by 6 years of age[14]
   C. If a child cannot sit but can roll at 2 years of age, there is a possibility that they may be able to walk unaided by 6 years of age[14]
   D. If a child cannot sit or roll at 2 years of age, they are unlikely to be able to walk unaided[14]
   E. General rule: Children with independent sitting by 2 years walk, those who are unable to sit by 4 years of age rarely walk[26]
   F. The type of CP further adds additional prognostic information as per available evidence.

1. Most children with hemiplegic CP will be able to ambulate independently. Usually, they walk by 2 years of life without any other major comorbidities[25,26]
2. More than 50% of spastic diplegia learn to walk[26]
3. Spastic quadriplegic CP, only 33% usually walk (mostly after 3 years) and 25 usually required completed total care[26]
4. Dyskinetic CP has an intermediate chance of walking.[26]

Poor prognostic factors for walking, in general, are bilateral spastic and dyskinetic CP, IQ <50, severe visual impairment, active epilepsy, absence of rolling over/sitting/crawling at 2 years of age, absence of functional hand use by 2 years, the persistence of primitive reflexes beyond 2 years of life, and GMFCS class IV to V. [Table 9] shows, the prognosis of CP based on MRI of brain.[27]

A study done by us, Surender *et al*.,[28] on caregiver-reported health-related quality of life (HRQOL) of children with CP and their families and its association with gross motor function. HRQOL in CP and their caregivers is highly impaired. The degree of impairment is associated with physical independence, mobility, clinical burden, and social integration dimensions.

PREVENTION OF CP

Primary prevention – preventing the occurrence of CP

1. Health promotion
   A. Health education for adolescent girls and improving anemia and nutrition
   B. Improvement on the nutritional status of the community
   C. Improvement in pre-natal, natal, and post-natal care
   D. Optimum health-care facility and infrastructure
   E. Awareness regarding developmentally supportive neonatal care.
2. Specific protection
   A. Rubella immunization for girls
   B. Folic acid supplementation during pregnancy

Table 9: Prognosis of cerebral palsy based on MRI of brain.

Type of involvement	Minimal	Moderate	Severe
Prognosis based on basal ganglia involvement			
Radiological description and involvement	Discrete lesions in posterior part of putamen	Marked focal lesions in posterior putamen with thalamus, usually have equivocal or abnormal posterior limb of internal capsule (PLIC)	Marked diffuse involvement of the posterior putamen and thalami with completely absent signal from myelin in the PLIC
Prognosis (at school age)	1.Dyskinetic or Athetoid CP 2.Minor neuromotor abnormality 3.Normal cognitive development		1.Dyskinetic/spastic CP 2.Microcephaly 3.Severe GDD
Prognosis based on white matter changes			
Radiological description and involvement	Mild discrete periventricular white matter changes only	Focal abnormalities in the white matter with or without cortical involvement	Diffuse and extensive signal changes throughout the white matter
Prognosis (at school age)	Normal	Normal or only minor motor abnormalities, such as poor hand function and balance	Microcephaly, GDD, walking with without support, spastic diplegia or quadriparesis, and poor perceptual-motor abilities

MRI: Magnetic resonance imaging, GDD: Global developmental delay

C. Universal iodization of salt
D. Prevention of exposure to teratogenic agents and radiation
E. Pre-natal tests such as triple test and quadruple test
F. Universal immunization for all children
G. Administering anti-D globulin to prevent Rh-isoimmunization
H. Intrapartum fetal monitoring to detect fetal distress
I. Improving immunization coverage and preventing accidents.

Secondary prevention

Halting and arresting disease progression by early diagnosis and treatment

1. Newborn thyroid screening
2. Neonatal metabolic screening for a treatable inborn error of metabolisms such as galactosemia and phenylketonuria
3. High-risk newborn follow-up clinics for early detection "at risk babies"
4. Cervical encerlage for cervical incompetence to prevent prematurity
5. Antenatal administration of magnesium sulfate to mothers at risk of preterm delivery before 34 weeks of gestation reduces the risk of CP[29]
6. Therapeutic hypothermia for neonates with hypoxic-ischemic encephalopathy.[30]

Tertiary prevention

Tertiary prevention is by preventing complications and maximization of functions by disability limitations and rehabilitation.

1. Assistive technology by equipment or ambulatory devices to improve independence, for example, walking frames, wheelchairs, etc.
2. Administration of botulinum toxin and giving anti-spasticity medicines to reduce spasticity
3. Refractory error correction and vision stimulation and rehabilitation
4. Communication skills may be enhanced by the use of bliss symbols, talking typewriters, electronic speech-generating devices, hearing aids, etc.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: Gowda VK. Recent advances in cerebral palsy. Karnataka Paediatr J 2020;35(1):4-18.

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Karnataka Pediatric Journal

Review Article

Clinicians dilemma in the management of acute flare-up wheeze with asthma: An update

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Received : 04 July 2020
Accepted : 24 July 2020
Published :

DOI
10.25259/KPJ_11_2020

Quick Response Code:

ABSTRACT

Asthma is the earliest onset of non-communicable respiratory disease with a significant psycho-socio economic burden. Each country have their own guidelines to manage asthma for their need based on availability, accessibility, and affordability. The acute flare-up of asthma, where there is a progressive increase of symptoms of asthma, causing higher morbidity and mortality. The clinician often confronts with a dilemma in the management – in confirming the diagnosis of asthma, look for the risks for flare-up and mortality, followed by assessing the severity of flare-up for proper management. There is some dilemma in using the nebulized steroid in acute flare-up of asthma. The author highlights the current knowledge in clearing those issues for the practicing clinicians.

Keywords: Asthma, Flare-up, Nebulization, Management

INTRODUCTION

Asthma is a chronic early-onset non-communicable environmental airway disease with significant psycho-socio economic burden to the family and society at large and characterized by airway inflammation, airway obstruction, airway hyperreactivity, and present with wheeze, cough, shortness of breath, and chest tightness. It is estimated that 1 billion people were suffering from asthma in the year 2015 and expected to reach 4 billion by 2050 as for WHO prediction, and it will be a global epidemic.[1]

Our Indian national health profile 2018 reveals that communicable diseases are decreasing from 61 to 33% and non-communicable diseases such as asthma, allergic rhinitis, COPD, cancer, and diabetes are increasing from 30–55% between 1990 and 2016.[2]

Each country kept their own guidelines to manage asthma and wheeze cases with training modules, to have uniformity and cost containment with their available resources.

ACUTE ASTHMA FLARE-UP

Acute asthma flare-up is characterized by a progressive increase in symptoms of shortness of breath, cough, wheeze, and chest tightness and progressive decrease in the lung functions, in a pre-existing diagnosed asthma patient or it can be the first presentation of asthma as well.[3]

Here, I want the clinicians to understand that the older terms are given up like – Exacerbation: Not suitable in clinical practice many patients cannot pronounce or remember. Attack: Has varying meaning may not perceive the gradual worsening of asthma symptoms.

Episode: Many patients and health care providers have not understood asthma.[3]

When a clinician confront a child with flare-up of wheeze, he should focus on three issues –

1. Is it asthma?
2. What are the risks for flare-up is there any risk for asthma-related death?
3. How severe the illness? For proper management.

Is this wheezing child, has asthma?

The diagnosis of asthma is mainly based on clinical evaluation and documenting reversible airway obstruction as a supportive evidence.[3]

a. Having a history variable respiratory symptoms, as shown in [Table 1]
b. b) One has to document variable respiratory airflow limitation by pulmonary function testing after inhalation of bronchodilators, more so before using any controllers such as steroids, as shown in [Table 2]

WHAT ARE THE RISKS FOR FLARE-UP OF ASTHMA

- Exposure to tobacco smoking; noxious agents and aeroallergens
- Children with chronic mucus hyper secretions may have reduced the growth of lungs. Usually, they present with more crackles in the chest than wheeze may be that they are different phenotypic categories
- Asthmatic children who are not on steroids
- Children whose sputum shows eosinophilia

Table 1: Respiratory symptoms.

Cough	More than one symptoms with variable time and intensity
Wheeze	Symptoms worse at night and early AM
Shortness of breath	Triggered by physical, emotional stress or cold air
Chest tightness	Often starts with viral infection

Table 2: Reversible airway limitations by lung function.

FEV1 by >200 ml and 12% of baseline in spirometry	PEF Increase by 15% in children (normal variation >13% in children, 10% in adults)
Reversibility is may be absent in Severe attack Viral infections	Clinical documentation in children under 4 years Improved social smile Good sucking efforts Less wheeze

- Children who have fixed airway obstruction like in premature babies, small for date children from air pollution, leading to placental vascular coagulopathy and children who gain weight rapidly in infancy as obesity is directly proportional to decreased lung function
- One has to watch these children in reducing the controller drug in asthma, and they have a higher risk for flare-up and future candidates of airway remodeling.[3]

RISKS FOR ASTHMA DEATHS

Here are the group of children where the clinician should be alert and proper management instituted at the earliest without any delay at a proper facilities. The risks are –

- History of near-fatal attack needing ventilation and having has tracheal intubation
- Having had previous admissions with similar episodes of wheeze
- Currently started using steroids or stopped the oral steroids or not using any inhaled corticosteroids
- Uses short-acting beta-2 agonist more than one canister per month
- Children with some psychosocial problems
- People with poor compliance of treatment
- Children with food allergy. Since they get anaphylactic reactions more often than others.

ASSESSMENT ASTHMA FLARE-UP

The clinician should assess whether it is mild/moderate, severe, or life-threatening flare-up based on clinical features, as shown in [Table 3].

The wheeze sound in medicine is a dry musical expiratory sound produced by air moving in high velocity past a fixed obstruction in the lower airway, and it cannot be felt on the chest. Its diagnostic value for asthma is the sensitivity of 74.7% and specificity of 87.3% positive predictive value is 12.4%.[4]

Table 3: Severity of asthma flare-up.

Mild/moderate	HR – 100–120
Prefers sitting	O_2 sat – 90–95%
Talks in phrases	PEF – >50%
Neck muscles are not used	
Not agitated	
Severe	HR – >120
Talks in words	RR – ↑ increased
Tripod position with a hunch	O_2 sat – <90%
Neck muscle are used with flaring	PEF – < 50%
Agitated	
Life-threatening	Urgently transfer to an acute care facility
Drowsy	
Confused	
Silent chest	

If it is a 1st time wheeze and had localized signs in lungs, the clinician should rule out other causes of wheeze since asthma may overlap with other airway disorders, making the differential diagnosis difficult.

Especially if the patient is an infant, other causes of wheeze to be ruled out such as – congenital anomalies, aspiration syndromes, structural lesion pressing on airways, infections, genetic diseases, and hyperventilation syndrome. Some of the clinical clues to suspect these conditions are shown in [Table 4].[5]

Our observation of 229 wheezing children who admitted to the hospital for evaluation as showed in [Table 5].

MANAGEMENT OF ACUTE EXACERBATION OF ASTHMA IN EMERGENCY ROOM

Step I:

- Use humidified oxygen to keep oxygen saturation of 93–98% in adolescents and 94–98% in children between 6 and 12 years

Table 4: Guidelines for the evaluation of resp. Distress with a wheeze.

Congenital lesions	Wheeze started early in life Intensifies with age and Worsens with URI
Structural lesions of central airways	Sound loudest during activity Disappear during quite breathing Alters with change of position Wheeze increased with bronchodilators
Extrinsic pressure on extra pulmonary airway	Extended neck with wheeze
F.B. aspiration	Choking followed by cough and asymptomatic for few days Followed by persistent wheeze
C.F	Wheeze with growth failure
Immune deficiency	Clubbing
Chr. aspiration syndrome	G.I. Symptoms Recurrent respiratory infection

Table 5: Causes of wheeze in hospital children (N-229).

Diagnosis	No	%
Asthma	112	55.46
Bronchiolitis	51	22.28
Bronchopneumonia	25	10.9
Laryngo tracho bronchitis	9	3.93
Mycoplasma bronchitis	5	2.18
Tuberculosis	2	0.9
Foreign body	2	0.9
Pertussis syndrome	1	0.45
GERD	1	0.45

- Use salbutamol (SABA) + Ipratropium (SAMA) every 20 min 3 times either by nebulization or meter dose inhaler in spacer.

Step II:

- Continue SABA + Ipratropium q30 min X 3 times followed by q 4-6hrs, to be weaned off and stopped in 24 h
- Use rescue steroids, either oral, hydrocortisone IV or methyl prednisone X 3 days
- I.V magnesium sulfate with monitoring facilities
- No improvement admit to ICU.[6,7]

Step III:

- I.V. Aminophylline infusion in ICU
- Non-invasive ventilation
- Mechanical ventilation as a last resort
- Wean off support systems with last in first out principle with improvement
- Discharge on SABA every 4-6hrs till the child is asymptomatic along with oral rescue steroids.

Always watch with the pulmonary index score while the patient is in the hospital.

DILEMMA IN USING NEBULISED STEROIDS IN ACUTE FLARE-UP OF ASTHMA

GINA – 2020 recommends inhaled corticosteroids in intermittent asthma cases since SABA only increases the risk of flare-up and low lung function and overuse of SABA more than 3 canister/year has a high risk of flare-up and more than 12 canister/year has a high mortality.

The review of literature on inhaled steroids in acute flare-up of asthma is controversial.[7-12] Our observations are –

- The use of nebulized steroids in acute flare-up of asthma is almost similar to oral prednisolone in response and not much of a satisfied improvement
- The use of nebulized budesonide in high doses is almost equal to oral steroids and did not decrease the hospitalization rate
- The use of fluticasone propionate nebulization is as beneficial as budesonide without the involvement of the adrenocortical axis
- At this stage, we clinicians have to keep in mind social determinants which dictate terms in the management. The societal preference is –
  - Oral medications
  - Single-dose medicines
  - Drugs with less adverse reactions
  - Less expensive drugs
  - Drug covered by health insurance.

In addition, we clinician should also pay attention to other logistics like –

- Maintenance of nebulizers at home
- Safety factors

- Patients compliance
- Impracticality
- Cost containment.

CONCLUSION

While evaluating flare up of acute wheezing in asthmatic children, the clinician should assess that it is asthma only, find out the risks for flare-up, and whether the patient had any previous near-fatal flare-ups and severity. If it is the first episode of wheeze, he has to rule out other possible causes which mimic asthma with red flag signs. While managing the patient of asthma with wheeze – the use of SABA +SAMA + steroids with humidified oxygen is recommended.

Inhaled high-dose steroid nebulization is still a controversial issue due to various factors, as discussed.

- SABA = Short-acting Beta- 2 agonists
- SAMA = Short-acting muscarinic agonist.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: Paramesh H. Clinicians dilemma in the management of acute flare-up wheeze with asthma: An update. Karnataka Pediatr J 2020;35(1):19-22.

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Karnataka Pediatric Journal

Review Article

Latest reviews regarding COVID-19 and its management

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Received : 03 June 2020
Accepted : 04 August 2020
Published :

DOI
10.25259/KPJ_4_2020

Quick Response Code:

ABSTRACT

We discuss briefly regarding the origin of the SARS-CoV-2 virus, it's structure, routes of transmission, and pathophysiology. Then, we go on to describe the symptomatology and clinical features based on different publications from different countries. Finally, we have summarized the variable guidelines available for the management and prevention of the COVID-19 disease.

Keywords: COVID-19, Corona, Corona in children, Management of Corona, Effect of corona in children

Coronavirus (CoV) is not a new virus. It is a large family of virus which has been causing different diseases such as common cold to Middle East respiratory syndrome (MERS-CoV) and severe acute respiratory syndrome (SARS-CoV).

Almost all viruses causing common cold go through genetic mutation and form new strains. Same way, the current coronavirus called SARS-CoV2 is a new strain that causes COVID-19 disease and bat appears to be the reservoir but the intermediate host(s) is unknown.[1]

Coronaviruses are zoonotic. Detailed investigations found that SARS-CoV transmitted from civet cats to humans and MERS-CoV came from dromedary camels.[2] There are more coronaviruses which are circulating in animals that have not yet infected humans.

SARS-CoV-2 viruses like other coronaviruses, are spherical, containing single-stranded RNA and have protein spikes protruding from their surface called spike protein [Figure 1]. These spikes latch onto human cells and undergo a structural change that allows the viral membrane to fuse with the host's cell membrane. The viral genes can then enter the host cell to be copied, producing more viruses.[3]

Latest work shows that, like the virus that caused the 2002 SARS outbreak, SARS-CoV-2 spikes bind to angiotensin-converting enzyme 2 (ACE2).[3]

SARS-CoV-2 spike is 10–20 times more likely to bind ACE2 which might be the reason why they are more infectious than the previous strains of CoV.[3]

Even though the structure of latest strains of virus is similar to SARS-CoV, three known antibodies against SARS-CoV could not bind to SARS-CoV2, which indicates that the treatment with antibodies of SARS-CoV is unlikely to be successful.[3]

ROUTES OF TRANSMISSION

- COVID-19 virus is transmitted through droplets and fomites, therefore, transmission can occur by direct contact with infected people and indirect contact with surfaces in the

immediate environment or with objects used on the infected person (e.g., stethoscope or thermometer).[4]
- Airborne transmission may be possible during procedures or support treatments that generate aerosols; that is, endotracheal intubation, bronchoscopy, open suctioning, administration of nebulized treatment, manual ventilation before intubation, turning the patient to the prone position, disconnecting the patient from the ventilator, non-invasive positive pressure ventilation, tracheostomy, and cardiopulmonary resuscitation.[4]
- Prolonged (up to a month) fecal shedding of viable virus has been identified in a limited number of case reports, but feco-oral route of transmission has not been reported to date.[4,5]
- Vertical transmission of COVID-19 to infant during delivery or breastfeeding remains to be confirmed.[6]

INCUBATION PERIOD

Incubation period varies from 1 to 14 days; mean period being 5–6 days.

CHILDREN

Limited data available in India regarding COVID-19 in children show that the prevalence of the disease is around 2% which corresponds to reports from other countries.

According to Joint Commission by China and CDC, COVID-19 seems to be rare and mild in individuals aged <18 years (2.4%) and out of these patients, only 2.5% developed severe and 0.2% went on to have critical disease.[1]

According to CDC report of the U.S. cases, 2% were of pediatric age group.[5,7]

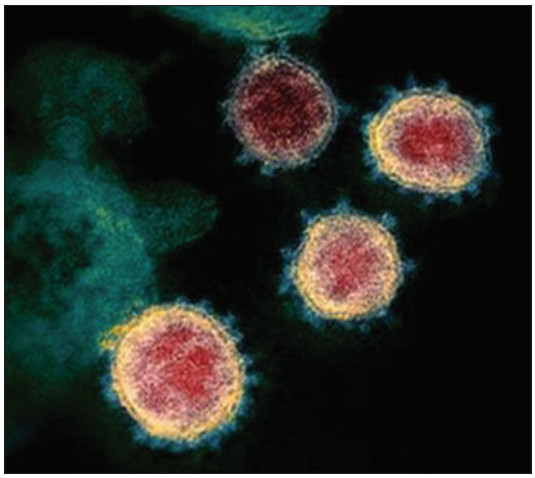

Figure 1: Transmission electron microscope image shows SARS-CoV-2.[3]

In Italy, 1.2% of COVID-19 cases were among the age group of <18 years.[8]

PATHOPHYSIOLOGY

ARDS

The primary pathology is characterized by diffuse alveolar damage through hyperinflammatory and direct effect of the virus activity.[9]

Cytokine storm

New evidences suggest that some patients respond to SARS-CoV2 with cytokine storm-like sepsis and HLH.[10]

THE SIGNS AND SYMPTOMS

Symptoms are non-specific and it can range from being asymptomatic to severe pneumonia and death [Table 1 and Figure 2].

Some children present in shock and with typical/atypical features of Kawasaki disease, which is a vascular inflammatory disease.

SEVERITY OF DISEASE

- Asymptomatic
- Mild-to-moderate disease: It includes non-pneumonia and mild pneumonia cases.[1]
- Severe disease: Categorized by dyspnea, respiratory distress, blood oxygen saturation ≤93%, PaO2/FiO2 ratio <300, and/or lung infiltrates >50% of the lung field within 24–48 h.[1]
- Critical: Respiratory failure, septic shock, and/or multiple organ dysfunction/failure.[1]

Table 1: Signs and symptoms among 291 pediatric (age <18 years) and 10,944 adult (age 18–64 years) patients* with laboratory-confirmed COVID-19 – United States, February 12–April 2, 2020.[7]

Sign/symptom	No. (%) with sign/symptom	
	Pediatric	Adult
Fever, cough, or shortness of breath	213 (73)	10,167 (93)
Fever	163 (56)	7794 (71)
Cough	158 (54)	8775 (80)
Headache	81 (28)	6,335 (58)
Sore throat	71 (24)	3,795 (35)
Myalgia	66 (23)	6713 (61)
Shortness of breath	39 (13)	4674 (43)
Diarrhea	37 (13)	3353 (31)
Nausea/vomiting	31 (11)	1746 (16)
Runny nose	21 (7.2)	757 (6.9)
Abdominal pain	17 (5.8)	1329 (12)

- High risk for severe and critical disease in younger age is underlying pulmonary pathology, immunocompromising conditions, obesity, and coinfection.[5]
- Pregnant women (8% had severe disease and 1% were critical): Risk of severity of the disease in pregnant and non-pregnant women of similar age appears to be equal.[1]

APPROACH TO DIAGNOSIS AND TREATMENT

History of epidemiology

1. Travel or residence history in containment zone and its surrounding areas or other communities with reported cases within 14 days before the onset of the disease.
2. History of contact with SARS-CoV2-positive patients within 14 days before the onset of the disease.

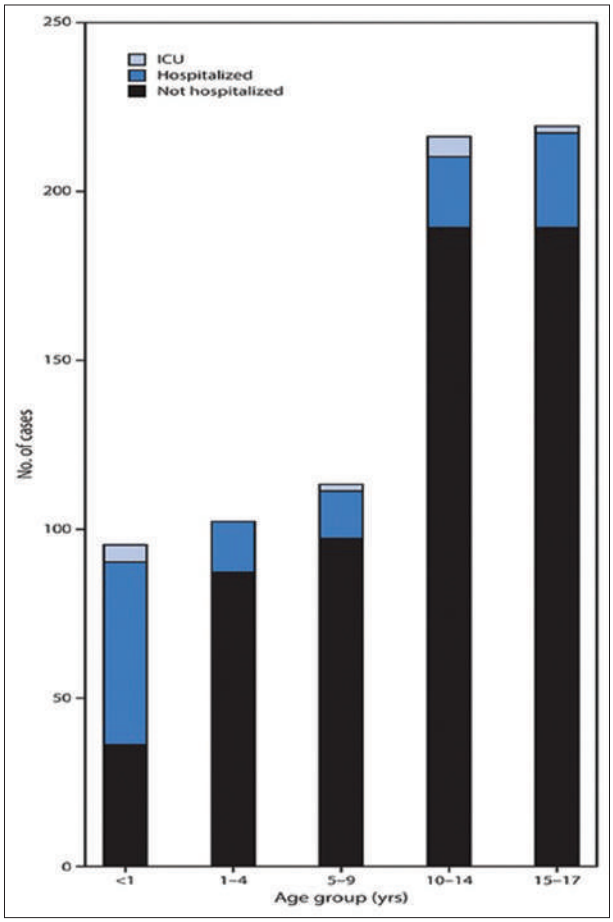

Figure 2: COVID-19 cases among children aged <18 years, among those with known hospitalization status (N = 745), †by age group and hospitalization status – United States, February 12–April 2, 2020.[7] †Number of children missing hospitalization status by age group: <1 year (303 of 398; 76%); 1–4 years (189 of 291; 65%); 5–9 years (275 of 388; 71%); 10–14 years (466 of 682; 68%); 15–17 years (594 of 813; 73%).

3. Contact with patients with fever or respiratory symptoms from containment zone and its surrounding areas or other communities with reported cases within 14 days before the onset of the disease.
4. Cluster infection: Within 2 weeks, 2 or more cases of fever, and/or respiratory symptoms occurred in small areas such as homes, offices, and school classes.

Clinical manifestations and laboratory findings

1. Fever and/or respiratory symptoms
2. Having the imaging features of COVID-19:
   a. Multiple patchy shadows and interstitial changes mostly in the lung periphery during the early stage of the disease.[10,11]
   b. Multiple ground-glass opacities (GGOs) and infiltration shadows in the later stage of the disease [Figure 3].
   c. Severe cases may develop consolidation of lung tissue.
   d. Diagnosis of hydrothorax is rare.[10,11]
3. The total leukocyte count is normal or decreased, or the lymphocyte count is normal or decreased in the early stage of the disease.[10,11]
4. They can have normal platelet count or thrombocytosis.
5. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are elevated, while procalcitonin is normal in adults, it may be elevated in pediatric patients.[11]
6. Some patients have an increase in liver enzymes, lactate dehydrogenase (LDH), muscle enzymes, and myoglobin.
7. Elevated troponin is seen in some critically ill patients.
8. In severe cases, D-dimer increases and peripheral blood lymphocytes progressively decrease.
9. Severe and critically ill patients often have elevated inflammatory factors.

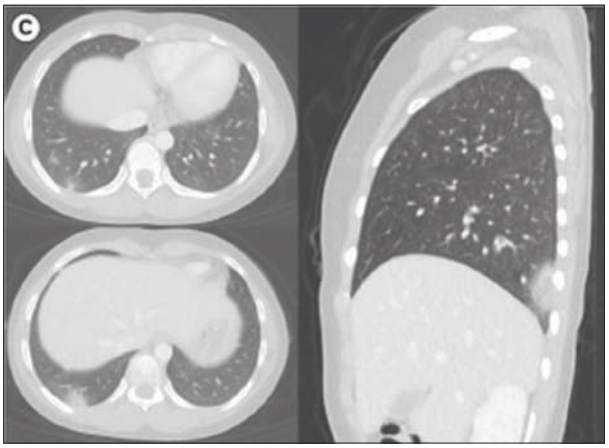

Figure 3: (C) Chest CT performed on the fourth day since symptom onset demonstrates patchy nodular consolidations with peripheral ground glass opacities in subpleural areas of the right lower lobe in axial and sagittal views of CT.[15]

10. Some present with multisystem inflammatory syndrome in children (MIS-C):[12]
    a. Defined by fever >24 h, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological); AND
    b. No alternative plausible diagnosis; AND
    c. Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks before the onset of symptoms

Some individuals may fulfill full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C.

Diagnosis of COVID-19

Is confirmed when suspected case with one of the following serological evidences:

1. The result of RT-PCR for SARS-CoV2 is positive.[13,14]
2. Serum IgM antibodies and IgG antibodies to SARS-CoV2 are positive; serum IgG antibodies to SARS-CoV2 turn from negative to positive or the IgG antibody titers of recovery period are 4 times or more higher than that of acute phase.[13,14]
3. The result of virus gene sequencing analysis is highly homologous with the known SARS-CoV2.[13,14]

PREVENTION

1. Practice good personal hygiene:
    a. Cover mouth and nose with a tissue when coughing or sneezing.
    b. Wash hands frequently.
    c. Do not touch mouth, eyes, and nose with dirty hands, and do not spit on the ground.
2. Avoid family gatherings and eat separately, as during meal everyone, are in close contact.
3. Avoid public places as much as possible.
4. Keep house well ventilated and sunlit.
5. Wear a mask if you have cold, cough, or fever. Consult a doctor and mention about travel history or if you have come across any individual who is suspected to have COVID-19 or diagnosed with COVID-19 in the past 14 days.[13]

TREATMENT

- Confirmed and suspected cases should be isolated and treated in designated hospitals with effective isolation and protective conditions, and suspected cases should be isolated in separate rooms.
- Self-isolation in pediatric age group is difficult. Considering the circumstances, the Korean Centers for Disease Control and Prevention and the Korean Society of Pediatric Infectious Diseases recommend one of the family members to be assigned as a caregiver for infants and young children who are suspected or confirmed with COVID-19, and the caregiver should take adequate measures to avoid being exposed to the virus. Thus, further pediatric-specific guidelines on the isolation and adequate personal protective equipment for caregivers should be prepared.[15]
- Multiple confirmed cases can be admitted in the same ward, and critical cases should be shifted to ICU as soon as possible.
- General treatments: Patients should be on bed rest, monitor vitals, connect them to pulse oximeter to monitor oxygen saturation, keep them well hydrated without causing fluid overload, prevent electrolyte imbalance, hourly visits to look out for respiratory distress and importantly, should receive adequate nutrition.
- Complete blood count, urinalysis, CRP, biochemical indicators (liver enzyme, myocardial enzyme, renal function, etc.), blood coagulation function, arterial blood gas analysis, and chest imaging should be investigated according to the conditions of the patients.
- Cytokines testing can be done if available.
- Effective oxygen therapy measures should be provided in time, using nasal cannula, oxygen masks, and high-flow nasal cannula oxygen therapy.
- Early intubation and protective mechanical ventilation are recommended and make sure closed tracheal aspiration systems are used.[16]
- NIV to be avoided due to high risk of aerosol dispersion.[16]
- Treatment with nitric oxide and/or sildenafil (0.5–2 mg/kg/dose Q4–6 h with a maximum of 20 mg/dose Q8 hours) for patients with persistent hypoxemia.[16]
- ECMO

ANTI-VIRUS TREATMENT

- Hydroxychloroquine/chloroquine (5–10 mg/kg/day of basic chloroquine for 10 days) and azithromycin (10 mg/kg on the 1st day, followed by 5 mg/kg/day for 4 days with a maximum dose of 30 mg/kg or 1500 mg).[16]
- Antiviral agents, such as oseltamivir, ribavirin, ganciclovir, remdesivir, lopinavir, and ritonavir, have been used to reduce the viral load to prevent potential respiratory complications without any success.[16]

IMMUNOMODULATORY TREATMENT IN CHILDREN WITH COVID-19

- Glucocorticoids to be considered in patients with COVID-19 and hyperinflammation.[17]

- Anakinra at >4 mg/kg/day I.V/S.C is found to be safe in severe infection and maybe be beneficial if administered before invasive ventilation.
- Tocilizumab (<30 kg: 12 mg/kg IV; >30 kg: 8 mg/kg IV, max: 800 mg) may be effective in reducing the mortality. It may increase risk of bacterial and fungal infection.[17,18]

ANTIPLATELET AND ANTICOAGULATION THERAPY IN MIS-C

- Low-dose aspirin (3–5 mg/kg/day; max 81 mg/day) in MIS-C and KD-like features and/or thrombocytosis (platelet count ≥450,000/μL) and continued until normalization of platelet count and confirmed normal coronary arteries at ≥4 weeks after diagnosis. Contraindicated in patients with a platelet count ≤80,000/μL.[17]
- Children with dilated coronary artery are recommended to receive enoxaparin at therapeutic dose along with low dose of aspirin.[17]
- For MIS-C patients who do not meet the mentioned criteria should have a tailored antiplatelet and anticoagulation therapy based on risk for thrombosis.[17]

IMMUNOMODULATORY TREATMENT IN MIS-C

- High-dose IVIG (typically 1–2 g/kg) is recommended for the treatment of MIS-C. Cardiac function and hydration status should be checked before IVIG administration. IVIG to be administered when cardiac function is restored.[17]
- Low-moderate-dose glucocorticoids to be considered for the treatment of MIS-C. High-dose, IV pulse glucocorticoids may be considered to treat patients with life-threatening complications, such as shock, especially refractory shock.[17]
- Anakinra (IV or SQ) can be considered for the treatment of MIS-C refractory to IVIG and glucocorticoids or in patients with contraindications to these treatments.[17]

DISCHARGE CRITERIA

- Clinical recovery:
  - Afebrile >3 days,
  - Resolution of symptoms and radiologic improvement.
- Two negative PCR tests taken 24 h apart.[14]

PROGRESSION OF DISEASE

- From the data available, the average time taken from the onset of disease to clinical recovery for mild cases is approximately 2 weeks, while it is 3–6 weeks for patients with severe or critical disease.[14]
- Onset of severe disease from initial symptoms, including hypoxia, is 1 week.[14]
- Among patients who have died, the duration of the disease ranges from 2 to 8 weeks.[14]

Early identification of cases and contacts allows for earlier treatment and better recovery.

PROGNOSIS

- Symptoms in infected children are relatively mild.
- According to the cases currently treated, most of the patients have a good prognosis and a few are in severe condition.
- The prognosis of the elderly and patients with chronic underlying diseases is relatively poor.
- Prognosis of COVID-19 in pregnant and non-pregnant women of similar age appears to be equal.[14]

RECOMMENDATIONS AFTER DISCHARGE

- After discharge, it is advised to continue to monitor self-health for 2 weeks, wear mask, and if possible, live in a single room with adequate ventilation.
- Avoid close contact with family members, eat separately, keep hands clean, and avoid outdoor activities.
- Go to the hospital for a follow-up visit at the 2nd and 4th weeks after discharge or at the onset of recurrence of any symptoms.[14]

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: Hossain MI, Raghunath CN. Latest reviews regarding COVID-19 and its management. Karnataka Pediatr J 2020;35(1):23-8.

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Karnataka Pediatric Journal

Review Article

Responsible antibiotic therapy simplified

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Received : 07 June 2020
Accepted : 04 July 2020
Published :

DOI
10.25259/KPJ_5_2020

Quick Response Code:

ABSTRACT

Antimicrobial resistance is a global problem and is particularly pressing in developing countries where the infectious disease burden is very high. In developing countries, where relatively easy availability and higher consumption of medicines have led to disproportionately higher incidence of inappropriate use of antibiotics and greater levels of resistance compared to developed countries. The bacterial disease burden in India is among the highest in the world; consequently, antibiotics will play a critical role in limiting morbidity and mortality in the country. Improving antibiotic prescribing and use is critical to effectively treat infections, protect patients from harms caused by unnecessary antibiotic use, and combat antibiotic resistance. Responsible antibiotic therapy is one of the most important components of antibiotic stewardship. The current article is an attempt to provide a set of key principles to guide efforts to improve responsible and rational antibiotic use.

Keywords: Antibiotic, Rational therapy, Antimicrobial resistance

INTRODUCTION

Antimicrobial resistance (AMR) is a global problem and is particularly pressing in developing countries where the infectious disease burden is very high. Easy availability and irrational use of antimicrobials and relatively higher use of these molecules are associated with higher levels of resistance in developing countries as compared to developed countries.[1] In India, the infectious disease burden is very high resulting in more rampant use of antimicrobial agents which are often found to be inappropriate and irrational leading to increase in the development of AMR.[2]

What is the need for responsible antibiotic therapy?

Penicillin, the first antibiotic, was discovered by Alexander Fleming the in 1928, and then it was introduced on a large scale for the treatment of bacterial infections in 1945. This marked the beginning of the so-called "golden era" of antibiotics (1945–1962). However, irresponsible use of antibiotics has made so many antibiotics a toothless weapon to fight against many bacterial infections. As a result antibiotic-resistant bacteria are emerging very fast and are becoming more and more difficult to manage, making available antibiotics ineffective. The antibiotic pipeline is becoming dryer and dryer and today, we are left with very few novel antibiotic classes in the pipeline [Figure 1].[3]

It is important to understand that the problem of antibiotic resistance cannot be "solved" by the discovery of one or few new antibiotics. Whenever an antibiotic is used, either in human beings or in animals or plants, whether appropriately or not, the chances of the development and spread of antibiotic-resistant bacteria are increased.[4] The bacterial disease burden in India is among

the highest in the world; consequently, antibiotics will play a critical role in limiting morbidity and mortality in the country. It is estimated that by the year 2050, Asia will have 4.7 million deaths that could be directly attributed to AMR.[5] AMR is rampant in India with up to 12–59% of *Escherichia coli* being extended beta-lactamase (ESBL) producers and up to 30% being carbapenemase producers. *Klebsiella pneumonia* has emerged over the last few years as a highly resistant pathogen with up to 50% resistance to carbapenems and rapidly increasing resistance to polymyxins. In addition, methicillin resistance in *Staphylococcus aureus* is seen in up to 30% of *S. aureus* isolates nationally.[5] There is not much data on high incidence of vancomycin-resistant enterococci in India. However, reduced susceptibility to vancomycin was observed in a study in about 12% of the isolates of *Enterococcus faecalis*.[6]

It is well documented that antibiotic abuse is one of the major drivers of antibiotic resistance and thus optimizing usage of antibiotics is the need of the hour.

What is irresponsible antibiotic use?

Antibiotics are being prescribed for indications in which their use is not warranted. In India, between 2005 and 2009, the units of antibiotics sold increased by about 40%.[7] Antibiotics are treated as antipyretics and all febrile illnesses are referred as antibiotic deficiency states. This is because of clinicians' erroneous trust in antibiotics which is further compounded by a wrong belief that they will prevent secondary bacterial infections. Few commonest situations for the antimicrobial misuse are as under:

1. Fever without focus
2. Minor skin infections
3. Nonspecific upper respiratory tract infections such as Rhinitis, and tonsillopharyngitis
4. Bronchitis
5. Asthma/Bronchiolitis/WALRI
6. Gastroenteritis
7. Non-infectious fever
8. To prevent secondary bacterial infection in viral illness
9. To prevent bacterial infection in normal newborns
10. Asymptomatic bacteriuria and pyuria including in catheterized patients
11. Microbial colonization and culture contamination.

RESPONSIBLE ANTIBIOTIC THERPY: A SIMPLIFIED APPROACH

When antibiotic is needed?

1. Definitive: Proven pathogen with or without antibiotic susceptibility result
2. Empirical: Infection most likely but exact organism and sensitivity not known
3. Pre-emptive: Infection probable but not proved
4. Prophylactic for certain conditions only (not discussed in this article).

Definitive antimicrobial therapy

Establishing microbial diagnosis

Antibiotics are ideally needed when there is proven bacterial infection, which can be identified by isolating an organism from sterile body fluids, blood, or tissue from site of infection by culture along with antibiotic susceptibility test. However, in clinical practice this is not always possible because of number of limiting factors.[8]

1. Tests for detection of organisms have been sent but results are awaited
2. Affordability and availability
3. Prior antibiotic use
4. Slow growing and fastidious organisms
5. Improper collection and transport of specimen and culture media.

In such cases, non-culture methods should be used to establish diagnosis of bacterial infections. This includes smear examination, antigen detection test, rapid tests, serological tests, and molecular tests such as PCR. Premature initiation of antimicrobial therapy without attempting microbial diagnosis can suppress bacterial growth and preclude the opportunity to establish a microbiological diagnosis, which is

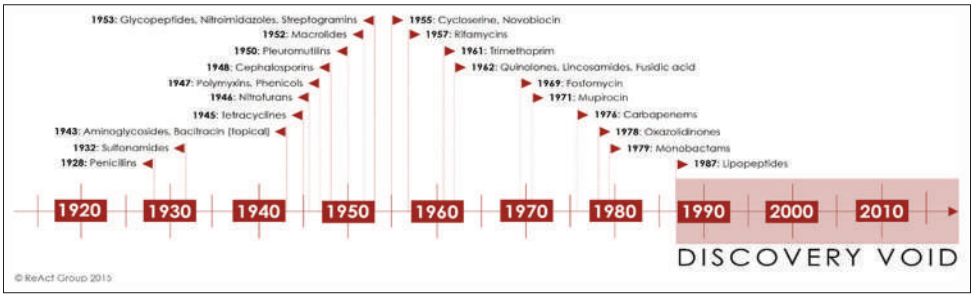

Figure 1: Time-line of the discovery of different antibiotic classes in clinical use. "The discovery void" refers to the period from 1987 until today, as the last antibiotic class that has been successfully introduced as treatment was discovered in 1987. Adapted from.

at times going to be so critical in the management of certain cases, who may require several weeks to months of directed antimicrobial therapy to achieve cure (e.g., endocarditis, septic arthritis, and meningitis). To optimize an accurate microbiological diagnosis, clinicians should ensure that diagnostic specimens are properly obtained and promptly submitted to the microbiology laboratory.

Initiation of antibiotic therapy pending culture and sensitivity reports

The best approach would be to rule out a life-threatening infection and if the child is stable, to wait and watch for the evolution of the illness. However, in cases, where it is reasonably certain that there is a possibility of a bacterial infection and waiting is dangerous/detrimental, initial therapy for infection is often empiric as guided by the clinical presentation, supportive lab evidences and will be modified or stopped as per the reports. Initiation of antibiotic too early, in such situation, will mask the gravity of illness, give false sense of security and results in poor outcome.

Interpretation of culture and sensitivity patterns to guide antibiotic therapy further

a. When an organism is identified, it is very crucial to start antibiotics pointed toward true pathogen. Contaminants and commensals should never be treated

Contaminants are the organisms from skin, unsterile instrument whereas colonizers are the organisms from non-sterile body parts, catheter, endotracheal tube, etc., and do not cause infection. Some of the examples are as under

- *S. pneumonia* and meningococci from nasopharynx
- Gonococci from vaginal secretions
- *E. coli* from stool or rectal swab
- *Pseudomonas* in the endotracheal tube
- *Candida* in urine
- Staph from throat
- CONS.

b. When a pathogenic microorganism is identified in clinical cultures, the next step performed is antimicrobial susceptibility testing (AST). AST measures the ability of a specific organism to grow in the presence of a particular drug *in vitro* and it indicates that the isolate is likely to be inhibited by the usually achievable concentration of a particular antimicrobial agent when the test is performed using guidelines established by the Clinical and Laboratory Standards Institute.[9] Data are reported in the form of minimum inhibitory concentration (MIC), which are the lowest concentration of an antibiotic that inhibits visible growth of a microorganism after an overnight incubation, and are interpreted by the laboratory as "susceptible," "resistant," or "intermediate," according to Clinical and Laboratory Standards Institute criteria. Some laboratory interprets susceptibility in terms of "zone of inhibition" and is presented as zone diameter. However, such methods are erroneous and hence MIC based reports are always recommended in clinical practice. However, one should not blindly follow the sensitivity reports and should be guided by the clinical condition of the child.

As described below, AST has some limitations that should be kept in mind.[10]

a. *In vivo* and *in vitro* mismatch – Some organisms carry enzymes that, when expressed *in vivo*, can inactivate antimicrobial agents to which the organism shows *in vitro* susceptibility. For example, ESBLs in Enterobacteriaceae are enzymes that mediate resistance to almost all β-lactam agents except carbapenems (e.g., meropenem or imipenem). The production of ESBL should also be suspected when treatment with β-lactams fails despite apparent *in vitro* susceptibility
b. One should also remember that *in vitro* sensitivities do not always result in clinical cure (e.g., aminoglycosides cannot cure enteric fever even though the report always shows salmonella sensitivity to all of them)
c. Clinical laboratories may provide different AST interpretations for different sites of infection (e.g., meningitis and non-meningitis AST results for *S. pneumonia*).

Empiric therapy

In certain cases, the empirical use of antibiotics may be scientifically acceptable, if few prerequisites are judiciously met with. These include clinically near-certain bacterial infections with or without indirect evidence of infection as determined by leukocytosis (or leukopenia in neonates), acute phase reactants (such as CRP, and procalcitonin), detection of antigen, serological tests, radiology (consolidation on X-ray), and exudates (pleural fluid, CSF, joint aspirates, abscesses, etc.). In such cases, antibiotics can be used without awaiting definite identification of the causative organism after sending investigations aimed at making a microbiological diagnosis (if available and feasible). Ideally, all empiric and preemptive therapy should end up to definitive therapy.

The followings are situations where empiric therapy is justified.

Clinically certain bacterial infection

In certain clear-cut clinical situations, specific microbiological tests are not typically performed, and one is justified to start antibiotics at a first stretch. Here, single antimicrobial agents with a narrowest spectrum should be

directed at the most likely pathogens for the duration of therapy for clinically certain bacterial infections such as community-acquired pneumonia, otitis media, diphtheria, bacillary dysentery, acute lymphadenitis, or cellulitis in the ambulatory setting.

High probability of bacterial infection while waiting for lab results

In stable clinical circumstances, antimicrobial therapy should be deliberately withheld until appropriate specimens have been collected and submitted to the microbiology laboratory. Important examples of this principle are suspected of enteric fever, urinary tract infection, infective endocarditis, osteoarticular infections, etc. Patients with these infections are frequently ill for a period of several days to weeks, and in such situations, antibiotic therapy should be delayed until multiple sets of blood cultures have been obtained.

High probability of bacterial infection and waiting is dangerous

In critically ill patients, such as those in septic shock, febrile neutropenic patients, and patients with suspected bacterial meningitis, sick looking neonate empiric therapy, often with a broad coverage, should be initiated as soon as possible, once appropriate diagnostic specimens have been collected. In these situations timing of first dose is very vital and it often decides the overall outcome. It has been shown that delayed and/or inadequate therapy for infections in critically ill, hospitalized patients are associated with poor outcomes, including greater morbidity and mortality, as well as increased length of stay.[11] Therefore, a common approach is to use broad-spectrum antimicrobial agents as initial empiric therapy (sometimes with a combination of antimicrobial agents) to cover multiple possible pathogens commonly associated with a given clinical situation. This is true for both community- and hospital-acquired infections. Once microbiology results have helped us to detect the etiologic agent with or without antimicrobial susceptibility reports, every attempt should be made to narrow the antibiotic spectrum (de-escalation). This is very crucial component of antibiotic stewardship because it can reduce the cost and toxicity and prevent the emergence of AMR in the community.

Atypical course of a viral infection

The atypical course of a viral disease may indicate the likelihood of post-viral bacterial complications, and it is justified to start antibiotic empirically after drawing appropriate samples, for example, post-measles pneumonia, H1N1, and COVID 19.

Choosing an empiric antibiotic

1. Establishing a clinical diagnosis: Viral or bacterial?

A clinical diagnosis most often helps us to predict causative pathogens fitting into a clinical syndrome which would tailor the correct antibiotic rather than blindly relying on fever, WBC counts, CRP, procalcitonin, cultures, or radiology to make a diagnosis of infection.

Fever is a cardinal symptom of infection. This infection can be viral, bacterial, or otherwise. Viral infections are disseminated through body systems (e.g., upper as well as lower respiratory tract), may affect multiple systems (respiratory and gastrointestinal), and generally spread from and to close contacts.

In short duration illnesses, the fever pattern gives us the diagnosis in the majority of the patients [Table 1].

Viral infection

High grade at the onset, fair response to paracetamol, a normal inter-febrile period and a rhythmic fever (comes up as soon as the antipyretic action of the drug wanes), the appearance of cold, cough on days 2–3, and decreasing fever by days 3–4. However, atypical progress in a suspected viral infection may a complicating bacterial infection, and antibiotics may be justified in such cases, for example, post-measles pneumonia, and pneumonia complicating flu.

Bacterial infection

Fever moderate to high at onset, poor response to paracetamol, sick inter-febrile period, and fever not abating or worsening by days 3–4. This suggests a localized bacterial infection. We should look for the focus of infection such as tonsillitis, urinary tract infection, adenoiditis, or bacillary dysentery. Once focus is identified that empirical antibiotic is justified.

Mild-to-moderate fever at the onset, child getting sicker in the inter-febrile period as the days progress, poor response to antipyretics, and trend of fever worsening by days 3–4. This suggests a bacteremic bacterial infection. It may localize to the lungs (pneumonia) or meninges (meningitis) by days 3–4 or may not localize (typhoid fever). In such situation, an empiric antibiotic is started after appropriate samples for culture, and other investigations are obtained.

At the same time, it is very important to remember non-infectious causes of fever such as Kawasaki disease, rhreumatological disorders, malignancy, dehydration fever, heat fever, and drug fever. Fever may also be absent in the presence of bacterial infection in certain situations such as sick neonate, immune-compromised child, whooping cough, chronic sinusitis, and tuberculosis.

Once it is reasonably certain that one is really dealing with a possible bacterial infection, an attempt should be made to

select the most appropriate antibiotic, while making such decision following factors are considered, [Table 2].

2. Which is the likely organism? Which antibiotic is appropriate for the given situation?

We need to know the likely pathogens generally causing a particular illness in a particular age group. Age and site of infection are very crucial to predict the offending bug, for example, pneumonia in a school going child; acute otitis media in a toddler; and sepsis in a neonate. Having considered the possible pathogenic organisms, think about the antibiotics to which each of these organisms is sensitive.

One may not undergo this exercise every time. It will be very easy and practical to follow protocols and guidelines suggested by various organizations such as WHO, CDC, IDSA, and IAP [Tables 3 and 4]. Remember that it should be evidence based and as per your local epidemiology and drug susceptibility pattern.

Hospital-acquired infections or nosocomial infections are also a global health issue and have different epidemiology and varied dynamics. The rate of nosocomial infections is higher in developing countries than in developed world. They are associated with cause prolonged stay, disability, and financial burden. Most prevalent hospital associated infections include central line-associated bloodstream infections, catheter-associated urinary tract infections, surgical site infections, and ventilator-associated pneumonia. They are commonly caused by drug-resistant organisms, both Gram-positive (e.g., methicillin-resistant *Staphylococcus aureus* [MRSA]) and Gram-negative (e.g., *Pseudomonas aeruginosa*) bacteria, which are often endemic in hospitals [Table 5].

In selecting empiric antimicrobial therapy for such infections, one should consider the following factors: (1) The site of infection; (2) the organisms most likely to be colonizing that site. It is well-known that, intravascular catheter-related bacteremia is frequently a result of colonization and infection caused by staphylococci present on the skin; (3) colonization with a known organism (e.g., a screening nasal swab for MRSA) before admitting patients to the intensive care unit in situation where MRSA is highly prevalent or an outbreak situation; and (4) the local bacterial resistance patterns or antibiograms when available.

Ensure chosen antibiotic has adequate tissue penetration at the site of infection. Antibiotic penetration at the site of infection is very crucial especially in severe life-threatening infections. An antibiotic that penetrates well into the meninges is a pre-requisite for treating meningitis or sepsis in a neonate. BL-BLI and to some extent Vancomycin has poor penetration in the brain and lungs, respectively, therefore may not be a good choice for meningitis or pneumonia.[12] Excretion of the antibiotic through the biliary tract is an advantage for treating cholangitis or enteric fever where the bacteria sequestrate in that tract. Furthermore, aminoglycosides have poor penetration into the cells and therefore are unsuitable for treating infections where the organisms are primarily intracellular, for example,

Table 1: Difference between viral and bacterial infection.

Viral	Bacterial
Affects multiple mucosal systems of body	Bacterial infection is localized to one system or organ
Fever high at onset but settles within next 5 days	Fever moderate at the start, peaks by 4–5 days
Child comfortable during inter- febrile period	Child looks sick and often toxic during interfebrile period
Similar cases in family and community	Draining lymph node often enlarged
CBC not contributory, as polymorphonuclear preponderance is seen in first 2 days of viral illness	
Antibiotics – no role	Narrow spectrum appropriate single antibiotic

Table 2: Factors to decide choice of antibiotic.

Host related factors	Organism and drug related factors
Clinical presentation including site of infection, and severity of the disease.	Microbial local drug sensitivity pattern
Age	Microbial drug resistance pattern
Nutrition	Local epidemiology
Immune status comorbidity	Pharmacokinetic and pharmacodynamic aspects of drug
Vaccination	
Prior antibiotic usage/ admission/procedure/ device	

Table 3: Organisms for community acquired infections.

Tonsillopharyngitis	GABHS, *Corynebacterium diphtheriae*
Acute otitis media/sinusitis	*S. pneumonia, H. Influenzae B, Moraxella catarrhalis*
Pneumonia	*S. pneumonia, H. Influenzae B, Staphylococcus aureus, Mycoplasma*
Enteric fever	*Salmonella* Typhi, Paratyphi
Dysentery	*Shigella*
UTI	*E. coli, Proteus, Klebsiella*
Pyogenic meningitis	*S. pneumonia, H. Influenzae B, Neisseria meningitides*

S. pneumonia: Streptococcus pneumonia, H. Influenzae: Haemophilus Influenzae

Table 4: Clinical aspects of common infections in office practice and choice of antibiotic.

Condition	Associated features	Remarks	Antibiotic choice
Tonsillopharyngitis	Fever, throat pain, exudates on tonsils, lymph node±	Age usually above 4 years	Amoxicillin for 10 days 40 mg/kg
AOM	Fever, excessive crying, URTI, ear discharge, otalgia	Otoscopy must	Amoxicillin 40 mg/kg for 10 days for <2 years, otherwise 7 days
Sinusitis	Fever, cough, nasal discharge	Often underdiagnosed	Amoxicillin 40 mg/kg for 10 days
Pneumonia	Rapid breathing Cough	Admit age <3 months severe disease oral switch as soon as possible	Amoxicillin 40 mg/kg or amoxiclav or ceftriaxone or cefotaxime 100 mg/kg for 5–7 days
Cellulitis, impetigo, pustulosis	Skin lesions	Topical mupirocin only in the absence of systemic manifestation and localized lesions	Cephalexin/cefadroxil 30–50 mg/kg for 5 days
lymphadenitis	Tender swelling	Check for recurrence, other lymph nodes, organomegaly, anemia chronicity general well-being, growth	Cephalexin/cefadroxil 30–50 mg/kg for 7 days
Bacillary dysentery	Macroscopic blood in stool	Toxemia temp tenesmus	Cefixime 8–10 mg/kg for 5 days
UTI	Urinary complaints, may may present fever without focus	Culture always, USG always, MCU as indicated, DMSA scan as indicated	Cefixime, amoxicillin for 7–10 days. Prophylaxis may be required
Typhoid fever	Fever, pain in abdomen, vomiting, toxemia	Admit if needed, blood culture must	Cefixime 20 mg/kg for 14 days ceftriaxone 100 mg/kg/day in admitted cases
Pyogenic meningitis	Fever, irritability, convulsion, vomiting, altered senses	Always IV, no oral switch, duration depends upon organism	Ceftriaxone 100 mg/kg plus vancomycin* for 7 – 10 days depending on the bug. Complete for 2 weeks if no bug is isolated

In most of the community acquired bacterial infections above the diaphragm amoxicillin or at the most amoxiclav is sufficient. For suspected *staphylococcal pneumonia* cloxacillin or cefazoline is recommended. For methicillin-resistant *Staphylococcus aureus* one can use vancomycin or linezolid. In bacterial infections below the diaphragm third generation cephalosporin is justified. Vancomycin until culture sensitivity report, in view of rising incidence of DRSP in meningitis*

Table 5: Organisms for hospital-acquired infections.

Vascular related bloodstream infection	CONS, enterococci, MRSA, Enterobacter, *Pseudomonas*
Shunt infection	CONS, MRSA, *Propionibacterium acnes*
Urinary catheter-related infections	*E. coli* and Gram-negative bacilli
VAP/HAP early onset	*Enterobacteriaceae, Haemophilus*, MSSA, *S. pneumonaie*
HAP late onset	*Pseudomonas, Acinetobacter,* MRSA

MRSA: Methicillin-resistant *Staphylococcus aureus*

Salmonella. Antimicrobial concentrations attained at some sites (e.g., ocular fluid, CSF, abscess cavity, and bone) are often much lower than serum levels. For example, first- and second-generation cephalosporins and macrolides do not cross the blood–brain barrier and are not recommended for the central nervous system infections. Daptomycin, an excellent bactericidal agent against gram-positive bacteria, is not useful for the treatment of pneumonia (e.g., pneumococcal pneumonia) because it is inactivated by lung surfactant.[13] Sometimes antibiotics belonging to the same class have different clinical implications, for example, quinolone group of antibiotics. Moxifloxacin does not achieve significant urinary concentrations, making it unsuitable for the treatment of UTIs. Levofloxacin and ciprofloxacin are excellent choices for UTIs caused by susceptible bacteria. Some quinolones such as levofloxacin and moxifloxacin are also used as respiratory quinolones while others are not. In addition, route, dose, and duration of therapy will also be decided by site of infection, for example, meningitis, septic shock, and febrile neutropenia where parenteral antibiotics for relatively longer duration is needed.

1. What is the route, frequency, and duration?

Route

Intravenous administration is compulsory in seriously ill patients where predictable concentration of drug is required such as bacterial meningitis, infective endocarditis, and neonatal sepsis. Patients with active infections on parenteral antibiotics, once show signs and symptoms of improving clinical status or resolving, can be switched on oral therapy. In invasive infections such as pneumonia, pyelonephritis,

or abscesses, oral formulation should be appropriately selected which has an excellent absorption and bioavailability and minimal GI side effects. Gastrointestinal bleeds, intolerance to oral medications, and adherence issues are the contraindications for oral route.

Please remember that more serious infections, in which high serum or CSF drug concentrations are desired, a switch to oral therapy is less reliable and not generally recommended. Such conditions include neonatal sepsis, bacterial meningitis, infective endocarditis, febrile neutropenia, brain abscess, and orbital cellulitis.

Dosing interval

This is very crucial factor as it helps

- To optimize empiric therapy
- To maintain therapeutic levels
- To reduce toxicity
- To prevent AMR.

Certain antibiotics such as β-lactams and vancomycin exhibit time-dependent activity [Figure 2]. They have relatively slow bactericidal action and are effective because of the extensive amount of time the antibiotic binds to the microorganism. Hence, for this group of antibiotics their serum concentration must exceed the MIC for the duration of the dosing interval, and this can be optimized either through continuous infusion or frequent dosing. On the other hand, certain antibiotics such as aminoglycosides, fluoroquinolones, metronidazole, and daptomycin exhibit concentration-dependent killing [Figure 3]. They achieve high concentrations at the binding site which eradicates the microorganism and their bactericidal activity is enhanced as the serum concentration is increased. With these agents, the "peak" serum concentration, are more closely associated with efficacy. The frequency of the dosing interval does not matter significantly.

Duration of antibiotic therapy

It is very important to optimize the duration of antibiotic therapy. The duration should be optimum to achieve desired therapeutic response with no or minimal side effects and to prevent resistance as well. Longer than necessary courses carry higher risks of adverse effects, non-adherence issues, selection pressure, and high cost. A number of studies have stressed an emphasis on shorter courses of therapy, especially in community acquired infections [Table 6].[13]

Use of rational antimicrobial combinations

Most of the time in clinical practice single-agent antimicrobial therapy is generally preferred. Antibiotic combinations of two or more agents are recommended in few selected cases.

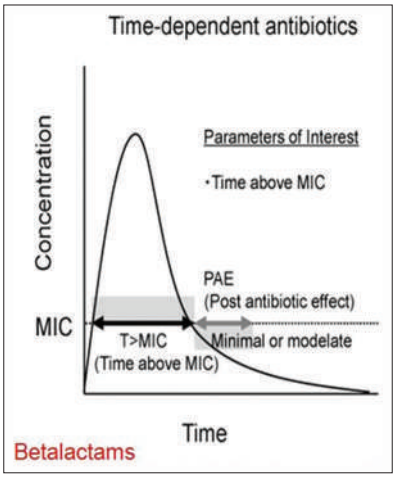

Figure 2: Time dependent activity of antibiotics.

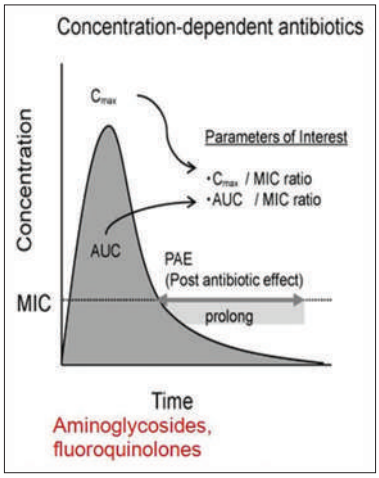

Figure 3: Concentration dependent activity of antibiotics.

Table 6: Short duration therapy.

Disease	Treatment, days	
	Short	Long
Community-acquired pneumonia	3–5	7–10
Nosocomial pneumonia	≤8	10–15
Pyelonephritis	5-7	10–14
Intra-abdominal infection	4	10
Acute bacterial sinusitis	5	10
Cellulitis	5–6	10

For synergistic activity against a microorganism

Synergistic action implies that *in vitro* the combined effect of the antimicrobial agents is greater than the sum of their independent activities measured separately.[14] For example, the combination of certain β-lactams and aminoglycosides exhibits synergistic activity against a variety of Gram-positive and Gram-negative bacteria and is used in the treatment of

serious infections, for which rapid killing is essential (e.g., treatment of endocarditis caused by *Enterococcus* species with a combination of penicillin and gentamicin). Here, penicillin alone is only bacteriostatic, and gentamicin alone has no significant activity but when gentamicin is used with penicillin, the combination imparts much desires bactericidal action. Similarly for endocarditis due to *S. viridans*, a combination of penicillin or ceftriaxone with gentamicin results in a more rapid clearance of microorganisms. With this synergistic combination 2-week duration of therapy can be as effective as penicillin or ceftriaxone used alone for 4 weeks.

In a critically ill patients empiric therapy before microbiological etiology and/or antimicrobial susceptibility can be determined

Combination therapy is used in this setting to ensure that at least one of the administered antimicrobial agents will be active against the suspected organism(s). For example, when a patient has been hospitalized for serious septic shock, it would be appropriate to provide initial therapy with two agents that have activity against both Gram-positive and Gram-negative organisms.

For treatment of polymicrobial infections

Certain infections are caused by more than one organism. In such instances a combination regimen may be preferred for a comprehensive broader spectrum to target possible polymicrobial agents, intra-abdominal infections brain abscess, necrotizing fasciitis, etc., are poly microbial infections. Antimicrobial combinations, such as a third-generation cephalosporin or a fluoroquinolone plus metronidazole, can be used as a potential treatment option in intra-abdominal infections and can be more cost-effective than use of single molecule like carabapenem.

To prevent emergence of resistance

The emergence of AMR is generally the result of selective pressure from antimicrobial therapy probability of emergence of resistance against two drugs is lower as compared with a single drug. While using combination therapy we are reassured that at least one drug will be effective, and this in turn prevents the resistant mutant population from emerging as the dominant strain. The classic examples for such combination drug therapy include use of more than 3 or 4 drugs in the treatment of infections requiring long duration therapy such as tuberculosis and the human immunodeficiency virus (HIV). Prolonged treatment duration is likely to provide more chances of emergence of resistance especially when the therapeutic agents are limited.[10]

HOST FACTORS

Age

Most pediatric drug dosing is guided by weight. Children below 3 months are more prone to have serious occult bacteremia and hence intravenous antibiotic/s are warranted. Tetracyclines should be used only in older children above 8 years of age, chloramphenicol not before 2 months, and quinolones should be avoided in children under the age of 12 years. Extremes of the age are considered very crucial while selecting antibiotic/s class and their dosages. These groups of patients handle drugs differently, due to differences in body size and kidney function and they often have very narrow safety window.

Renal and hepatic function

Efficiently working kidney and the liver are often prerequisite during antimicrobial administration. These are the primary organs responsible for the elimination of drugs from the body. Dose adjustments are advocated to prevent accumulation and toxicity in patients with reduced renal or hepatic function. For example, aminoglycoside in during compromised renal function ceftriaxone in jaundiced neonates.

Genetic variation

Genetic susceptibility to the adverse effects of antimicrobial agents, which has been demonstrated for several antimicrobial agents, is occasionally significant enough to warrant testing for such variability before administration of certain drugs, classic example is that of glucose-6-phosphate dehydrogenase deficiency, which can result in hemolysis in individuals when exposed to certain antimicrobial agents, such as dapsone, primaquine, and nitrofurantoin.

History of allergy or intolerance

A history of antimicrobial allergy or intolerance should be routinely obtained in the evaluation and management of infection. A history of drug allergy may preclude the use of certain groups of antibiotics such as penicillins or sulfa.

History of recent antimicrobial use

Eliciting a history of exposure to antimicrobial agents in the recent past (approximately 3 months) can also help in selection of antimicrobial therapy.[15] The causative microorganism for a current episode of infection is likely to be resistant to the drug and/or drug class which has been used recently due to selection pressure. Here, it would be prudent and logical to use an alternative agent. For example, the emergence of MRSA and ESBL in a child has previously prescribed third-generation cephalosporin or quinolones.

Assessment of response to treatment

Desired successful therapeutic response is associated with improvement in vital signs, clinical parameters, and investigation findings. These include improving symptoms and signs (e.g., a decrease in fever, tachycardia, or toxemia), laboratory values (e.g., decreasing leukocyte count, CRP etc.), and radiologic findings (e.g., decrease in the size of an opacity). However, radiologic improvement can frequently lag behind clinical improvement, and routine radiographic follow-up of all infections is not always necessary.

If one judges that the empirical antibiotic has failed, it is important to reassess the diagnosis and also to rule out non-infective causes. Even in reasonably diagnosed bacterial infections, if one change of antibiotic fails, it is best to search for an alternative diagnosis or complications.[8,15]

ANTIBIOTIC DE-ESCALATION

It is a key element within antimicrobial stewardship programs. When microbiological information is not available yet, the use of broad-spectrum antimicrobial(s) constitutes the backbone of the empirical therapy in critically ill patients. De-escalation refers to the reassessment of treatment when culture results are available, and it generally incorporates a reduction in the spectrum of administered antibiotics either by discontinuation of antibiotics or switching to an agent with a narrower spectrum. Hence, once the pathogen(s) are identified, the empiric antibiotic(s) should be stopped or reduced in number and/or narrowed in spectrum. This strategy appears to be, capable of promoting therapeutic appropriateness, averting AMR and reducing toxicity and costs.

Failure of an antibiotic

In an immuno-competent host with community acquired infection most of the time correctly selected antibiotic works. If it does not work assess the dose, duration, compliance, and adherence. Once all these factors are reassessed, it is irrational to continue trial with different empirical antibiotics and it is not ideal to add or change antibiotics empirically. Do not go on adding the antibiotics and expand the spectrum. Try to find out the cause of a failure of an antibiotic prescription.

The common causes for such a failure are as below.

- Collection of pus: Empyema, subdural collection
- Foreign body: Nonresolving/recurrent pneumonia
- Necrotic tissue: Polytrauma, burns, SSSS, TEN, and SJ syndrome
- Different organism: Mycoplasma, TB, viral, leptospirosis, rickettsial disease, and fungal
- Improper diagnosis: Non-infectious cause like Kawasaki disease
- Antibiotic-resistant bacteria: MDR TB, MRSA, and ESBL
- Immunocompromised HOST: HIV,
- Special situations: Cystic fibrosis, asplenia, and splenectomy.

Please note that the maintenance of vitals, including oxygenation, perfusion, euglycemia, asepsis measures, etc., is prerequisite for favorable outcome. Any abscess needs to be drained, offending material such as foreign body, and catheter needs to be removed, and in the skin and soft-tissue infections, debridement of necrotic tissues with meticulous wound care are important aspects of successful antibiotic therapy on individual case based situation. It is important to realize that recurrent bacterial infections are always a result of some background abnormality which may be anatomical, functional (mucociliary), or immunological. Hence, it should be a rule to thoroughly investigate a case where repeated bacterial infections occur or when it fails to respond.

CONCLUSION

Irresponsible and overuse of antimicrobials are one of the world's most vital public health problems. Microbes adapt to the antimicrobials easily in no time resulting into emergence of AMR. People infected with such antimicrobial-resistant organisms are more prone to have serious disease with longer and expensive hospital stays, are often victims of infection associated complications and more likely to die as a result of a serious infection. It is very important to be an antimicrobial steward by practicing responsible antibiotic therapy. Antibiotic stewardship promotes the appropriate use of antimicrobials (including antibiotics) to improve patient outcomes. It is also an attempt to reduce the emergence and spread of infections caused by multidrug-resistant organisms.

Important considerations when prescribing antimicrobial therapy include obtaining an accurate diagnosis of infection and understanding the difference between empiric and definitive therapy. One should identify every opportunity to stop or to switch to narrow-spectrum, cost-effective oral agents for the shortest duration keeping type and site of infection, pharmacological characteristics of drug and host factors in mind. This will result into favorable outcome with no or minimal adverse effect and reduced chance of emergence of AMR.

Take home message

- Try to obtain an accurate microbial diagnosis
- Prescribe an antibiotic when it is absolutely needed, i.e., in the presence of true bacterial infection
- Always prescribe first line, possible narrowest spectrum of antibiotic for optimum duration in optimum dosages
- Assess the response and look for side effects
- Avoid overuse of antibiotics/irrational combinations

- In case of non-response look for compliance, complications, and alternative diagnosis
- Do not use antibiotic/s in nonbacterial conditions
- Develop culture of culture
- In health-care associated infections start broad spectrum and de-escalate/revise the regimen as per culture and sensitivity reports
- Observe infection control measures – hand hygiene is the cheapest and most cost effective
- Improve vaccination coverage
- Try to establish microbial diagnosis by other point of care non culture methods
- Self-audit your antibiotic usage.

Let us understand the importance of antimicrobial stewardship and observe self-discipline in antibiotic prescription to combat the ever expanding menace of AMR.

Declaration of patient consent

Institutional Review Board permission obtained for the study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: Shah AK, Shah AA. Responsible antibiotic therapy simplified. Karnataka Paediatr J 2020;35(1):29-38.

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Karnataka Pediatric Journal

Review Article

Vitamin-D status and bone mineral density in asthmatic children on long-term inhaled corticosteroids

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Received : 09 June 2020
Accepted : 10 August 2020
Published :

DOI
10.25259/KPJ_7_2020

Quick Response Code:

ABSTRACT

Asthma is the most common chronic respiratory illness affecting children. Inhaled corticosteroids (ICS) form the main treatment modality in asthma. Reduction in bone mineral density (BMD) is an important adverse effect of steroid usage. This side effect is an established entity with oral corticosteroids but minimal with ICS therapy. However, there are reports regarding the detrimental effect of chronic therapy with ICS. Long-term high-dose budesonide more than 800 μg/day has been shown to reduce the BMD. However, this effect was not consistently seen with moderate doses of 400–800 μg/day. Anticipating the impact of steroids on bone metabolism and monitoring for it is essential. Annual monitoring of Vitamin-D levels and BMD in children on chronic therapy is beneficial for the early detection and management of steroid-induced osteopenia. Judicious ICS use at the lowest effective dose should be tailor-made for every individual.

Keywords: Asthma, Bone mineral density, Inhaled steroids, Vitamin-D

INTRODUCTION

Asthma, the most common chronic respiratory illness affecting children worldwide is defined by the Global Initiative for asthma as: "History of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that varies over time and in intensity along with variable expiratory airflow limitation."[1] In 2016, the Global Burden of Disease study gave a worldwide asthma estimate of 339.4 million, which represents a 3.6% increase in age-standardized prevalence since 2006.[2] About 10% of the asthmatics are from the Indian subcontinent.[3] The age-wise global prevalence of asthma, according to CDC, is 8.6% in less than18 years, 10.6% in 5–11 years, and 9.7% in 12–17 years age-group.[4] According to the International Study of Asthma and Allergies in Childhood Phase 3, there is variation in asthma prevalence: 2.4–37.6% in 6–7 years old and 0.8–32.6% in 13–14 years old children.[5] There is rising trend in India from 5% in 2002 to 7.3% in 2008 and 10.3% in 2010.[6-8]

Glucocorticoid utility in childhood is to the tune of 10%, and the largest contribution to chronic-steroid exposure in children is by inhaled corticosteroid (ICS).[9] ICS is the most effective controller drugs with multiple mechanisms of action: Anti-inflammatory, reduction of airway responsiveness, reversal of β_2 receptor downregulation, and prevention of airway remodeling.[1,10] Benefits are seen within 2–3 weeks of starting therapy.[10] There have been widespread, long-standing concerns regarding adverse-events such as decreased bone mineral density (BMD), fractures, and reduction of growth in children with corticosteroid usage.[11] High-dose ICS and

oral corticosteroid (OCS) can be associated with decreased BMD.[12,13] Some studies have shown no detrimental effects of ICS on BMD.[14,15]

There continues to be conflicting evidence regarding the effect of inhaled steroids on BMD.[14-21] The aim of our article is to review the effect of ICS on Vitamin D and its interplay with BMD in asthmatic children.

ICS IN ASTHMA

Many factors and comorbidities affect the severity of asthma and its control. Failing to provide the deemed attention to these factors can lead to poor control and poor quality of life. In sensitized individuals, reduction or elimination of food and aero-allergens is necessary for adequate asthma control along with pharmacological therapy.[22] The common pathophysiological mechanism of inflammation and atopy makes the clinicians to use controller medications and hence ICS is one of the important components of asthma therapy since its introduction in the 80s. ICS is very effective in childhood asthma and is superior to other drugs used.[23] Even low-dose of ICS is known to reduce mortality in asthma. The benefits of long-term therapy are emphasized in national and international guidelines.[1,10]

Responsiveness to therapy varies, and it refers to how easily asthma-control can be achieved with treatment. Based on the management patterns, asthma can be classified as: Easy-to-control, difficult-to-control, exacerbators, and refractory (poorly controlled in spite of multiple and high-dose ICS).[22]

Controllers are used to reduce inflammation of airway, symptoms, exacerbations, and decline in pulmonary function. In mild asthma, low-dose ICS-formoterol can be taken as needed to reduce the risk of exacerbations.[1] Best outcomes are obtained when ICS is initiated soon after the diagnosis of asthma because:

- Early initiation of low-dose ICS provides an improvement in pulmonary function
- Severe exacerbation in those not on ICS have a greater long-term decline in pulmonary function[24]
- In occupational asthma, early removal of sensitizing agent exposure and initiation of controller treatment increases the likelihood of recovery.[25]

Systemic steroids are important in hastening the recovery from acute exacerbations and also preventing replase. They are used in all but the mildest exacerbations, preferably administered within 1 hour of presentation.[26]

It is particularly important if:

- Initial treatment with SABA (short-acting beta-2 agonist) fails to achieve improvement
- Exacerbation developed while on OCS
- Previous history of exacerbations requiring OCS.

Route of delivery in acute exacerbations: Oral route is as effective as intravenous. The oral route is preferred as it is less invasive, quicker, and cheaper. Liquid formulation enables easier dosage adjustment and administration. OCS requires a minimum 4 hours to produce clinical improvement. Intravenous corticosteroids are preferred if patients are dyspneic, unable to swallow, vomiting, or when they require ventilation.[27]

A Cochrane review (six trials; 374 patients) found that the use of corticosteroids was associated with a significant reduction in the relapse rate, hospitalization rate, and SABA use.[28] In another review of 12 studies involving 863 patients, corticosteroid administration within 1 hour of presentation significantly reduced hospital admission rates with no increase in side effects.[29] A 5–7 days short-course of OCS is as effective as 10–14 days therapy.[30] In patients receiving systemic steroids, tapering is not needed if the duration of treatment is less than 2 weeks.[31]

In acute exacerbations, ICS was associated with lesser hospital admissions in patients with mild-moderate exacerbations. However, in combination with systemic corticosteroids, ICS provides no additional benefits.[32-34] Patients who are already on ICS should continue their medication during the acute attack.[35]

ICS is the controllers of choice for stable asthma management.[33]

- All ICS is efficacious when used in equipotent doses
- Most benefits are obtained at low-moderate doses. Increasing the dose benefits only a minority
- ICS should be started and used at the lowest possible dose
- High-dose ICS should be avoided to reduce the side effects.

NORMAL BONE FORMATION AND ROLE OF VITAMIN-D

Bone is a metabolically active rigid organ undergoing constant modeling and remodeling. It is the major reserve of calcium, phosphorus, and magnesium.[36] The bone composition is as follows: 50–70% minerals, 20–40% organic matrix, 5–10% water, and less than 3% lipids. The major mineral content is calcium-hydroxyapatite found deep in the bone matrix; the surface coating of remodeled bone is by amorphous calcium-phosphate. Calcium and phosphate binding-proteins regulate the formation of hydroxyapatite crystals and lead to mineral deposition in an orderly manner.[37]

Osteoprogenitor cells originate from pluripotent stem cells. The new bone matrix is synthesized by osteoblasts and supported by osteocytes. The stem cells enhance the apoptosis of osteoclasts and decrease the apoptosis of osteoblasts and osteocytes. The differences in trabecular microarchitecture at

various skeletal sites and site-specific variations in different diseases are determined by the heterogeneity of osteoblasts.[37]

During the primary bone formation and in states of increased bone-turnover, woven bone is produced. Trabecular bone is metabolically more active than cortical bone. The collagen fibrils are laid down alternatingly in a lamellar pattern providing strength. Bone formation is more than the resorption on the periosteal surface, whereas the reverse is true on the endosteal surface.

The bone grows both in length and radius during childhood and adolescence. The chondrocytes proliferate in the epiphyseal and metaphyseal regions resulting in longitudinal growth. Subsequently, mineralization occurs, resulting in new bone formation. Bone remodeling starts *in utero* and continues till death so as to maintain the strength of the bone and mineral homeostasis. This is regulated by local and systemic factors.[36,37]

Vitamin-D-Parathormone-FGF-23 axis maintains the serum calcium and phosphorus levels to facilitate bone mineralization [Figure 1]. Parathormone increases the calcium levels by bone resorption, renal reabsorption, and stimulating calcitriol synthesis. Vitamin-D helps in bone mineralization by enhancing intestinal calcium and phosphorus absorption. It stimulates osteoblast differentiation and expression of bone specific-alkaline phosphatase (ALP) and moderates the skeletal cell proliferation and apoptosis. While renal regulation is important for phosphate, intestinal control is key for calcium homeostasis.[36,37]

ROLE OF VITAMIN-D DEFICIENCY IN ASTHMA

Awareness of low serum Vitamin-D levels in the general population is coming to light, and the reason behind this could be due to the changing lifestyle such as reduced outdoor life, working indoors, use of sunscreen, decreased sunlight exposure, and dietary modifications. Vitamin-D can contribute to lung health by reducing inflammation through regulatory T-cells and induction of intrinsic antimicrobial resistance. Hence, in asthmatic children with the lower Vitamin-D levels, it has been observed that they are more symptomatic, there is a higher risk of exacerbations, reduced pulmonary function, and increased need for reliever-use.[38] Asthmatic children seem to have a greater risk of Vitamin-D deficiency, and asthma-control in those children with Vitamin-D deficiency has been noted to be sub-optimal.[38,39]

ROLE OF STEROIDS ON VITAMIN-D METABOLISM

Glucocorticoids can reduce the serum calcium levels by impairing its absorption in the intestine, reduced calcium-binding protein synthesis, increased renal excretion, reduced reabsorption from the tubules, and depletion of mitochondrial ATP. They cause renal excretion of phosphate by directly acting on the kidney and indirectly by inducing secondary hyperparathyroidism. This hyperparathyroidism is contributed to by direct stimulation of its secretion by

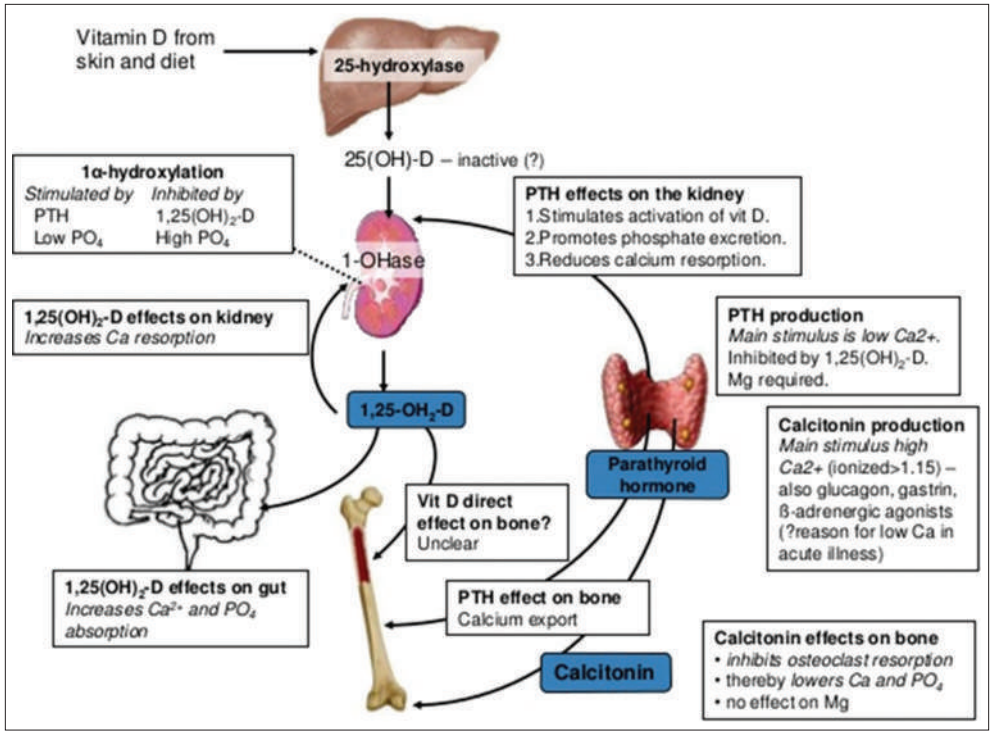

Figure 1: Interplay of Vitamin-D and parathormone on calcium-phosphorus homeostasis.

the steroids. Varying levels of the active form of Vitamin-D, that is, 1,25-dihydroxyvitamin-D [1,25$(OH)_2$D] may be present. While the rate of Vitamin-D synthesis and clearance is usually normal, this variation could be due to differences in the diet, absorption, and sunlight exposure. The steroid-induced negative calcium balance can be overcome partly by supplementation of Vitamin-D and calcium.[16]

RELATIONSHIP BETWEEN VITAMIN-D AND BMD

Vitamin-D plays a significant role in bone metabolism. 1,25$(OH)_2$D enhances bone mineralization by increasing intestinal calcium and phosphorus absorption and osteoclast maturation. In the pediatric population, the association between severe Vitamin-D deficiency and rickets and reduced BMD is well established.[40] A positive correlation was seen between Vitamin-D levels and BMD.[16]

An important function of 1,25(OH)2D is the regulation of calcium-phosphorus balance for bone mineralization and remodeling. With the deficiency of Vitamin-D, dietary calcium will not be absorbed, leading to an increase in serum parathormone, which increases tubular reabsorption of calcium and resorption from the bones at the cost of BMD [Figure 1]. In the long run, this weakens the bones and makes them brittle. About 40–60% of the skeletal mass is accumulated during childhood and adolescence. Inadequate mineralization of growing bone results in rickets, biochemical abnormalities include hypophosphatemia, elevated ALP and low serum 25(OH)D.[41]

Studies have revealed that BMD is generally low in children from India and China compared to Caucasians for corresponding height. The growth parameters were normal in Indians, but they had poorer Vitamin-D status, and their dietary calcium intake was low. Groups receiving calcium and Vitamin-D had a greater increase in bone mass than Vitamin-D alone. The appendicular bone mass increased in children with modest calcium supplementation, but the benefit was lost in 18 months after stopping the supplementation. Growth was not altered with calcium supplementation.[42] Tse *et al*. concluded that Vitamin-D levels significantly modified the effect of OCS on bone mineral accretion in boys. However, this study did not consider the impact of diet and physical activity on Vitamin-D levels and its link with BMD. Further research is needed to establish whether Vitamin-D supplementation in poorly-controlled asthma may confer benefits to bone health.[43]

Vitamin-D deficiency (less than 5 ng/ml) was 65% among 100 school-going children in a study by Sharawat and Dawman. In the Vitamin-D deficient group, the mean BMD (g/cm^2) of lumbar-spine was 0.439 ± 0.098 and 0.606 ± 0.071 (P< 0.001) in controls.[40]

STEROID-INDUCED OSTEOPENIA

ICS is the largest form of steroid usage. Osteopenia has been noted in children even with oral prednisolone less than 0.16 mg/kg/day. OCS therapy is known to delay growth and puberty and reduce final height, temporary retardation of bone growth, and altered turnover of bone and collagen can occur even with ICS. The predominant effect on growth and BMD occurs within 6 months (pronounced effect in the first few weeks) of therapy.[44]

There are evidences demonstrating increased fracture risk with chronic OCS, but such strong evidence is not found with chronic ICS. A study of bone biopsy among patients on steroid therapy for at least 1 year showed an increased resorption, reduced formation, and reduced volume of trabecular bone, the loss being higher in metaphysis than diaphysis. Although the trabecular bone is mostly affected, with prolonged therapy, the cortical bone also becomes affected, increasing the fragility of long bones. Most asthmatics are on low-dose steroids, but some show an increased susceptibility to steroid-induced adverse effects on the bone than others, implying the role of genetic differences along with other factors such as dose and duration of therapy.[45]

The specialty of corticosteroid-induced osteoporosis is that there is rapid initial bone loss. There is a dual disadvantage as there is both decreased bone formation and increased resorption, leading to increased fractures risk at a higher BMD. This risk reduces on stopping the steroids, but, the bone recovery is not complete. The specific sites involved in this condition include the cancellous bone such as the spine, neck of femur, and the Ward's triangle.[45]

Along with the steroid, the underlying disorder itself can affect the bone health independently by local cytokine-induced bone resorption, malabsorption states, reduced physical activity, hypoxia, and acidosis. Other factors which add to the burden of osteoporosis include age, gender, and genetic influence, endocrine disorders such as hyperthyroidism, hyperparathyroidism, Cushing's disease, gonadal-insufficiency, and Type-1 diabetes mellitus, and other diseases such as chronic kidney disease, inflammatory bowel disease, and rheumatoid arthritis. In the pediatric age-group, predisposing factors to low-BMD include overweight/obesity, reduced muscle mass, and low physical activity.[45] The review article by Seibel *et al*. in 2013 summarized that the therapeutic use of glucocorticoids is often limited by adverse outcomes such as osteoporosis, diabetes, and obesity.[12]

The route of steroid administration plays an important role with respect to the equivalent dose and the corresponding effect on the BMD. While a high-dose of up to 1 g methylprednisolone given intravenously may not be taxing to the bone, prednisone, when given as a 2.5 mg single oral dose, can have an immediate detrimental effect on the secretion of osteocalcin. With regard

to bone health, though ICS does have an impact on the skeletal tissue, they are better than systemic or OCS.[44,45]

Steroids can affect bone health through a multitude of mechanisms [Figure 2].[46] They suppress genesis of osteoblasts, decrease bone formation by promoting the apoptosis of osteocytes and osteoblasts, extend the lifespan of osteoclasts thus enhancing bone resorption, promote a renal and intestinal calcium loss, impair bone growth through direct effect on the physis, and delay/impair the attainment of peak bone mass.[44]

ICS AND BMD

Local and systemic side effects of ICS are a major concern on a long-term use. Parameters influencing the side effects: Local drug deposition, type of drug, frequency, and dose.[47] A higher dose can lead to suppression of hypothalamic-pituitary-adrenal axis.[48] Common systemic side effects include lower respiratory infection, tuberculosis, growth-suppression, reduced BMD, ocular side effects, cutaneous infections, and easy bruisability.[49,50]

In children on ICS, there can be a growth retardation. The impact of steroids on bone metabolism is based on the route of administration, dose and bioavailability of steroids. Intranasal steroids can lead to systemic absorption and reduction in growth velocity. Although studies in asthmatic children have not shown a significant reduction in BMD, an error may be that children on low-dose ICS were taken into consideration.[44]

Fuhlbrigge and Kelly [Table 1], in their review, concluded that long-term ICS had a greater impact on growth, while BMD is more sensitive to short-courses of OCS.[11] Another review article by Mortimer *et al*., with databases from 1966 to 2004, concluded that with ICS therapy, though there was a reduction in growth velocity, target adult height was achieved.[13] When metered-dose ICS is used with spacers, compliance to therapy and efficacy is improved, local and systemic side effects such as oral candidiasis, dysphonia, suppression of growth, and loss of BMD can be reduced.[51] In the case of dry powder inhalers, rinsing the mouth after inhalation reduces the systemic absorption of steroids.[52]

MANAGEMENT OF CORTICOSTEROID-INDUCED OSTEOPENIA

Chronic steroid therapy can lead to reduction in bone mineral density.[53-55] So, it is important to have a watchful eye. The early changes in BMD can be detected by dual-energy X-ray absorptiometry and quantitative computed-tomography. Choi *et al*., in 2019, used an indirect parameter-trabecular bone score, calculated using projections of DEXA in the lumbar spine, and found it useful as an early indicator of bone loss.[56] However, this was a retrospective study, and it included subjects on a short duration of controllers. It is preferable to do a biannual assessment in those not on preventive therapies and annually in those who are receiving preventive therapy. We should use the lowest-effective-dose of steroids for chronic therapy.[45]

The goal is to minimize or prevent further bone loss, enhances the BMD, and try to revert the effects of glucocorticoid excess.[45] Studies have revealed that bisphosphonates, which are anti-resorptive agents, help prevent bone-loss or improve

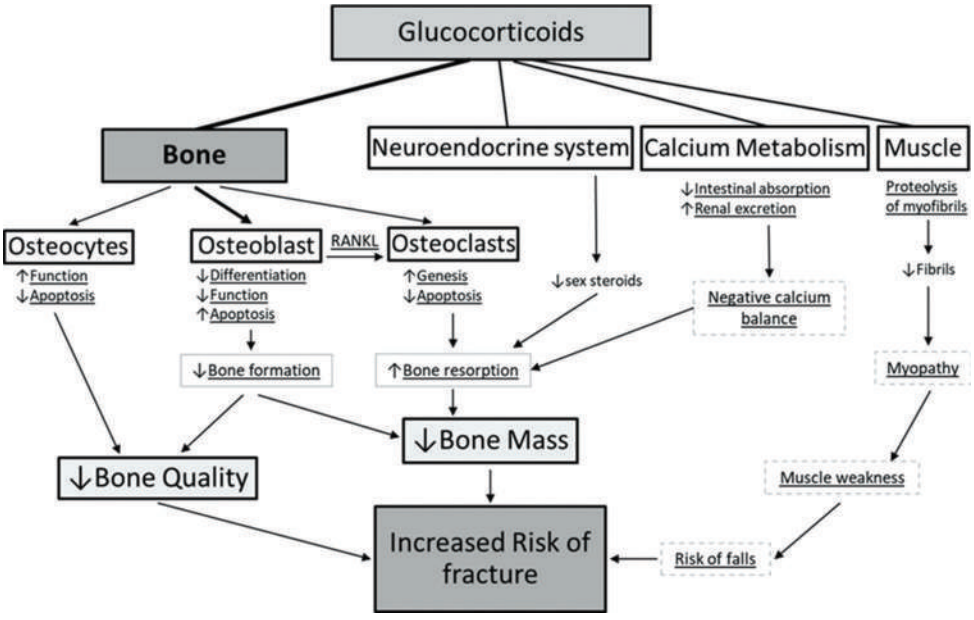

Figure 2: Effects of glucocorticoids on bone.[46]

Table 1: Effects of corticosteroids on BMD.

Study	Steroid	Duration	Age-years	Sample size	Outcome
Jones *et al.*[16] (2000-Tasmania)	ICS 479 µg/day (range 50–1000)	8 years follow-up	8.2 (median)	330 (110 asthma-51 used ICS)	ICS use in the past 1 year was associated with decreased total-body-BMD, for doses >400 mcg/day
Harris *et al.*[14] (2001-Australia)	Moderate-dose ICS (400–800 µg), high-dose ICS (800 µg), high-dose ICS+OCS, no ICS	6 months of ICS	4–12	76	Children on >800 µg/day ICS + intermittent OCS had a significantly lower Lumbar-Spine BMD than 400–800 µg/day of ICS Bone mass was similar in children not on ICS and those on 400–800 µg/day ICS
Van Staa *et al.*[17] (2003-UK)	OCS versus non-systemic corticosteroids	Treatment duration: 6.4 days	4–17	37562 cases, 345748 controls	Children who need >4 OCS courses had a dose-dependent increased risk of fracture humerus. Risk was increased with ≥30 mg prednisolone/day
Tse *et al.*[43] (2012-Boston)	Inhaled budesonide 400 µg), nedocromil (16 mg), or placebo	Mean 4.3 years follow-up	5–12	780	Vitamin-D levels significantly modified the effect of OCS on bone mineral accretion in boys. Vitamin-D-insufficient boys exposed to >2 OCS courses/year had twice the decrease in accretion rate
Sidoroff *et al.*[18] (2015-USA)	ICS: Budesonide 1000 µg for 8 weeks, 500 µg for 8 weeks	>6 months	12.3 (median)	89	Regular use of ICS <6 years of age was associated with reduced lumbar spine-BMD later in childhood High cumulative ICS-dose was associated with decreased BMD in the femoral neck
Bahceciler *et al.*[15] (2002-Turkey)	Long-term inhaled budesonide (mean daily dosage: 419±154 µg)	13.0±9.8 months	6.4±2.2 (22 males, 30 females)	52 cases, 22 controls	No significant difference in total and spine BMD
Griffiths *et al.*[19] (2004-Australia)	High-dose inhaled fluticasone propionate (≥1000 µg daily)	6 months	13.63±3.2	49 cases, 32 controls	No significant reduction in bone metabolism or bone-age corrected BMD
Zieck *et al.*[20] (2017-Australia)	Asthmatics on ICS versus non-asthmatics not on ICS	6 months	6–18	211 cases, 216 controls	No difference in the incidence of fractures with low or high-dose ICS
Kelly *et al.*[53] (2008)	OCS (2 mg/kg for 2 days, 1 mg/kg for 2 days) versus ICS (400 µg/day budesonide)	Median 7 years follow-up	5–12	531 boys, 346 girls	OCS bursts produced a dosage-dependent reduction in bone mineral accretion and an increase in risk for osteopenia in boys. Cumulative ICS use was associated with a small decrease in bone mineral accretion in boys but no increased risk for osteopenia
Allen *et al.*[54] (2000-Australia)	Inhaled beclomethasone dipropionate or budesonide (0.67±0.48 mg/m^2/day)	9–20 month follow-up	Cases: 7.8±2.4 controls: 8.4±2.1	48 cases, 9 controls	ICS at an average dose of 0.67 mg/m^2/day reduced the bone mineral acquisition
Boot *et al.*[55] (1997-Netherland)	Moderate-to-high dose ICS. Beclomethasone dipropionate or budesonide	6 months-2 years	7 (median)	40 (21 boys, 19 girls), 148 controls	Lumbar spine-BMD was not affected by ICS. Children who used ICS daily for 3–8 years had lower total-body-BMD

BMD. Among this class of drugs, only pamidronate and alendronate were studied. While reducing the osteoclastic resorptive activity, they simultaneously enhance the apoptosis of osteoclasts, and reduce the apoptosis of osteocytes and osteoblasts. Hence, they are beneficial for the prevention and treatment of glucocorticoid-induced osteoporosis.[45]

A combination of Vitamin-K_2 (menatetrenone) with alfacalcidol helps in preserving BMD. Calcium-alfacalcidol combination is more effective in preventing bone loss than Vitamin-K_2. Calcium-calcitriol combination reduces the bone loss, but cannot prevent it altogether. It is better to start a combination of Vitamin-D with calcium rather than calcium alone with any chronic therapy. Children on long-term glucocorticoid therapy or with reduced BMD should be considered for treatment with bisphosphonates along with calcium and Vitamin-D supplementation.[49] Calcium and protein-rich low-sodium diet, good physical activity, and protection from falls help prevent reduction in BMD.[45]

Other modalities of treatment include anabolic medications, recombinant parathormone, and sex hormones. Newer therapeutic agents in the pipeline are recombinant-osteoprotegrin, receptor activator of nuclear-factor-kB ligand inhibitors, osteoclast enzyme inhibitors, and antagonists of integrin.[45] Sirufo *et al.*, in 2020, found that nuclear-factor-kB has a key role in allergy-induced inflammation and regulation of bone resorption, hence a potential target for therapy and further research. A definite link exists between bone-loss, therapies, and etiology, but the final effect is based on mutual interaction of various factors.[57]

CONCLUSION

ICS is an integral part of asthma management. However, chronic high-dose therapy can cause a reduction in BMD and pose a risk for fractures. There are conflicting evidences in the literature regarding the impact of ICS on BMD. Benefits of therapy outweigh the risk of adverse effects. However, it is imperative to use steroids judiciously with appropriate monitoring and preventive measures in anticipation of the side effects.

Recommendations to prevent the risk of ICS-induced osteopenia

- Use the lowest-effective dosage of ICS
- Annual assessment of BMD for children who have received at least 6 months of ICS therapy
- Start Vitamin-D and calcium supplementation for children predicted to need chronic therapy
- Treat Vitamin-D insufficiency and deficiency and continue monitoring Vitamin-D status
- Use metered-dose inhalers with spacers and stress on good compliance to avoid the need of burst OCS courses
- While using inhaler, rinse the mouth after each use
- Advise appropriate non-pharmacological methods to improve bone health such as exercise, calcium, and protein-rich diet.

Declaration of patient consent

Patient's consent not required as patients identitiy is not disclosed or compromised.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: Thanuja B, Savitha MR. Vitamin-D status and bone mineral density in asthmatic children on long-term inhaled corticosteroids. Karnataka Pediatr J 2020;35(1):39-47.

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Karnataka Pediatric Journal

Review Article

Surgery for drug refractory pediatric epilepsy: Saving and nurturing the developing brain

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Received : 15 June 2020
Accepted : 16 June 2020
Published :

DOI
10.25259/KPJ_9_2020

Quick Response Code:

ABSTRACT

The drug refractory epilepsy in the pediatric age group can wreak havoc on the developing brain affecting all the important developmental milestones. This not only affects the child but also creates a socioeconomic burden to the family. Pediatric epilepsy poses a special challenge in not only the diagnosis of focal drug refractory epilepsy but also in the selection of surgical candidate. Awareness about the myriad numbers of focal epilepsies, current standard in pre-surgical evaluation, and the available minimally invasive surgical options are important in raising the standard of both the primary epilepsy care and a timely referral to a specialized center. Authors have made an attempt to emphasize the importance of early recognition and intervention along with the reviewing of the current evidences on the surgical management so that any treating pediatrician are informed well enough for a better clinical judgment.

Keywords: Pediatric epilepsy surgery, Drug refractory, Pre-surgical evaluation

INTRODUCTION

Case capsule: A mother noticed frequent smiling and laughing episodes in her male child, at the age of 3 months. This made her happy too and was thought to be a normal milestone and was ignored. One-year later, child started having generalized tonic-clonic seizures for which the medical attention was sought. Magnetic resonance imaging (MRI) was done, which was reported as normal and medication was started with a single drug. However, the seizures progressed in duration, severity, and frequency and the number of drugs was increased to four eventually over a period of next 1 year. Mother also noticed aggressive behavior and appearance of secondary sexual features in a child who is now 4 years. This child was then referred to a specialized center for further evaluation. The initial evaluation with VEEG demonstrated the classical semiology of gelastic seizures with interictal and ictal discharges from frontotemporal region. However, the MRI done in an epilepsy protocol picked up a small DeLalande type I hypothalamic hamartoma measuring 1.5 cm in size. Neuropsychological evaluation showed severe mental retardation with maximal dependency. As there was a good anatomoclinical correlation, child underwent minimally invasive MRI-guided stereotactic radiofrequency ablation of this lesion under general anesthesia. At 1 year follow-up, the child became seizure free and the quality of life score improved. Child was continued on hormonal therapy under endocrinological care. This is a case scenario of one child and a mother among many others who go through this rather heart-wrenching experience of moving from one hospital to another until a final answer was found in a specialized center. Had this been diagnosed early at the age of 3 months or even at

the age of 1 year, the burden on the family could have been prevented. The learning points to be noticed in this case were that: (1) An early semiological features was missed, (2) the MRI done in a non-epilepsy protocol can easily miss a small epileptogenic lesion such as hamartoma or cortical dysplasia, (3) even a VEEG can give an ambiguous picture in a child with an immature brain and a complex epileptogenic lesion, and (4) above all a minimally invasive surgical option rendered the child seizure free. Epilepsy is largely treated with medicines successfully; however, there are subsets of patients who are drug refractory like an above-mentioned case. An estimated 10.5 million children worldwide have epilepsy. The annual incidence is reported to be 61–124/100,000 children in developing countries.[1] Any child affected with seizures is not only an awful experience to the family but also it is equally prone to an unexpected sudden death. Hence, raising the index of suspicion by creating awareness among all the pediatricians who can come across such a child in day-to-day practice is the sole purpose of this review article that follows.

Definitions

As per the ILAE guidelines, the drug refractory epilepsy is defined as a failure to achieve seizure freedom after an adequate trials of two drugs with an optimal dosage for 2 years and with good compliance.[2] This definition can be easily followed in adults, however, for pediatric age, this period of 2 years is not practical as lot more damages can happen in a developing brain as explained earlier. Hence, the subcommission of ILAE was formed to address this and they defined the condition as a failure of either 2 or 3 appropriate AEDs or causing disabling seizure side effects and/or disabling AED side effects.[3] The incidence of drug refractory epilepsy in a child depends on the pathological substrate for the same. However, in general, the incidence is 20–30%,[4] which can be higher in patients with hypothalamic hamartoma for which the mainstay of treatment is surgical and lower in cases like absence seizures, which are treated by drugs.

PRE-SURGICAL EVALUATION

The MR imaging of brain of infants is complex in terms of interpretation due to immature myelination. A "normal" study does not rule out subtle cortical abnormalities, and as per the guidelines, the imaging has to be repeated at an interval of 6 months or after 2 years of age if there is a strong index of suspicion for focal onset seizures.[5] Similarly, electrophysiological evaluation of cortical activity in infants and young children is extremely difficult because of poorly defined "normal" and "abnormal" electroencephalography (EEG) patterns of the immature brain, the absence of well-defined epileptiform discharges, rapidly spreading ictal activity, and the great variability of electrophysiological seizure patterns. These characteristics make the localizing value of EEG findings for children very controversial as opposed to those for adults. As a result, defining the epileptogenic zone in the immature brain is a Herculean task in many cases, one needs to be handled with a great deal of expertise. This in most pediatric cases would require phase wise evaluation with Phase-I involving non-invasive imaging investigations and Phase-II involving invasive depth electrode evaluation. Phase-I investigations consist of nuclear medicine with positron emission tomography and single-photon emission computed tomography used to detect the cellular metabolic changes during the interictal and ictal periods. Magnetoencephalography uses magnetic field to detect the neuronal field changes, which are depicted then on an anatomical head model. If the Phase-I evaluation reveals a focal potential epileptogenic zone with good concordance among different investigations, then one can proceed with surgery. If any of these investigations are discordant, then the pre-surgical evaluation is complemented with invasive depth electrode insertion after which, extraoperative electrophysiological recordings are done to detect and confirm the origin of seizures.

INDICATIONS FOR SURGICAL MANAGEMENT

Some of the potential epileptogenic lesions, which commonly present with drug refractory epilepsies, are as follows: (1) Developmental lesions such as cortical dysplasia, hamartoma, and heterotopia; (2) tumors such as low-grade gliomas, ganglioglioma, and dysembryogenic neuroepithelial tumor; (3) vascular lesions such as AVM and cavernous malformations; (4) injury-related lesions like gliosis (from CVA or trauma); and (5) infectious lesions such as granuloma or parasitic cyst.

Other pediatric epilepsy syndromes, which are drug refractory and are amenable to surgery, are Rasmussen encephalitis, tuberous sclerosis, Sturge-Weber syndrome, hemiconvulsion-hemiplegia-epilepsy syndrome, and hemimegalencephaly. With recent advances in imaging, electrophysiology, and surgical techniques, the infantile spasms, which were largely considered as medical condition hitherto, are now recognized as a surgical condition as well.

TIMING OF A SURGICAL MANAGEMENT AND ITS ADVANTAGES

Surgery is often the treatment option for some of these children with drug refractory epilepsy not only to control seizures but also to prevent and improve the comorbid conditions mentioned previously. Young children have a much greater potential for recovery after a surgery and a significant capacity for reorganization of neurological function.[6] It is of utmost importance that the pediatric

epilepsy surgery team members fully appreciate the functional plasticity and potential of the young brain and take these characteristics into consideration when making pre-surgical assessments and surgical decisions. Because many types of pediatric epilepsy syndromes are inherently medically refractory, there is no need to "prove" medical intractability before embarking on a surgical course of action. The harmful effects of prolonged seizures and the toxic effects of AEDs on synaptogenesis, brain development, and cognitive and psychosocial development bolster the argument for early surgery in pediatric epilepsy patients. All India Institute of Medical Sciences, New Delhi, became the first center to conduct a randomized controlled trial (RCT) trial in pediatric age group to look at the benefits of early surgery which confirmed that children and adolescents with drug-resistant epilepsy who had undergone epilepsy surgery had a significantly higher rate of freedom from seizures and better scores with respect to behavior and quality of life than did those who continued medical therapy alone at 12 months.[7] The potential for significant recovery is highest during the period of high synaptic and dendritic density (ages 3–7 years), when the plasticity of the brain peaks.[8] Surgery performed within this time frame may help hasten recovery, and anticipated post-operative impairments may be milder.[9] In well-selected patients, early surgical intervention may prevent the negative cognitive, psychosocial, and developmental effects of seizures. Hence, the goals of surgery in these patients should be to prevent the possible harmful consequences of uncontrolled seizures; to prevent continued interictal activity resulting in permanent cognitive, behavioral, and psychosocial problems; to prevent secondary epileptogenesis; and to avoid the adverse effects of AEDs.

SURGICAL OPTIONS

Surgery is a well-established modality of treatment in these conditions and the various surgical options can be grouped into those that can render seizure freedom and those, which are palliative. Curative options are hemispherotomy, electrocorticography-guided lobar resections, or disconnective procedures, minimally invasive radiofrequency ablations. The palliative options for generalized seizures are corpus callosotomy for drop attacks and neuromodulative options of deep brain stimulation (open loop – DBS) of anterior thalamic nucleus and other targets, responsive neuro stimulation (closed loop – RNS) and vagal nerve stimulation (VNS). However, timely recognition of these conditions and referral to specialized center is an important predictor of the final outcome. Most important concern w.r.t surgery is safety or the risks involved. The advances in the field of neurosurgery from the introduction of operative microscope onward the results have been tremendous to an extent that now in India we have robotic assisted minimally invasive surgeries as well using which the depth electrodes can be inserted and even the hemispherotomies are performed through tiny twist drill openings. These advances have brought down both the morbidity and mortality. By definition, serious adverse events included, hospital admission or prolongation of an existing hospital stay, and events that resulted in persistent or substantial disability or incapacity or that were considered to be life threatening.[10] The AIIMS group reported 33% of serious adverse events in the randomised controlled trial, which looked at the benefits of early surgical intervention in children. Partly, this is due to the hemiparesis following the large numbers of hemispherotomy, which needs to be considered as an expected consequence of the surgery itself. However, the mortality in this study was zero highlighting the safety.[7]

DISCUSSION

Epilepsy in a child is different from adults in numerous ways. Most importantly, it is the developing brain, which faces the arrest in the growth and development due to on-going seizures. The brain, which is normally bustling with activity in a child, comes to a standstill whenever the seizure spreads. This affects the dendritic formation and the neuronal processing in a significant manner. All the important milestones are achieved and new skills are acquired in the first decade of life. This is lost due to the engagement of brain in seizure activity. The continuous postictal state and frequent interictal epileptiform discharges may cause an irritable, dysfunctional cortex, and, possibly, secondary epileptogenesis. In childhood, intractable seizures can be quite atypical and poorly defined compared with the relatively well-defined clinical and electro-physiological characteristics of epilepsy syndromes in adults.[3] Unilateral localized or hemispheric etiologies in children may present with generalized seizures and EEG patterns, progressive neurological disorders, and bilateral congenital brain syndromes. The seizures in these patients are also frequently extratemporal and cover large cortical areas, including the eloquent cortex. Invasive monitoring, cortical mapping, and stimulation studies may be needed more frequently in these children than in adults. Rapid brain maturation during early infancy and childhood is responsible for a complex evolution of clinical seizure semiology and EEG and neuroimaging findings. This complexity makes the assessment of the clinical, electrophysiological, and imaging findings very challenging.

Although spontaneous remission of the seizure is possible, the risk of permanent neurologic, psychosocial, and cognitive impairment from their recurrence and from the adverse effects of AEDs is significant during this crucial period of brain development. In addition, sudden unexpected death

due to epilepsy (SUDEP) is a definite possibility if the seizures are drug refractory. The incidence of SUDEP goes up from 0.9 to 2.3/1000 person-years in general epilepsy populations to 6.3 to 9.3 per 1000 person-years in epilepsy surgery candidates. One of the major risk factor is the age <16 years and the incidence is known to decrease after the successful surgery.

It is a well-known fact that the comprehensive care of children with epilepsy is challenging. Specialized knowledge of and expertise in the medical and surgical management of such patients are required. Thus, a well-coordinated, collaborative relationship between medical and surgical teams in a multidisciplinary environment is critical for successfully managing pediatric epilepsy patients.

CONCLUSION

To summarise, it is necessary to strike a balance between the two groups of patients.The one who is drug refractory and faces the adverse effects of AEDs because of unrealistic expectations of a spontaneous remission and the other, who undergoes unnecessary surgery and inadvertently causing a patient to experience psychosocial deterioration. This is the unique challenge that the paediatric epilepsy surgery team now faces and are attempting to overcome with a good clinical judgement, pre-surgical evaluation and a timely management.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: Girishan S, Pradeep R, Somashekar AR. Surgery for drug refractory pediatric epilepsy: Saving and nurturing the developing brain. Karnataka Pediatr J 2020;35(1):48-51.

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Karnataka Pediatric Journal

Original Article

Pulmonary function tests in children with beta-thalassemia major

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Received : 02 June 2020
Accepted : 04 June 2020
Published :

DOI
10.25259/KPJ_2_2020

Quick Response Code:

ABSTRACT

Objectives: The objective of the study was to study the pattern of lung functions in thalassemia major children and correlation of pulmonary function tests (PFTs) with serum ferritin.

Materials and Methods: A hospital-based cross-sectional descriptive study done from January 2017 to December 2017. Inclusion criteria: Children with confirmed diagnosis of beta-thalassemia major in the age group of 5–15 years were included in the study. Exclusion criteria: Already diagnosed cases of pulmonary dysfunctions, CHD and RHD were excluded from the study. All enrolled children underwent a detailed clinical history, physical examination and blood sample were sent for Hb and serum ferritin before blood transfusion (BT). PFT was done within 24 h of BT using spirometer (Helios-401). Statistical analysis was done using SPSS (Version22).

Results: Forty-five children enrolled in the study and majority of them were <10 years (37 children) with M:F ratio 1.6:1. The pulmonary dysfunction was present in 35 (77.8%), but none of them had respiratory symptoms. The pulmonary dysfunction observed was restrictive 31 (88.5%), obstructive 2 (5.7%), and combined 2 (5.7%). A reduced forced vital capacity (FVC) % in 33 (73.3%), a reduced forced expiratory volume in the 1st second (FEV_1%) in 25 (55.5%), a normal FEV_1/FVC in 41 (91.2%), and a reduced FEF 25–75% in 23 (51.1%) children were observed. Risk factors such as, age, height, and duration of chelation (>5 years) were significantly associated with pulmonary dysfunction ($P < 0.05$). There was no correlation between serum ferritin levels and PFT. However, PFT values were found to be decreased in patients with a high serum ferritin (>2500 ng/ml), but these differences were statistically not significant.

Conclusion: Abnormal patterns of lung function were common (restrictive type, predominant), even though none of these children had any respiratory symptoms.

Keywords: Pulmonary function tests, Serum ferritin, Thalassemia, Children

INTRODUCTION

Thalassemia is an autosomal recessive disorder and is the most common monogenic disorder worldwide. About 10% of the total world thalassemics are born in India every year.[1] In India, the prevalence of beta-thalassemia is 1–17% and carrier frequency is 3–4%.[2] Over the past three decades, regular blood transfusions (BTs) and iron chelation have dramatically improved the quality of life and thalassemia is transformed from a rapidly fatal disease to a chronic disease and is compatible with prolonged life. Regular BT causes generalized iron overloading in organs such as heart, liver, and pancreas. Lung impairment in thalassemia is also noted. Although, it does not produce any symptoms and is not the most significant clinical manifestation of thalassemia.

Most studies found that restrictive dysfunction is the predominant pattern of lung function abnormality,[3-11] although some others found obstructive lung dysfunction[12-14] and combined[15] pattern also. The precise causes and pattern of pulmonary dysfunction in thalassemia has not yet been established. Most of the studies have tried to correlate serum ferritin levels with pulmonary function abnormalities, but the results are conflicting.[3-6,9,12,16] However, lung dysfunction has never been adequately focused upon and remains to be one of the least understood complications, hence, we propose to study the pattern of lung functions in thalassemia major children and correlation of lung function test with serum ferritin.

MATERIALS AND METHODS

Prospective hospital-based cross-sectional study, during January 1, 2017, to December 31, 2017, in children aged between 5 and 15 years with beta-thalassemia major admitted for periodic BT in pediatric ward, at Karnataka Institute of Medical Sciences, Hubli.

Inclusion criteria

Children with confirmed diagnosis of beta-thalassemia major in the age group of 5–15 years were included in the study.

Exclusion criteria

(i) Thalassemia children who were already diagnosed cases of pulmonary dysfunctions (i.e., asthma, bronchiectasis, and other chronic lung diseases) and (ii) children with congenital heart disease/rheumatic heart disease were excluded from the study.

Sample size

Based on the previous literature, data indicate that the prevalence of abnormal pulmonary function test (PFT) in children with beta-thalassemia admitted to pediatric ward is 86–95%. To estimate the prevalence of abnormal PFT in children with beta-thalassemia within 6 percentage points of the true value of 90% with 80% confidence, we require a minimum of 41 beta-thalassemia major children to be studied.

Methodology

Ethical clearance was obtained from the Institutional Ethics Committee. Children who fulfill the inclusion/exclusion criteria for the study were selected. Informed and written consent was obtained from parents of all cases. All enrolled children were taken detailed clinical history including age at first BT, number of BT, duration of iron chelation therapy, and general physical examination findings which were recorded on a predesigned pro forma. Before BT, for all enrolled children, one blood sample was sent for serum ferritin level and another sample for pre-transfusion Hb. Serum ferritin level was measured by electrochemiluminescence technique using Cobas 6000 analyzer. PFT was done using spirometer (RMS Helios-401), within 24 h of BT. Standard procedure for PFT was carried out to all enrolled children and then checked test for acceptability and reproducibility.[17] The following parameters were recorded in the spirometry – forced vital capacity (FVC), forced expiratory volume in the 1st second (FEV_1), ratio of FEV1/FVC, peak expiratory flow rate (PEFR), and forced expiratory flow between 25 and 75% vital capacity (FEF 25–75%). Interpretation of PFT was done according to the recommended guidelines by asthma training module.[17]

Statistical analysis

Data were entered into Microsoft Excel data sheet and were analyzed using SPSS 22 version software (IBM SPSS Statistics, Somers NY, USA) that was used to analyze data. Chi-square test was used as test of significance for qualitative data. Continuous data were represented as mean and SD. Analysis of variance was the test of significance to identify the mean difference between more than 2 groups for quantitative data. Independent *t*-test was the test of significance to identify the mean difference between less than 2 groups for quantitative data. Pearson correlation was done to find the correlation between two quantitative variables.

RESULTS

Total number of children included in the study was 45. Thirty-seven (82.2%) children were <10 years and 8 children (17.8%) were more than or equal to 10 years, with mean age 7.78 ± 2.4 and male:female ratio 1.6:1. All children (100%) presented with easy fatigability and progressive pallor. Only 2 (4.4%) children had presented with cough secondary to URTI. None of the children presented with rapid breathing, chest in drawing, and chest pain. On per abdomen examination, all children had hepatomegaly (100%) and 34 children (75.5%) had splenomegaly, remaining 11 (24.5%) children were splenectomized. [Table 1] shows baseline character of enrolled children.

Total number of children with abnormal PFTs was 35 (77.8%). Among 35 children with pulmonary dysfunction, 31 (88.5%) children had restrictive pattern, 2 (5.71%) children had obstructive pattern, and 2 (5.71%) children had combined pattern.

[Table 2] shows mean values of various parameters of PFT. Twenty-five (55.5%) children had reduced FEV1 and 33 (73.3%) had reduced FVC. However, 41 (91.1%) had normal FEV_1/FVC%, whereas PEFR and FEF 25–75% were reduced in 22 (51.1%) children each.

[Tables 3 and 4] show risk factors for pulmonary dysfunction. There was a significant negative correlation between age and height with respect to FVC%, FEV_1%, and PEFR, but there was no significant correlation between BMI and PFT parameters ($P > 0.05$). [Figure 1] depicts scattered plot showing comparison between height and FVC% predicted (negative correlation). There was a significant difference in mean FVC%, FEV_1%, and PEFR with respect to the duration of chelation ($P < 0.05$%). Mean FVC%, FEV_1%, and PEFR were significantly reduced among those with duration of chelation (>5 years).

Mean serum ferritin levels in children with normal PFT, restrictive pattern, obstructive pattern, and combined pattern were 2868.70 ± 2985.58, 3267.93 ± 1995.89, 2792.40 ± 2096.01, and 1633.15 ± 32.03, respectively. There was no significant difference in mean values of PFT parameters, age, BMI, and pre-transfusion Hb with respect to serum ferritin levels; however, FVC and FEV1, PEFR, and PEF 25–75% values were found to be decreased in children with a high ferritin level (>2500 ng/ml) as compared with children with a low ferritin level (<2500 ng/ml), but these differences were statistically not significant [Tables 5 and 6].

Table 1: Baseline characteristics of thalassemia children (*n*=45).

Baseline characteristics		Mean±SD
Anthropometry		
Weight (kg)		17.8±4.8
Height (cm)		111.8±13.7
BMI		14.0±1.4
No. of blood transfusion		
<50 (*n*=9)		36.4±6.9
50–100 (*n*=19)		78.8±10.6
>100 (*n*=3)		106.3±3.0
Duration of chelation (years)		
Total (*n*=45)		
<5 years	*n*=25 (55.5%)	4.2±1.4
>5 years	*n*=20 (44.4%)	
Pre-transfusion HB (g/dl)		5.7±1
Post-transfusion HB(g/dl)		9.7±0.8
Serum ferritin (ng/ml)		
Total		3085.4±2184.7
<2500 (*n*=23)		1545±461.5
>2500 (*n*=22)		4695.6±2112.6

Table 2: Mean levels of various indices of pulmonary function tests (*n*=45).

PFT parameters	Mean±SD	Number of cases (*n*=45)	
		Normal (%)	Decreased (%)
FEV_1%	81.7±40.6	20 (44.4)	25 (55.5)
FVC%	68.9±20.6	12 (26.7)	33 (73.3)
FEV_1/FVC%	121.4±39.8	41 (91.1)	4 (8.9)
PEFR	99.3±49.9	22 (48.9)	23 (51.1)
PEF 25–75%	82.4±31.6	22 (48.9)	23 (51.1)

DISCUSSION

Lung dysfunction is among the least studied complication in children with beta-thalassemia major, probably due to the lack of pulmonary symptoms presenting compared to cardiomyopathy or endocrine complication.[16] We observed that 35 (77.8%) children had abnormal PFT. The pulmonary functional abnormality of frequency was restrictive 31 (88.5%), obstructive 4 (5.7%), and combined 4 (5.7%) pattern. Impairment in respiratory function among thalassemia children has been reported in the range of 29–86%.[7-9]

Table 3: Correlation between age, height, and BMI with PFT (*n*=45).

	FVC%	FEV_1%	FEV_1/FVC%	PEFR
Age				
Pearson correlation	−0.435**	−0.324*	−0.081	−0.507**
P-value	0.003	0.03*	0.595	<0.001*
Height				
Pearson correlation	−0.474**	−0.414**	−0.195	−0.574**
P-value	0.001*	0.005*	0.199	<0.001*
BMI				
Pearson correlation	0.127	0.148	0.086	−0.092
P-value	0.405	0.332	0.573	0.546

*Significant, **highly significant

Table 4: Comparison of PFT and duration of chelation therapy (*n*=45).

PFT	Duration of chelation (year)		*P*-value#
	Mean with SD		
	<5 years (*n*=25)	>5 years (*n*=20)	
FVC%	75.08±22.46	61.25±15.14	0.023*
FEV_1%	92.68±49.24	68.05±19.93	0.042*
FEV_1/FVC%	124.64±52.63	116.74±11.32	0.514
PEFR	117.84±58.86	75.46±18.77	0.003*
PEF 25–75%	83.92	80.45	0.719

#Using independent *t*-test, *$P<0.05$

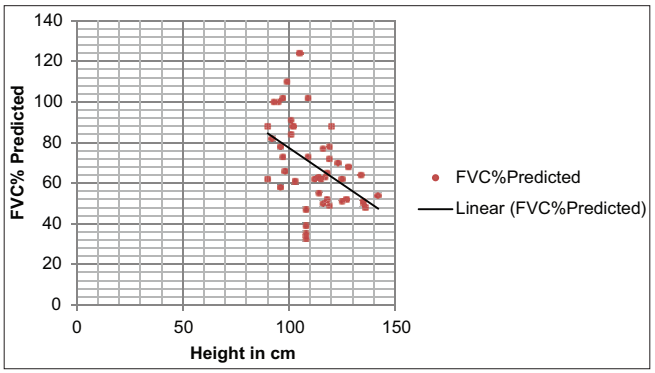

Figure 1: Scattered plot showing comparison between height and forced vital capacity % predicted.

Table 5: Correlation between serum ferritin and PFT (***n***=45).

		Serum ferritin	FVC%	FEV_1%	FEV_1/FVC%	PEFR	PEF 25–75%
Serum ferritin	Pearson correlation	1	0.036	0.026	0.022	−0.075	0.128
	P-value		0.814	0.866	0.885	0.626	0.402

Table 6: Comparison of PFT, age, BMI, PT-HB, and serum ferritin (*n*=45).

	Serum ferritin						*P*-value[#]
	<2500 ng/dl (*n*=23)			>2500 ng/dl (*n*=22)			
	Mean	SD	Median	Mean	SD	Median	
FVC%	71.04	22.81	65.00	66.73	18.16	62.50	0.488
FEV_1%	87.17	46.31	80.00	76.05	33.73	70.00	0.364
FEV_1/FVC%	122.60	48.09	123.00	119.59	29.77	122.00	0.803
PEFR	102.35	51.55	76.00	95.50	49.19	83.00	0.651
PEF 25–75%	77.30	30.34	78.00	87.68	32.74	82.00	0.276
Age	7.22	2.15	7.00	8.36	2.59	8.50	0.113
BMI	13.90	1.55	13.60	14.06	1.29	13.88	0.711
PT-Hb	5.63	1.17	5.70	5.86	0.79	6.00	0.449

[#]Independent *t*-test (*P*>0.05)

Restrictive lung function abnormality was observed as major pulmonary abnormality in our study. Several other studies[3-11] have shown similar restrictive pattern as major pulmonary dysfunction. However, none of them found exact etiopathogenesis. We analyzed various risk factors for abnormal lung function including age, height, BMI, number of BT, duration of chelation therapy, organomegaly, and serum ferritin. Of these, age, height, and duration of chelation therapy (>5 years) were significantly associated with pulmonary dysfunction (FVC%, FEV_1, and PEFR). Our findings were consistent with the previous literature, as reported by others.[4,8] The severity of restrictive abnormalities of thalassemic children was found to increase with age. In many other studies, different etiopathogenetic mechanisms for the development of restrictive lung dysfunction were reported such as multiple BT,[18] hypoxia,[18] iron overload,[4,5,9] drug like desferrioximine,[8,18] and genetic structure.[18]

Four children (5.7%) had obstructive type of lung dysfunction. Similar results were found in other studies.[6,9] However, Gulhan *et al.*[12] found more number of obstructive dysfunction (46.2%). We also observed the combined pattern in 4 children (5.7%). Similar finding was also observed in Said[15] (3.1%). The probable reason for small number of cases could be due to limitations in screening.

The mean values of various parameters of PFTs were reduced. A reduced FVC% 33 (73.3%), a reduced FEV1 25 (55.5%), a normal FEV_1/FVC ratio 41 (91.2%), and a reduced FEF 25–75% 23 (51.1%) were observed. In our study, pulmonary function abnormality may be partially explained by insufficient anatomic and functional development of lung during early infancy,[4] as we observed age and height negatively correlated with various parameters of PFT. The other reasons could be iron overload as serum ferritin (>2500 ng/ml) had significantly associated with pulmonary dysfunction.

Although the measurement of serum ferritin is not the best quantitative estimate of body iron stores, thalassemic patients with a serum ferritin concentration of ≥3000 ng/dL have been reported to have a high probability of lung injury.[19] Levels >2500 ng/dL have been reported to be associated with a 4-fold higher risk of death.[3] In the present study, no correlation was found between serum ferritin levels and PFT; however, we observed, FVC and FEV_1, PEFR, and FEF 25–75% values were found to be decreased in patients with a high ferritin level (>2500 ng/dL) as compared with children with a low ferritin level (<2500 ng/dL), but these differences were statistically not significant. Probably, as our numbers are less. A complex mechanism in addition to iron overload has been proposed to play important role in the development of lung dysfunction.[13]

In the present study, age and height were inversely correlated with FVC%, FEV_1%, and PEFR. There was a significant negative correlation between height and FVC%, FEV_1%, and PEFR, that is, with increase in height, there was a decrease in FVC%, FEV_1%, and PEFR. Probable cause could be the growth retardation which was observed in thalassemic children and the predictive lung volume, which was derived from age and height, might not be an accurate value, even if the effect of thalassemia on lung growth could be different from one on general growth.[18,20]

Keens *et al.*[21] suggested that good compliance to chelation therapy is crucial to prevent complications in these children.

In our study, FVC%, FEV1%, and PEFR were significantly reduced among those with duration of chelation (>5 years). Even though all children had received chelation therapy, still we found significant reduction in PFT parameters; this could be probably due to inadequate dosage or non-compliance of the drug. Similar results found Said study.[15]

CONCLUSION

Majority of our thalassemia children (78%) had abnormal patterns of lung function even though none of these children had any respiratory symptoms. We suggest, all children with thalassemia on regular BT should undergo PFT annually to prevent the sequelae.

Declaration of patient consent

The Institutional Review Board permission obtained for the study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: Harsoor J, Ratageri VH, Shilpa C, Illalu S, Wari P. Pulmonary function tests in children with beta-thalassemia major. Karnataka Paediatr J 2020;35(1):52-6.

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Karnataka Pediatric Journal

Case Report

Senior-Loken syndrome: A case report

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Received : 07 July 2020
Accepted : 16 August 2020
Published :

DOI
10.25259/KPJ_12_2020

Quick Response Code:

ABSTRACT

Senior-Loken syndrome refers to a combination of nephronophthisis and retinal dystrophy. Nephronophthisis progresses to end-stage renal disease during the second decade. The retinal lesions vary from severe infantile onset retinal dystrophy to milder pigmentary retinopathy. There is a spectrum of associated features, including skeletal, dermatological, and cerebellar anomalies. Here, we report a case of first genetically proven Senior-Loken syndrome in India, who presented with growth failure, polyuria, polydipsia, nystagmus, and defective night vision.

Keywords: Senior-Loken, Nephronophthisis, Retinal dystrophy

INTRODUCTION

Renal nephronophthisis, a renal ciliopathy, is a disease causing cystic kidneys or renal cystic dysplasia. It is the most common genetic cause of chronic kidney disease in the first two decades of life.[1]

Retinal dystrophy is one of the extrarenal associations of nephronophthisis. It manifests as congenital amaurosis of the Leber type or late-onset pigmentary retinal degeneration. It begins in childhood or early adolescence and produces a visual handicap ranging from night blindness to functional blindness.[2,3]

Senior-Loken syndrome refers to a combination of nephronophthisis and retinal dystrophy. It was first described in 1961 by Senior *et al.*[4] who described a family in which 6 of 13 children had nephronophthisis and tapetoretinal degeneration. Loken *et al.*[5] described the same condition in two siblings who had blindness and severe renal failure with renal tubular atrophy and dilatation on biopsy. This syndrome contributes to 10–15% of overall nephronophthisis, a group of illnesses affecting 1 in 50,000 births. The onset is insidious, and most cases do not present until end stage renal failure.

There have been 150 cases of Senior-Loken syndrome reported worldwide. Few cases are also reported from India based on typical renal, retinal changes, and a consistent clinical picture.[1,6-10] The Indian cases reported have not been genetically proven. Our case is the first genetically proven case of Senior-Loken syndrome in India.

CASE REPORT

A 15-year-old boy, first born out of third degree consanguineous marriage, presented with easy fatigability, defective night vision, polyuria, polydipsia, growth failure, and unsteadiness of

gait which is worsening at night. On examination, he was pale with generalized edema, had a pulse rate of 90/min and no radiofemoral delay, blood pressure of 144/110 mmHg (Stage 2 hypertension: AAP guidelines 2017), respiratory rate of 20/min, and SpO_2 of 96% with room air and had no dysmorphic features. His height and weight were 135 cm and 27 kg, respectively (<3rd percentile: IAP growth charts 2015). Systemic examination was normal, with no cerebellar signs except for rapid fine horizontal nystagmus. A detailed ophthalmology evaluation revealed retinal pigmentary epithelial changes along with evidence of dystrophy confirmed by electroretinogram (ERG). Investigations revealed hemoglobin: 5.2 g/dl (10.8–15.6 g/dl), normocytic normochromic blood picture, calcium: 5.7 mg/dl (7.6–11 mg/dl), magnesium: 2.26 mg/dl (1.7–2.55 mg/dl), phosphorus: 8.7 mg/dl (3–5.4 mg/dl), parathyroid hormone: 664.4 ng/L (4.5–36 ng/L), 25-hydroxyvitamin D: 23.64 ng/ml (30–47 ng/ml), creatinine: 14.9 mg/dl (0.2–0.87 mg/dl), and urea: 265 mg/dl (10–48 mg/dl). Urine complete analysis revealed isosthenuria and ultrasound KUB showed bilateral shrunken kidney with increased renal parenchymal echoes and multiple cysts at corticomedullary junction. MRI brain was not done. 2D ECHO showed a normal heart and normal great vessel anatomy and function. Suspecting Senior-Loken syndrome, clinical exome sequencing was done which revealed contiguous homozygous deletion encompassing exons 2–5 and 8–16 of NPHP1 gene, confirming the disease [Figure 1]. The child was under renal replacement therapy, antihypertensives, and other supportive measures and later underwent renal transplantation.

DISCUSSION

Nephronophthisis is characterized by chronic tubulointerstitial nephritis that progresses to end-stage renal disease during the second decade.[11] At least 14 different NPHP genes have been identified as causes for nephronophthisis: Nephrocystin genes including (NPHP1, NPHP2, NPHP3, NPHP4, NPHP5, NPHP6, NPHP7, NPHP8 and NPHP9, NPHP10, NPHP11, NPHP12, NPHP13, and NPHPL1)[1] and mutation in IQCB1 (also called NPHP5) identified as the most frequent cause.[8]

Senior-Loken syndrome also known as hereditary renal-retinal syndrome or renal-retinal dysplasia, is a rare autosomal recessive disorder[1] caused by mutation in NPHP1 gene. It is a progressive ciliopathy affecting the kidney and retina primarily.

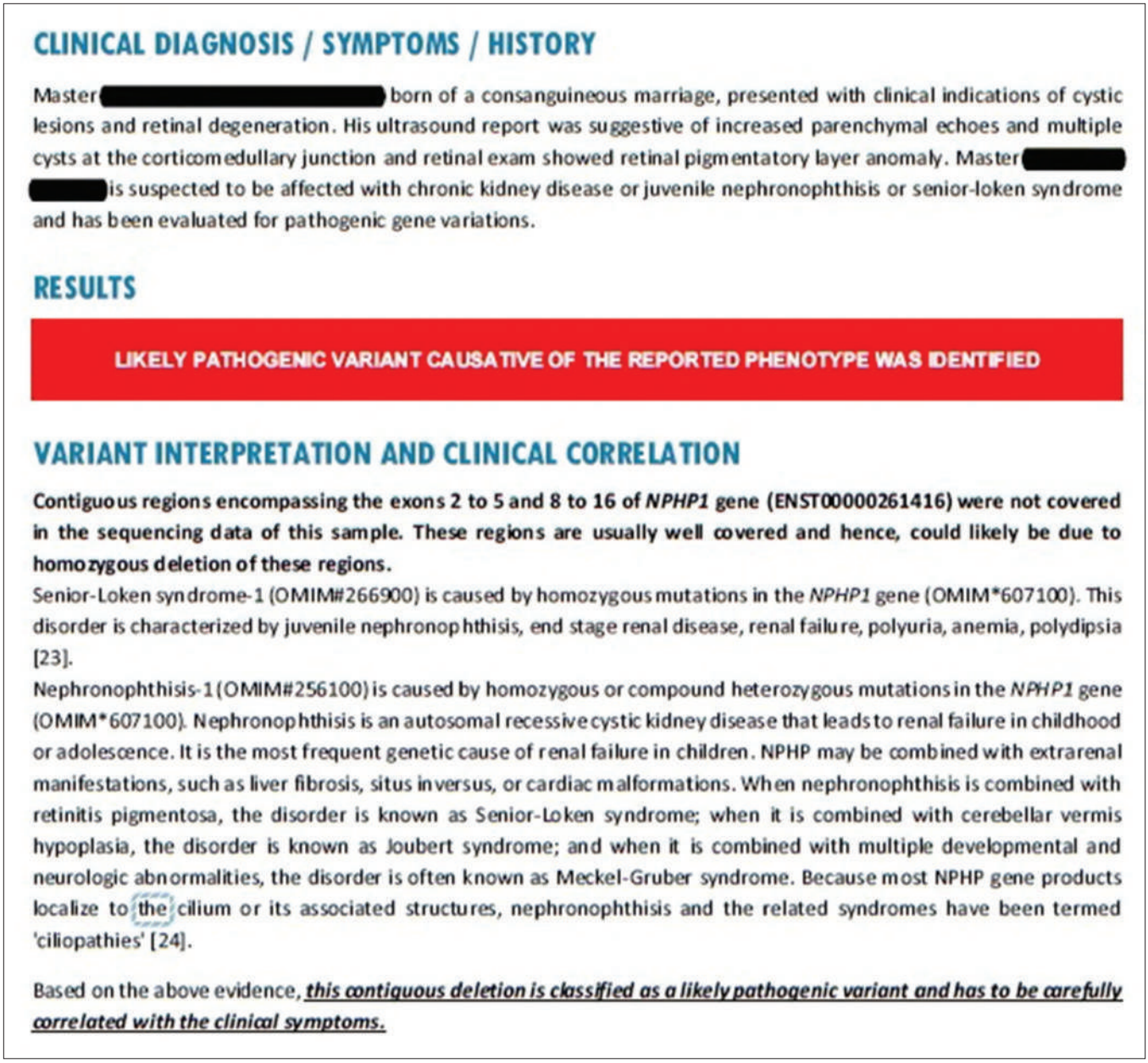
Nephronophthisis is caused by dysfunction of primary cilia, which are sensory organelles that connect mechanosensory, visual, osmotic, and other stimuli for cell cycle control leading to multisystem involvement and broad spectrum of extrarenal manifestations[1] which includes retinal degeneration, oculomotor apraxia (Cogan type), coloboma, aplasia of cerebellar vermis, polydactyly, and neonatal tachypnea (Joubert syndrome); cranioectodermal dysplasia and electroretinal abnormalities (Sensenbrenner syndrome).[8]

Severe infantile, juvenile, and adolescent are the three clinical types of nephronophthisis.[12] These are described based on the age of onset of end-stage renal disease in these patients.[12] Early symptoms include polyuria, polydipsia, and enuresis due to a concentrating defect. The disease usually progresses to end-stage renal disease before 20 years, although late onset in the third decade has also been reported.[13] The ultrasonographic findings of juvenile nephronophthisis may be normal or may show increased renal parenchymal echogenicity, poor corticomedullary differentiation, a small kidney, or medullary cysts.[14] Renal histology is characterized by the triad of interstitial infiltration, renal tubular cell atrophy with cyst development, and renal interstitial fibrosis.[15] Primary management depends on delaying the progression of renal failure and the need for dialysis and transplantation.[2] Renal transplantation is the preferred treatment as disease does not recur in the transplanted kidney.[16] Vasopressin V2 receptor antagonists, which alter the cystogenesis and progression of the disease have been tried.[2]

The ocular manifestation may be in the form of tapetoretinal degeneration, most common form, characterized by progressive choroid and retinal degeneration, Leber type congenital amaurosis, or late-onset pigmentary retinal degeneration.[3] It can also be manifested in the form of cataracts, Coats disease, or even keratoconus. ERG typically shows reduced rod cell function and also helps in early diagnosis of the disease, even before the symptom onset or fundoscopic examination. Annual eye examination is recommended to monitor the progression of retinal involvement of the disease.[2] Management of the ocular disease is primarily supportive.

Patients having this disorder require dialysis or kidney transplant by the time they reach adolescence. Nephronophthisis patients must have a periodical ophthalmological evaluation with an ERG. Children with primary tapetoretinal degeneration should have routine measurements of blood pressure, urinary concentrating ability, and renal ultrasound scan. Early diagnosis, hypertension control, and protein intake restriction may delay dialysis.[9]

Proving a genetic diagnosis of the disease offers help in both the patient management and in genetic counseling for parents to prevent recurrence in subsequent pregnancies.



CLINICAL DIAGNOSIS / SYMPTOMS / HISTORY

Master [redacted] born of a consanguineous marriage, presented with clinical indications of cystic lesions and retinal degeneration. His ultrasound report was suggestive of increased parenchymal echoes and multiple cysts at the corticomedullary junction and retinal exam showed retinal pigmentatory layer anomaly. Master [redacted] is suspected to be affected with chronic kidney disease or juvenile nephronophthisis or senior-loken syndrome and has been evaluated for pathogenic gene variations.

RESULTS

LIKELY PATHOGENIC VARIANT CAUSATIVE OF THE REPORTED PHENOTYPE WAS IDENTIFIED

VARIANT INTERPRETATION AND CLINICAL CORRELATION

Contiguous regions encompassing the exons 2 to 5 and 8 to 16 of *NPHP1* gene (ENST00000261416) were not covered in the sequencing data of this sample. These regions are usually well covered and hence, could likely be due to homozygous deletion of these regions.

Senior-Loken syndrome-1 (OMIM#266900) is caused by homozygous mutations in the *NPHP1* gene (OMIM*607100). This disorder is characterized by juvenile nephronophthisis, end stage renal disease, renal failure, polyuria, anemia, polydipsia [23].

Nephronophthisis-1 (OMIM#256100) is caused by homozygous or compound heterozygous mutations in the *NPHP1* gene (OMIM*607100). Nephronophthisis is an autosomal recessive cystic kidney disease that leads to renal failure in childhood or adolescence. It is the most frequent genetic cause of renal failure in children. NPHP may be combined with extrarenal manifestations, such as liver fibrosis, situs inversus, or cardiac malformations. When nephronophthisis is combined with retinitis pigmentosa, the disorder is known as Senior-Loken syndrome; when it is combined with cerebellar vermis hypoplasia, the disorder is known as Joubert syndrome; and when it is combined with multiple developmental and neurologic abnormalities, the disorder is often known as Meckel-Gruber syndrome. Because most NPHP gene products localize to the cilium or its associated structures, nephronophthisis and the related syndromes have been termed 'ciliopathies' [24].

Based on the above evidence, ***this contiguous deletion is classified as a likely pathogenic variant and has to be carefully correlated with the clinical symptoms.***

Figure 1: The genetic report confirming the diagnosis.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: Duraiswamy A, Babilu CO. Senior-Loken syndrome: A case report. Karnataka Pediatr J 2020;35(1):57-60.

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Karnataka Pediatric Journal

Letter to the Editor

The real heroes in PICUs

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Received : 15 June 2020
Accepted : 15 June 2020
Published :

DOI
10.25259/KPJ_8_2020

Quick Response Code:

Pediatric intensive care is undoubtedly one of the most challenging of all other pediatric sub Specialities. Most children admitted to the PICU are critically ill with the prognosis being grave. Of course, it is immensely fulfilling to diagnose accurately, treat on time, and save a life, yet there are situations when things go beyond our purview. Even with the best intentions and right interventions, we sometimes fail to save a life. Yes, life as an intensivist is challenging, but the real hero who I want to talk about today is not the doctor, but that person who silently bears it all and helps us treat the child, the mother.

A petrified yet brave woman hovering around the child is a common sight in all pediatric wards. We see her often standing silently by the side, sponging the head of a child with fever, feeding a morsel to a reluctant kid, caressing the hand with the iv line or wiping froth off a convulsing baby. It is the mother who faces the biggest of all challenges when her child is sick. While she bears the brunt of seeing her kid suffer, she also remains the main pillar of support in treating the child in more ways than one.

To us pediatricians, the mother is often a valuable resource. I remember our professor once told us, "Never ignore the story given by a mother; however, trivial or overly detailed, it may sound. It often leads us to the diagnosis." It is rightly so because no one observes the child as much keenly as a mother. A little change in the behavior, a minor fluctuation of temperature, a slowly progressing weakness, a faint lethargy, a tad poor feeding, every little detail is precisely noticed by the mother and spending some time talking to her even in the busy ER will definitely yield tremendous clues about the diagnosis.

Like this, 11-year-old child once came to our PICU in shock. While we resuscitated, did the needful, no positive history was forthcoming from the father who insisted that the child was totally alright a day back. However, on careful probing, the mother revealed that he had been waking up at nights frequently to urinate and had been losing weight despite eating very well. It clinched the diagnosis. Although the clinical signs such as acidotic breathing and GRBS that are routinely done as the first thing while inserting a line would have told that it was DKA, the history from the observant mother sealed it and saved our time from contemplating other differential diagnoses.

So was it in another case that I recall? In my early PG years, when I was on a night duty and was all by myself in the PICU, there arrived a 12-year-old girl with active generalized convulsions. I did panic. The nurses around helped me with securing a line, and after two loading doses of anticonvulsants, she stopped seizuring. There was no significant history. No fever, headache, or vomiting and no head injury. When I was contemplating imaging and other complex investigations the following day after sending the basic laboratories, the mother dropped in to

say, she had looked a little puffy that morning. A bell just rang. The high blood pressure on a second recording and the high colored urine, we found later, everything did clinch the diagnosis, but I knew it right when the mother told that little history that it was indeed acute glomerulonephritis with hypertensive encephalopathy.

Not just with diagnosis but mothers are invaluable in managing the children, while we get busy with our procedures as well. In our PICU set up, we allow the mothers to stay by the kids. While all awake kids protest painful interventions, sick kids resent even harmless procedures such as nebulization or HFNC or even a simple oxygen mask or a pulse oximeter. Mothers again turn out to be a boon in such situations, pacifying the child to bear it and comforting him or her in the best possible way she can. Some bright mothers even alert us when the infusion pump is not working consistently or when the monitor is alarming, or an iv line shows a mild swelling. Many mothers are keen listeners and are well versed with the names of the medications and even their dosage and schedule. I have seen some mothers, even from the humble background, write down the recorded temperature, the BP readings, and the urine output meticulously and turn out to be the best monitors in PICU. It only goes on to show that mothers can don any role when it comes to caring for their child.

Surprisingly, even when it is the question of the end of life care, mothers turn out to be the bravest. While I see fathers either panic and mortify or go on to get wild and violent, mothers remain heroes until the end. I remember a mother of a child with astrocytoma who had undergone multiple surgeries and chemo and radiotherapy sessions and had come to our PICU in the end for palliative care. I observed that she never cried when in front of the child and till the night he died, she cheerfully brought his favorite dish masala dosa to feed him though he managed to take just a mouthful of it. She played his pet songs and even made him call his friends and talk over the phone, making sure till the end that he had a peaceful farewell. Of course, the fact that she howled uncontrollably and fell unconscious later is another heart-wrenching story.

I have seen mothers who have unfortunately had more than one kid with the same genetic abnormality or rare disease who miraculously manage to remain cheerful and care for their children with equal zeal during all their repeated admissions. There are also mothers of children on long days of ventilation who sit by their sedated kids and talk to them continuously, even telling them about their plans for the kids after discharge. While it is very moving, it, in a way, keeps our hopes up and pushes us to try till the very end.

Mothers, to me, appear to be the real warriors who fight for their child incessantly. We are mere facilitators in their recovery. As I see the brave mothers in the PICU, I admire and salute the inherent astounding strength of every woman in handling adversities.

May God give us the strength to save the kids for these wonderful mothers.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

How to cite this article: Manjunath MA. The real heroes in PICUs. Karnataka Pediatr J 2020;35(1):61-2.

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Karnataka Pediatric Journal

Journal Review

KPJ journal rounds

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Received : 11 August 2020
Accepted : 11 August 2020
Published :

DOI
10.25259/KPJ_15_2020

Quick Response Code:

Source: Sundararajan, S., Rabe, H. *Prevention of iron deficiency anemia in infants and toddlers*. Pediatr Res (2020). https://doi.org/10.1038/s41390-020-0907-5

The authors in this comprehensive review discuss feasible options, recommendations, interventions for tackling iron deficiency anemia (IDA), and iron deficiency states. Despite interventions at various levels across the world, IDA remains a significant problem to tackle. IDA contributes to death and disability and is an important risk factor for maternal and perinatal mortality, including the risks for stillbirths, prematurity, and low birth weight. Reduction in early infantile anemia and newborn mortality rates is possible with easily implemented, low- to no-cost intervention such as delayed cord clamping (DCC). DCC until 1–3 min after birth facilitates placental transfusion and iron-rich blood flow to the newborn. DCC, an effective anemia prevention strategy, requires cooperation among health providers involved in childbirth, and a participatory culture change in public health. It goes without saying that public intervention strategies must consider multiple factors associated with anemia listed in this review before designing intervention studies that aim to reduce anemia prevalence in infants and toddlers.

Source: Medvedev MM, Brotherton H, Gai A, Tann C, Gale C, Waiswa P, Elbourne D, Lawn JE, Allen E. *Development and validation of a simplified score to predict neonatal mortality risk among neonates weighing 2000 g or less (NMR-2000): an analysis using data from the UK and The Gambia*. The Lancet Child & Adolescent Health. 2020 Feb 28. DOI: https://doi.org/10.1016/S2352-4642(20)30021-3

This population-wide study, including data from 110 176 newborn babies at 187 hospitals in the UK and 550 newborn babies at one hospital in the Gambia, has derived and validated NMR-2000 for predicting in-hospital mortality. A strength of this work is that, to the best of our knowledge, this is the largest dataset that has been used to develop and validate a neonatal mortality risk score. About 18 candidate variables were selected for inclusion in the modeling process. The final model included three parameters: Birth weight, admission oxygen saturation, and highest level of respiratory support within 24 h of birth. Among neonates born at 32 weeks' gestation or earlier, the discriminatory ability of NMR-2000 was superior to that of CRIB-II, one of the most widely used neonatal risk scores. The authors interpret NMR-2000 as a validated mortality risk score for hospitalized neonates weighing 2000 g or less in settings where pulse oximetry is available. The score is accurate and simplified for bedside use.

Source: McCann ME, Soriano SG. *Does general anesthesia affect neurodevelopment in infants and children?* bmj. 2019 Dec 9;367. doi: https://doi.org/10.1136/bmj.l6459

In this state-of-the-art review, the authors deal with all the relevant neurological issues associated with the use of general anesthetics in children. The possibility of anesthetic-induced

neurotoxicity occurring in children has led to concerns about the safety of pediatric anesthesia. A spectrum of behavioral changes has been documented after general anesthetic exposure in young children, including emergence delirium, which may be evidence of toxicity. Most clinical studies are retrospective; specifics about medications or monitoring are unavailable and many of the outcomes may not be sensitive to detect small neurocognitive deficits. Some of these retrospective studies have shown an association between anesthesia exposure at a young age and neurocognitive deficits, but others have not. Practitioners and families should be reassured that although general anesthetics have the potential to induce neurotoxicity, very little clinical evidence exists to support this.

Source: van derMade CI, Hoischen A, Netea MG, van de Veerdonk FL. *Primary immunodeficiencies in cytosolic pattern-recognition receptor pathways: Toward host-directed treatment strategies.* Immunol Rev. 2020;00:1– 26. https://doi.org/10.1111/imr.12898

In this excellent review, the authors simplify the approach to the ever-increasing types of primary immunodeficiency diseases (PIDs) and have also discussed a host-directed treatment approach, in which functional immunological testing in patients with and without a genetic diagnosis can illuminate the predominant disease mechanism and provide a rational basis for drug therapy.

Patients with PIDs constitute a formidable area of research to study the genetics and the molecular mechanisms of complex immunological pathways. The advancing understanding of cytosolic pattern recognition receptor pathways in the host innate immune response creates opportunities for the development of new treatment strategies.

The future therapeutic arsenal will, therefore, become increasingly tailored to the patient's unique molecular fingerprint. This personalized medicine approach will allow the titration of optimal treatment efficacy based on both clinical and biochemical improvement, weighed against the relatively minor harm inflicted by the targeted immunomodulatory drugs.

Source: Edwards BL, Dorfman D. *High-risk Pediatric Emergencies.* Emerg Med Clin North Am. 2020;38(2):383-400. doi:10.1016/j.emc.2020.01.004

Although data from India are not available in the countries that the authors have included, they have found that more than half of pediatric malpractice cases arise from emergency departments, primarily due to missed, or delayed diagnoses. All providers who take care of children in emergency departments should be aware of this risk and the most common diagnoses associated with medicolegal liability.

This article focuses on the diagnosis and management of high-risk diagnoses in pediatric patients presenting to emergency departments, including meningitis, pneumonia, appendicitis, testicular torsion, and fracture. It highlights challenges and pitfalls that may increase the risk of liability.

Children are not small adults. The diagnoses associated with malpractice are unique to the pediatric population and vary by age. All providers who take care of children in the emergency setting should be cognizant of the medicolegal risk associated with this population, not only to protect against liability but also to increase awareness of the pitfalls of these critical but complex diagnoses to improve outcomes for all pediatric patients. It concludes with a discussion on recognition and management of abuse in children, including when to report and decisions on disposition.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

How to cite this article: Kumar VS. KPJ journal rounds. Karnataka Pediatr J 2020;35(1):63-4.