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Editorial

Wheezing in Child

Wheezing is a common presentation in young children. Most infants and children with recurrent wheezing have asthma, but other causes should be considered in the differential diagnosis. This Diagnosis and treatment of these children can be challenging, as arriving at a final diagnosis often requires a process of elimination. Almost 60% of children with wheeze in the first few years of life have ceased wheezing by age 6years.

Most children with wheeze in the first three years of life have a transient syndrome that may be related to pre-existing reduced airways function (possibly on the basis of decreased airway size) at birth and this condition is not associated with features of atopy or future development of asthma.Only half the children with persistent wheeze at age 6 years had commenced wheezing before age 3years..

Non-asthmatic wheeze in early childhood is associated with intercurrent viral infections.

The risk factors for this syndrome appear to be:

(i) Reduced lung function that may reflect impaired lung growth in the intrauterine period.

(ii) Exposure to tobacco smoke either during the prenatal or early childhood period

Asthma is the most likely cause of recurrent wheezing in children younger than five years.

The other common causes of wheezing in young children are allergies, gastro esophageal reflux disease, infections, and obstructive sleep apnea.Uncommon causes are bronchopulmonary dysplasia and foreign body aspiration. Rare causes are bronchiolitis obliterans. Congenital vascular abnormalities, Congestive heart failure, Cystic fibrosis, Immunodeficiency diseases, meditational masses, primary ciliary dyskinesia, tracheobronchial anomalies, tumor or malignancy and vocal cord dysfunction.

Response to bronchodilators may help differentiate asthma from other causes of wheezing.

Chest radiography should be performed in children with recurrent wheezing or a single episode of unexplained wheezing that does not responds to bronchodilators

Few questions are help to distinguish the etiology of wheezing in children

1. How old was the patient when the wheezing started?

The age at onset helps to distinguish between congenital and noncongenital causes of wheezing.

In infants, wheezing is more likely to be caused by a congenital abnormality than in older children.

2. Did the wheezing start suddenly?

Sudden onset wheezing is generally associated withforeign body aspiration.However, symptoms are not always dramatic and are often difficult to diagnose if foreign body lodged into the subglottic area.

Laryngotracheal foreign bodies are usually discovered within 24 hours, and 90 percent of children with laryngotracheal foreign bodies are diagnosed within one week. Foreign body aspiration can occur anytime, but it is most common age of onset between eight months and four years of age. High airway obstruction gives the symptom of coughing, gagging, choking, and wheezing. . Children may have recurrent symptoms or non resolution of pneumonia as aresult of obstructive atelectasis.

3. What is the patternof wheezing?

The pattern of wheezing may suggest the etiology Episodic wheezing that is seasonal or is associated with environmental exposures is likely to be caused by asthma.

Persistent wheezing from birth is likely the result of a congenital anatomic anomalyor genetic cause.Children with persistent respiratory illnesses with wheezing should be evaluated for cysticfibrosis, bronchopulmonary dysplasia, ,laryngomalacia,agammaglobulinemia, andprimary ciliary dyskinesia

4. Is the wheezing associated with a cough?

If wheezing associated with a cough it may be associated with GERD, sleep apnea, asthma and allergies. A cough after eating in a wheezing child suggests GERD. A dry, unproductive cough that worsens at night can be a resultof GERD, allergies, or asthma Obstructive sleep apnea should be considered in children whose coughing or wheezing awakens them at night and is associated with snoring. sleep apnea in infants is usually a result of craniofacial anomalies, but the main cause in older children is adenotonsillar hypertrophy.

5. Is the wheezing associated with feeding?

Wheezing after feeding is usually caused by GERD. Tracheoesophageal fistulas and laryngeal clefts arealso rare causes of vomitingand wheezing after feeding.Infants with GERD typically have poor weight gain and may have been offered numerous formulas for "milk intolerance." A small randomizedcontrolled trial that found that giving a protonpump inhibitor to asthmatic children with GERD did not reduce asthma symptoms.

6. Is the wheezing associated with multiple respiratory illnesses?

Multiple respiratory illnesses without obviouscause in the first year of life suggest cystic fibrosis, immunodeficiency syndromes,or primary ciliary dyskinesia.cysticfibrosis is associated withsteatorrhea and failure to thrive.Continuous rhinitisfrom birth is consistent with primary ciliarydyskinesia. Another uncommon causeof wheezing is congenital laryngomalacia,which can present as multiple respiratoryinfections and can present later inchildhood

7. Is there any association of positional change with wheezing?

Tracheomalacia and anomalies of the great vessels should be considered when wheezing occurs with positional changes in infants.

8. Is there a family history of wheezing?

A family history of asthmaallergies or eczema increases suspicion of Asthma.

Diagnostic testing should be modified according to the child's age and the suspected etiology&treatment to be given according to etiology.

Investigational approach after presumptive diagnosis.

Signs and Symptoms	Presumptive diagnosis	Investigations
Episodic pattern, cough; patient responds to bronchodilators	Asthma	Allergy testing Pulmonary function test Trial of bronchodilators
Auscultatory crackles, fever	Pneumonia	Chest radiography
Seasonal pattern, nasal flaring, intercostal retractions	Bronchiolitis (RSV), croup, allergies	Chest radiography
Associated with feeding, cough, and vomiting	GERD	24-hour pH monitoring Barium swallow
Sudden onset of wheezing and choking	Foreign body aspiration	Bronchoscopy
Associated with positional changes	Tracheomalacia; anomalies of the great vessels	Angiography Bronchoscopy Chest radiography CT or MRI Echocardiography
History of multiple respiratory illnesses; failure to thrive	Cystic fibrosis or immunodeficiency	Ciliary function testing Immunoglobulin levels Sweat chloride testing
Stridor with drooling	Epiglottitis	Neck radiography
Exacerbated by neck flexion; relieved by neck hyperextension	Vascular ring	Angiography Barium swallow Bronchoscopy Chest radiography CT or MRI
Heart murmurs or cardiomegaly, cyanosis without respiratory distress	Cardiac disease	Angiography Chest radiography Echocardiography

Key points

1. Determining the cause of wheeze in young children can be difficult and sometimes is determined only following a trial of treatment.
2. Response to bronchodilators may help differentiate asthma from other causes of wheezing.
3. Asthma is very common but other causes are also common and worth considering in the event of poor efficacy of asthma treatment.
4. Historical data that help in the diagnosis include family history, age at onset, pattern of wheezing, suddenness of onset, and association with feeding, cough, respiratory illnesses, and positional change,
5. A cough after eating in a wheezing child suggests gastro esophageal refluxdisease
6. A focused examination and targeted diagnostic testing guided by clinical suspicion also provide useful information
7. Children with recurrent wheezing or a single episode of unexplained wheezing that does not respond to bronchodilators should undergo chest radiography.
8. Treatment to be given according to cause

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Management of Status Asthmaticus

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Bronchial asthma is the commonest chronic disease in children affecting 300 million children worldwide. In the United States of America, exacerbations of asthma lead to 15 million OPD visits, 2 million emergency room visits and 50, 000 hospitalisations every year. Data from AIIMS, New Delhi mentions that around 4% of emergency room visits are due to exacerbations of asthma and PICU admissions were to the tune of less than 1%.

Definition and other terminologies

Status asthmaticus is severe asthma that fails to respond to inhaled beta 2 agonists, oral or intravenous steroids and oxygen and requires admission to hospital for treatment. Another terminology that is interchangeably used is Severe Acute Asthma which essentially is used to convey the same meaning.

A flare up or exacerbation is an acute or subacute worsening of symptoms and lung function compared with patient's usual status.'Flare up' is the preferred term for discussion with parents and patients whereas 'exacerbation' is a term difficult for parents and patients to comprehend. 'Attack' has highly variable meaning for patients and clinicians. 'Episode' does not convey clinical urgency.

'Near Fatal asthma' denotes an exacerbation of sudden onset that rapidly progresses to hypercapnia and hypoxemia leading to respiratory arrest.

'Sudden asphyxic asthma' is used to describe an exacerbation which undergoes rapid decompensation in matter of 3 hours after onset of symptoms characterised by severe hypercapnia, silent chest and high incidence of respiratory arrest.

'Acute fatal asthma' is used to describe a condition where there is respiratory failure and death occurrs within minutes of exacerbation onset.

Factors which can lead to an exacerbation

(a) The commonest reason for an exacerbation is that the patient's disease was not well controlled to start with. These could be related to the dose of controllers used, device related problems (empty canister), poor adherence to therapy which could be unintentional (forgetfulness, cost, confusion etc) or intentional (no perceived need, fear of side effects, cultural issues etc). In such patients, an acute exacerbation may be triggered by triggers such as

(b) Exercise

(c) Viral infections with viruses such as Rhinovirus and Respiratory syncytial virus

(d) Certain weather conditions such as during thunder storms

(e) Allergen exposure such as during Diwali

Identification of patients at risk of asthma related deaths

Patients at increased of asthma related deaths must be

identified and should be flagged for more frequent review. The following patients may be considered to have higher risk of asthma related deaths

(a) Any history of near – fatal asthma requiring intubation and ventilation

(b) Hospitalization or emergency care for asthma in last 12 months

(c) Not currently using inhalational corticosteroids (ICS), or poor adherence with ICS

(d) Currently using or recently stopped using oral corticosteroids (OCS) – indicating severity of recent events

(e) Over use of short acting beta 2 agonists (SABA), especially if more than 1 cannister per month

(f) Lack of written asthma action plan (HOME PLAN)

(g) History of psychiatric disease or psychosocial problems

(h) Confirmed food allergy in patient with asthma

Asthma action plan

When combined with self-monitoring and regular medical review, action plans are highly effective in reducing asthma mortality and morbidity. All children who are diagnosed to have asthma must also have a written asthma action plan to refer to during exacerbations which should outline how to recognise and respond to worsening asthma. It should be individualized for the patient's medications, level of asthma control and health literacy. For children, this asthma action plan should be based on symptoms only. The plan should clearly outline the following

(a) The patient's usual asthma medications

(b) When/ how to increase reliever and controller and to start OCS

(c) How to access medical care if symptoms fail to respond

Recognition of an exacerbation

Recognising that a child is having an exacerbation is crucial for early institution of therapy. Initial symptoms of an exacerbation are

- An acute or subacute increase in wheezing and shortness of breath
- An increase in coughing, especially when the child is asleep
- Lethargy and reduced exercise tolerance
- Impairment of daily activities
- A poor response to reliever medication

Exacerbations frequently follow a trigger such as an upper respiratory infection (colds).

Immediate medical attention should be sought (at any stage) if:

- The child is acutely distressed (breathless, lethargic, cyanosed , sweating)
- The child's symptoms are not relieved promptly by inhaled bronchodilator
- The period of relief after inhaled SABA becomes progressively shorter
- Inhaled SABA is required repeatedly over several hours

Home management of an exacerbation

Parents are briefed to start initial management at home (Written asthma action plan) with

I. If child was using DPI (dry powder inhaler), to start using pMDI (pressurised metered dose inhaler) with spacer (with or without face mask depending on age of the patient) for the acute symptoms.

II. Reliever: Start 2 puffs of inhaled salbutamol/ levosalbutamol (200mcg salbutamol or equivalent), via spacer (+ mask, depending on child's age). May be repeated further two times at 20 min intervals. Home nebulisersare to be avoided for delivering SABA as they use compressed air instead of oxygen, require power supply and have erratic and inadequate drug delivery. (nebulisers deliver only 1-5% drug into smaller airways whereas MDI with spacer delivers 10-15% drug into airways)

III. Controllers: Recently, there is some evidence to suggest that increasing the dose of inhaled ICS to

quadrupled dose of ICS reduces severe exacerbations.

IV. Oral corticosteroids:Start Prednisolone 1-2 mg/kg upto a maximum of 40 mg.

Assessment of the severity of an exacerbation:

When a child presents with an acute or subacute exacerbation, the child may be assessed by various ways and one may take the help of scoring systems (e.g; Table 1: Pulmonary score index) which essentially tries to qualify the severity as follows:

Mild or moderate - The child talks in phrases, prefers sitting to lying, not agitated. Respiratory rate increased. Accessory muscles not used. Pulse rate 100-120 bpm. O_2 saturation (on air) 90-95%. PEF > 50% predicted or best.

Severe – The child talks in words, sits hunched forward and is agitated. Respiratory rate > 30/min. Accessory muscles in use. Pulse rate > 120 bpm. O2 saturation (on air) < 90%. PEF < 50 % predicted or best.

Life threatening – Drowsy, confused or silent chest

Management

1. Severity - Mild or Moderate

Such patients can be managed at primary care centre or paediatrician's office or outpatient department.

Management

SABA: 4-10 puffs (actuations) by pMDI +spacer + mask. Repeat every 15-20 mins for max 3 times

Prednisolone: 1-2 mg/kg. Max 40 mg

Controlled oxygen: target saturation 93-95%

Reassess after 1 hour – if the child is improves sufficientlyi.e, does not require SABA, PEF improving to more than 60 – 80% of personal/ predicted bestand saturation is > 94% in room air and if parents are capable of taking care of the child at home,the child can be discharged.

On discharge

Reliever will continue as needed usually for the next several days.

Send the child home on the high dose of controller which had been started because of the exacerbation. If the child has not been initiated on controller, controller (ICS) has to be started. If the child is already on controllers, consider stepping up treatment after looking at level of control.

Prednisolone will be continued for 3-5 days. Prednisolone can be stopped without tapering if used for 14 days or less.

Follow up within 2-7 days.

On follow up –

Reduce the reliever to as per need.

The high dose of controller will continue for short term (1-2 weeks) or long term (3mo) depending on the reason for which the exacerbation occurred.

Relook at trigger control.

Check to see whether the asthma action plan was properly understood and implemented. Does the action plan need any modification?

2. Severe

The child with a severe exacerbation of asthma needs to be managed in an acute care centre such as a well-equipped emergency room(ER) or Paediatric Intensive Care Unit (PICU).

Initially a rapid cardiopulmonary examination is necessary to assess severity and type of disorder.

One can use several asthma scoring systems such as the Pulmonary score index, Becker asthma score or PICU paediatric asthma score to grade the severity and need for PICU care.

Oxygen : All patients will have VQ mismatch and will therefore require supplemental O_2. Additionally, SABA will cause bronchodilation which will decrease vasoconstriction and worsen hypoxia by increasing VQ mismatch. O_2 should be given by non-rebreathing mask or by any other device to maintain saturations > 92%. Oxygen should be the driving force for running the nebulisers to deliver SABA. The nebulisers should be driven by oxygen flow rates of 6 lts or more.

Steroids:

Steroids directly reduce inflammation in this condition where inflammation is the pathognomonic feature. It is preferable to use steroids early to reduce fatality in severe cases. Oral steroids are as effective as parenteral steroids except if the child is vomiting or if child is not able to take orally. There is inadequate evidence for use of inhaled steroids in severe asthma.

Hydrocortisone – 2-4 mg/kg stat followed by 1-2 mg/kg 6 hrly. Oral switch to Prednisolone 1mg/kg when child is able to eat.

High dose ß2 agonists :

Inhaled ß2 agonists are drugs of choice in asthma and are a bridge to support ventilation and oxygenation till anti-inflammatory efforts of steroids take effect. Patients with acute severe asthma require and tolerate higher doses. Tachycardia in severe asthma is related to respiratory distress and lower airway obstruction. Relieving the obstruction reduces tachycardia.

When tidal volumes are severely reduced, MDI with spacers are not as effective and nebulisers must be used. SABA should always be diluted with normal saline, never with distilled water.

Continuous salbutamol nebulisation– 0.3 mg/kg/hr. Continuous nebulisations are superior to intermittent nebulisations. However, the continuous nebulisation system requires use of an infusion pump to deliver the medication at a constant rate to the nebulising chamber; this rate equals the rate of nebulization. This is technically difficult.

OR

Back to back nebulisations – 3 doses of back to back salbutamol nebulisations each over 15-20 mins.

Dose of nebulized salbutamol for severe asthma-

<20 kg – 2.5 mg (0.5 ml)

> 20 kg – 5mg (1ml)

Usual dose in non-severe asthma is 0.15mg/kg

Reassess the child every 20 mins, if no improvement, one has to consider subcutaneous or intravenous ß2 agonists.

Subcutaneous ß agonists –

Terbutaline or Adrenaline. Adrenaline is the more potent bronchodilator but has more cardiac side effects. Subcut terbutaline or adrenaline must be used in preference over nebulised drugs when the child has a life threatening attack with severe airflow limitation.

SC dose of terbutaline or adrenaline: 0.01 mg/kg/dose, max 0.3 mg, can be repeated every 15-20 mins x 3 doses

Intravenous ß2 agonists –

Salbutamol – 5 µg/kg loading dose over 1 hour followed by continuous infusion 1 µg/kg/min

Terbutaline – initial bolus of 5-10 µg/kg over 10 mins followed by 2-10 µg/kg/hr

Higher doses may be required if there is inadequate response.

When IV ß2 agonists are being used, ECG and K+ must be monitored. With higher doses, cardiac enzymes (Trop – T or CPK – MB) should also be monitored.

*An increase in HR by > 20 bpm in patients with **ß** agonist therapy, dose reduction OR review of diagnosis should be done*

*Total **ß** agonist dose (inhaled + SC + IV) should not exceed 20mg/hr*

Ipratropium bromide –

(250 µg) should be added to each initial nebulised dose of salbutamol (mixed together) every 20 mins X 3 doses, then every 4 hrly. Use should be limited to 24 hrs. Has synergistic effect with salbutamol.

Magnesium sulphate –

Is a smooth muscle relaxant. Used in a dose of 20-50 mg/kg over 20 mins. Second dose has not been found to be of benefit and increases the risk of toxicity. Side effects are mainly cardiorespiratory – tachycardia or bradycardia, hypotension and/or respiratory paralysis

with high serum levels.

Aminophylline –

Patients respond variably to salbutamol and some patients do not respond at all and in these patients, it is worth while trying aminophylline. Aminophylline has high incidence of side effects (30-40%) which include arrhythmias, hypotension, confusion, disorientation, fits, GI symptoms.

Dose – Loading 5-10 mg/kg/hr followed by 0.5 – 1 mg/kg/hr. Loading dose to be avoided if patient was already on theophylline. Dose of IV terbutaline should be reduced by 50% if used concurrently with aminophylline. Usual time taken for breaking cycle of bronchoconstriction is 6-12 hrs after which it may be discontinued.

IV Fluids

For shock, use Normal saline.

For maintenance therapy, one should use half normal saline with 5% dextrose with 40-60 mEq of K+per litre of fluid. Fluid needs to be restricted to 2/3 of maintenance if serum Na+ is < 138 mEq/lt. potassium infusions are required if serum K+is < 3 mEq/lt

3. Life threatening attack

Red flag signs:

1. Unable to talk or cry
2. Cyanosis
3. Feeble chest movements
4. Absent breath sounds
5. Fatigue or exhaustion
6. Agitated
7. Altered sensorium
8. Saturation <90%

Features of a life threatening attack are drowsiness, confusion and/or silent chest.

If a child presents with red flag signs in office or OPD, the child has to be immediately referred to a PICU aftertreatment. Such a child should receive Inj Adrenaline or Terbutaline SC, receive initial doses of inhaled SABA with Ipratropium preferably with nebuliser, IV steroid, Oxygen and IV fluids. Transfer should be arranged in a well equipped transport vehicle.

At PICU: Ongoing treatment for severe asthma should be continued. If possible, a CXR to rule out pneumothorax should be done. Initial management should aim at non-invasive ventilation if patient is alert – facial BiPAP.

Intubation & ventilation in severe asthma is fraught with dangers and should be avoided if possible. The ET tube is a foreign body and promotes further bronchospasm. Risk of barotrauma and hypotension is increased with positive pressure ventilation. Air trapping following ventilation is troublesome. Steroids increase the risk of myopathy. Paralysis further compromises breathing.

The indications of intubation are cardiorespiratory arrest, severe hypoxia, rapid deterioration in mental state & severe acidosis not improving. Whereas elevated CO2 levels alone are not an indication.More weightage is given to clinical parameters rather than laboratory values. The goal of ventilation is to maintain adequate gas exchange until bronchodilators and steroids relieve obstruction.

Technique:Preoxygenate with 100% O_2. Decompress stomach. Ketamine (1-2 mg/kg) should be used for sedation along with midazolam (0.1 mg/kg) with or without Fentanyl(1-2 µg/kg). Vecuronium can be used for neuromuscular blockade. Cuffed tube recommended.

One should allow permissive hypercapnia, bronchodilators and steroids are continued and aim should be fast weaning. Ventilation should be started in PRVC mode with FiO_2 of 1 with low respiratory rates (10-15 breaths/min); I:E ratio of 1:3 or more; Tidal volumes of 5-7ml/kg; PEEP should be 2-4 cm of H_2O Pplat should be < 30 cm of H_2O.

Complications of Status Asthmaticus

Atelectasis

Secondary infection

Pneumothorax

Pneumo mediastinum

Subcutaneous emphysema

Therapy related – hypokalemia, arrhythmia, hypotension etc

Therapies which do not have any role in management

Antibiotics

Mucolytics

Cough suppressants

Sedatives

Chest physiotherapy

Steam inhalation

Nebulised steroids

Heliox

Stepping down care

The principle of drug that was introduced "last in – first out" is followed. Terbutaline/ aminophylline drip and Ipratropium nebulisation is stopped in 24 hrs. SABA is reduced to 2-4 hrly, then 4-6 hrly. IV steroid is replaced with oral steroid.

Discharge criteria

Pulmonary score < 3

Sleeping well at night

Eating well

Appears comfortable

Not on any continuous infusion and receiving infrequent ß2 agonists (e.g; 6hrly)

Sent home with asthma action plan

Discharge plan

Inhaled SA ß2 agonists vide MDI with spacer + mask every 4-6 hrly till symptoms abate

Oral steroids are continued for upto 7 days (tapering not required)

Educate regarding action plan/ long term strategy

Plan follow up visit at 7-14 days

Review compliance, trigger elimination, controller regime. The patient who is on controller therapy will require revision of level of therapy at discharge.

Score	Respiratory rate		Wheezing	Accessory muscle Sterno mastoid activity
	<6 yrs	>6 yrs		
0	<30	<20	None	No apparent activity
1	31-45	21-35	Terminal expiration with stethoscope	Questionable increase
2	46-60	36-50	Entire expiration with stethoscope	Increase apparent
3	>60	>50	During inspiration and expiration without stethoscope	Minimal activity
Score	≤ 3 Mild 4-6 Moderate > 6 Severe		* If no wheezing due to minimal air exchange, score >3	
Those children whose score is > 6 should preferably be managed in a PICU				

Table 1 : Pulmonary Score Index

Table 2: Commonly used drugs in status asthmaticus		
Drug	**Preparation**	**Concentration**
Salbutamol	MDI	100 μg/dose
	Nebulising solution	5mg/ml
	Respule	2.5 mg/2.5 ml
	Injection	0.5 mg/ml
Terbutaline	Injection	0.5 mg/ml
Adrenaline	Injection	1mg/ml
Ipratropium bromide	MDI	20 μg/dose
	Nebulising solution	0.25 mg/ml
	Respules	0.5 mg/2ml
Magnesium sulphate	Injection	50% solution = 500 mg/ml
Aminophylline	Injection	250 mg/ml

Further Reading :

1. Pocket guide for asthma management and prevention (for adults and children older than 5 years) – A Pocket Guide for Health Professionals Updated 2016. Published by Global Initiative For Asthma
2. Global Initiative for Asthma (GINA) Teaching slide set 2016 update
3. RanjitSuchitra, Manual of Pediatric Emergencies & Critical Care, Paras ; 2010 (2nd edition); 53-59; 133-135
4. Lodha R, Kabra SK, Management of Status Asthmaticus in children in Pediatric Intensive Care Protocols of AIIMS; IJP, New Delhi, 2016; 171-185
5. Asthma Training Module 2016
6. Asthma by consensus, 3rd Edition, 2016, Consensus Guidelines for Diagnosis and Management of Asthma in Children, Published by Indian Academy of Pediatrics, Respiratory Chapter

Stepwise management of Acute Exacerbation of Asthma
1. Start Home Plan – SABA with MDI + Spacer; Oral corticosteroids, Increase ICS
2. Office / OPD – Intensify home plan. Add Ipratropium. Maybe nebulisers. Oxygen
3. ER/PICU – High dose SABA with nebulisers + Ipratropium + IV steroids
4. IV Magnesium Sulphate
5. IV SABA
6. IV Aminophylline
7. SC Terbutaline/ Adrenaline
8. Non invasive ventilation – Bi PAP
9. Intubation & ventilation – Cuffed tube, IV Ketamine, IV Midazolam, Vecuronium, PRVC mode, Low RR, I:E - 1:3, PEEP – 2-4 cm of H_2O, FiO_2 1, Permissive hypercapnia, Fast track weaning
10. High frequency oscillatory ventilation
11. ECMO

Some Emerging Viral Diseases

Jaydeep Choudhury
Pediatrician, Institute of Child Health, Kolkata

The most important factor for new disease emergence is genetic changes in the pathogen that make it possible to become established in a new host. Thus it may infect new individuals in the new hosts, like humans which lead to local or global health threats.

Influenza

Influenza virus A frequently undergoes genetic mutations as well as the reassortment of the various genomic segments between virus strains. Influenza virus A subtypes are identified based on the antigenic characteristics of the surface glycoproteins hemagglutinin (16 subtypes of HA) and neuraminidase (9 subtypes of NA).

Avian influenza

Migratory birds are the major animal reservoirs of Influenza A. All the possible combinations of HA-NA subtypes have been isolated from them. Currently only subtypes H5 or H7 have caused significant disease in birds. Contact between domestic and wild birds allows for and subsequent mutations in the virus can lead to outbreaks.

Among the human H5N1 cases, there are family clusters but it is unclear if these represent infection from a common environmental source or limited human-to-human transmission. More than half the cases are under 20 years age.

Human influenza

Human influenza refers to the subtypes that spread widely among humans. H1N1, H1N2, and H3N2 are the only known Influenza virus A subtypes currently circulating among humans. The increased prevalence of amantadine resistance in circulating human influenza is of growing concern.

SARS

Severe acute respiratory syndrome (SARS) appeared late in 2002 in southern China. Initial cases were recognized as atypical pneumonia characterized by high fever, shortness of breath, cough, and pneumonia.

Clinically, cases present following a short incubation with fever. There is malaise, nonproductive cough, dyspnea, chills, rigors, and headache. Rhinorrhea and a sore throat are rare. Radiological signs after the onset of fever show consolidation that increases progressively in size, predominantly in the lower lung fields but pleural effusions are absent.

Adenovirus 14

Adenovirus 14 is a sporadic cause of acute respiratory disease (ARDs). An emerging serotype sometimes causes severe and occasionally fatal respiratory illness in patients of all ages, including healthy young adults.

The cases are associated with a broad spectrum of clinical illness, including conjunctivitis, febrile upper

respiratory illness, pneumonia, and gastrointestinal disease. Severe illness can occur in newborn or elderly patients or in patients with underlying medical conditions but is generally not life-threatening in otherwise healthy adults.

Human Polyomavirus

Infection with the viruses is geographically widespread, though at low frequency and the extent of clinical disease is mild. The most common clinical findings are cough, upper respiratory tract symptoms, tachypnea and infiltrates or consolidation on radiography.

Chikungunya virus

Chikungunya virus is transmitted by the Aedes mosquito in a cycle between mosquitoes and various wildlife species. Sporadic spillover to humans has been characterized by localized outbreaks.

Clinical signs and symptoms are sudden onset of high fever, fatigue and disabling joint and muscle pain, occasional maculopapular rash and gastrointestinal complaints. A mild hemorrhagic syndrome also has been described. In some individuals severe arthralgias may persist for up to six months, though most resolve within two months. Other complications reported are neurologic (meningoencephalitis, polyneuropathy), hemorrhagic, and cardiac (pericarditis, myocarditis, cardiac arrhythmias) involvement.

Conclusions

Patterns of infectious disease transmission are a dynamic and ever changing process. Human activities like travel, agriculture, land use changes, introduction of exotic species play a role in the changing levels of risk. To a large extent the continued emergence of new, highly pathological agents is beyond our ability to specifically predict or to prevent their occurrence. It is the careful monitoring of human populations and the recognition of unusual patterns of disease that will provide us with that important initial clue of the appearance of the next emerging infectious disease.

Announcement

Blood – The Gift of GOD

Chingthang Ksh*, Ksh.Chourjit SIngh**

**Fellow in Neaonatology (RGUHS), Consultant Pediatrician and neonatologist, **Retd.Prof & Head*
Mother Care and Child Care Research Centre, Imphal, Manipur

Life to live with is impossible without blood. Blood is the priceless gift of God. Modern scientists talk much about their achievements in science and has shown their superiority by landing on the surface of the moon, atom-bombing on Hiroshima and Nagashaki and the maximum of human comfort of what we have to-day but in spite of these, so far, no scientist has been able to manufacture a drop of blood in any labora¬tory or factory. How precious is this liquid? This is beyond the knowledge of man-kind. We, the human beings, know little about this fluid. It has many unknown and unidentified quali¬ties. Probably God has kept away many a secret which may never be known to us. This may be a reason why blood is not on sale in any counter of a departmental store.

Blood transfusion is life-saving. Modern intensive care unit, patients with cancer, deficiency and malnutrition, transplant recipients, surgical and other emergencies would be impossible without the facilities of blood transfusion but the transfusion of blood is not without a risk. They should be given only when the true benefits are likely i.e. to correct a deficiency or defect of a blood component that has caused a life threatening or significant clinical problem. Blood transfusion is required in all age groups such as neonate, infant, children and adolescents as those in adults. Principles of transfusion support are also similar for children and adolescents with those of adults but neonates and infants have many a special need.

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Nephrogenic Diabetes Insipidus

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Introduction

Polyuria in children represents a diagnostic challenge and Diabetes Insipidus (DI) often comes in its differential diagnosis. Apart from suggesting a structured approach towards a child with polyuria we will also briefly discuss the salient features of the nephrogenic variant of diabetes insipidus (NDI).

Definitation

The term NDI previously also called as diabetes insipidus-renalis was first used in medical literature in 1947. It is a rare congenital or acquired disorder of water metabolism characterized by inability to concentrate urine despitepresence of normal or elevated plasma concentration of Anti diuretic hormone (ADH).

Types of NDI

1. Congenital NDI:

(a) X-linked recessive (90%) -results from inactivating mutations of vasopressin V2 receptors

(b) Autosomal dominant \ Autosomal recessive –results from defects in aquaporin -2 genes.

2. Acquired NDI

(a) Seen in disorders affecting renal tubular functions for example: obustructive uropathies, renal cystic diseases, polycystic kidney disease, nephrocalcinosis, interstitial nephritis, sickle cell disease, medullary cystic disease, Sjogran syndrome etc.

(b) Secondary to: Hypokalemia, lithium, demeclocycline, foscarnet, clozapine, amphotericin, methicillin and rifampicin.

Pathogenesis

(a) Tubular unresponsiveness to ADH- The ability to concentrate urine(usually through absorption of free water) is dependent on the ADH, which controls water permeability in collecting tubule (CT).

(b) Under basal conditions CT is impermeable to water.

(c) In response to increased serum osmolarity or volume depletion, ADH is released into systemic circulation.

(d) ADH binds to V2 receptor on basolateral membrane of CT cells which activates a cyclic AMP dependent cascade that results in movement of water channels (aquaporin 2)to luminal membrane of CT, rendering it permeable to water.

Defects in V2 receptor or aquaporin channels results in congenital form of NDI.

Clinical manifestations

Congenital NDI-usually presents in newborn period. First manifestation could be even recognized during first week of life. Infants are irritable, cry almost constantly, and

although eager to suck but will vomit soon after ingestion. Mother gives a history of unexplained fever, persistent constipation and not gaining weight. Almost all infants havemassive polyuria,volume depletion,hypernatremia,hyperthermia,irritability, crying, constipation and poor weight gain.

Longstanding excretion of large volume of water can lead to non obstructive hydronephrosis, hydroureter and mega-bladder.

Chronic cases can have developmental disabilities, mental retardation and behavioral problems eg hyperactivity and short term memory loses.

Secondary NDI-presents later in life with hypernatremia and polyuria.Mental retardation and or behavioral problems are less common

Diagnosis and approach

Differential diagnosis of polyuria :

(a) Diabetes mellitus

(b) Diabetes insipidus –central / nephrogenic

(c) Psychogenic polydipsia\iatrogenic

(d) Solute or osmotic diuresis- renal sodium wasting (loop diuretics and barter syndrome)

– exogenous sodium chloride or bicarbonate loading

– diabetic ketoacidosis

– diuretic phase of ATN

– post obstructive diuresis

Stepwise approach to a child with polyuria

First step always involves confirming polyuria.In older childrenthis is doneby asking the parents to maintain a record of child's daily intake /output,noting both timing and quantity of urine volume. In case of infants one may even require hospitalization and urinary catheterization to get a true estimate of 24 hour urinary volume.

Subsequent investigation includes a step wise approach as shown in Figure 1.

Laboratory findings

Urinary osmolality below 150mOsm\kg

Serum sodium levels high, often above 170mEq/L with corresponding increase in serum chloride and osmolality.

With persistent polyuria urinary tract may be dilated on imaging.

During dehydration blood urea and creatinine may be high but usually normalizes after hydration.

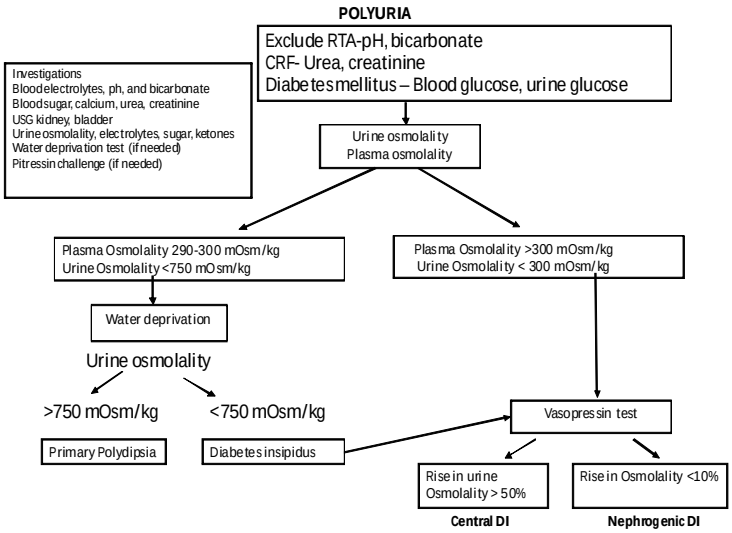

Figure 1: (Step wise approach)

Diagnosis is suspected by inappropriately diluted urine despite increased serum osmolality or failure of the urinary osmolality to increase following water deprivation test. In patients with NDI despite elevated serum osmolality, urine osmolality does not increase above 200mOsm\kg even after vasopressin injection.If the vasopressin results in an appropriate increase of urine osmolality then it is likely due to vasopressin deficiency such as in cranial DI.

Treatment

Acquired NDI-eliminating the underlying disorder eg offending drugs, hyperkalemia, hypokalemia or obstruction can often correct the problem.

Congenital NDI- In contrast to acquired variant, congenital NDI are difficult to treat.

Goal of treatment:

- Optimal growth by ensuring intake of adequate calories
- Avoid severe dehydration

Diet- poor solute content i.e. low salt,low protein diet is recommended.Food with highest ratio of calorie content to osmotic load (Na <1mmol\kg\24 hrs) is recommended.

Pharmacological approach-

1. Thiazide diuretics: It might seem paradoxical but thiazides actually decrease overall urine output as it induces a state of mild volume depletion by enhancing sodium excretion at the expense of water and by causing a decrease in GFR which results in proximal tubular sodium and water reabsorption.
2. Indomethacin and amiloride are often used in combination with thiazide to decrease polyuria.

All children with NDI should take frequent bathroom breaks to avoid over distention of bladder which may cause long term problems.

Most important is to ensure constant access to lots of water. Not keeping up with fluid losses can lead to severe dehydration and electrolyte imbalances with can be fatal.

Prognosis

Early diagnosis and treatment of affected infants can reduce the incidence of physical and mental retardation associated with episodes of dehydration.

Complications of NDI can be kept under control by adequate water intake but even with early start of therapy growth failure and developmental disabilities are not uncommon.

Monitoring

Patients require regular follow up to monitor growth and electrolytes. Issues to be discussed with parents include dietary review particularly salt intake and access to free water.

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Flexible Bronchoscopy of the Upper Airway

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Physiologically, the upper airway starts from the nostrils and ends at the thoracic inlet. It therefore includes the nares, choanae, pharynx, larynx and the part of the trachea above the thoracic inlet.

Thus, most anomalies of the upper airways lead to stridor and noisy breathing that can be 'seen'! As a result, they constitute a major chunk of indications for referral for flexible bronchoscopy. Other common presenting symptoms of upper airway anomalies are coughing, hoarseness,wheezing, shortness of breath, reflex apnea, choking with feeds and aspiration.Congenital malformations of nose, nasopharynx, larynx and upper trachea pose a medical emergency as they invariably compromise the respiratory function.

Among the airway anomalies, most commonly encountered arechoanal atresia / stenosis, laryngomalacia, vocal cordparalysis, laryngeal web,laryngeal cleft, congenital / acquired subglottic stenosis, tracheoesophageal fistulas.

Early diagnosis is the key to prevent pulmonary damage and associated morbidity. A detailedclinical history and thorough physical examination play an important role in the diagnosis of congenital malformations of the upper respiratory tract. Persistent wheeze and persistent stridor are the common respiratory sounds that warrant investigation.

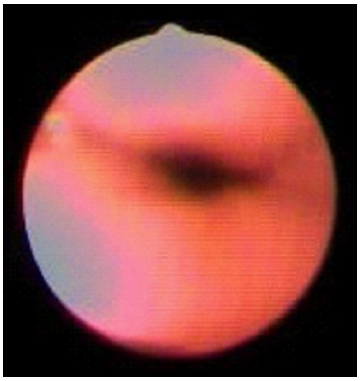
Flexible bronchoscopy under local anesthesia / mild sedation has the ability to directly observe airway anatomy / function and make an accurate diagnosis. Flexible bronchoscopy is considered as gold standard tool in the diagnosis of anomalies with dynamic movements like laryngomalacia or tracheomalacia and various vocal cord pathologies.

Bronchoscopy is commonly done transnasally after local application of 2% lignocaine to the nose and1% lignocaine in the dose of 5 mg/kg through the working channel is sprayed 'as you go', after observing the anatomy and movement of the laryngeal structures. Supplemental humidified oxygen is administered by 'blow-by', keeping the oxygen catheter close to the other nostril and the SpO2 is monitored by pulse oximetry.

Some common upper airway anomalies are discussed below.

Choanalstenosis/atresia

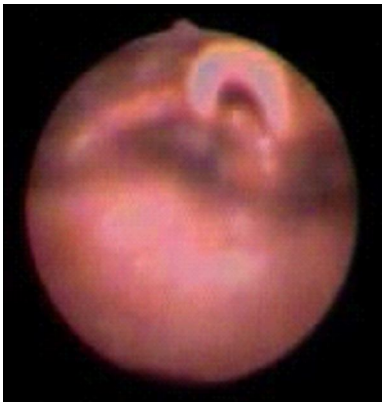
This is the commonest congenital anomaly of the nose, with an incidence of 1:7000. Unilateral choanal atresia is twice as common as bilateral. It is usually bony in nature, but may be membranous in some cases. Unilateral atresia



presents much later, usually as feeding difficulties and persistent rhinorrhea. The importance of this anomaly is that it is commonly associated with other anomalies like the CHARGE syndrome.

Laryngomalacia

Laryngomalacia is the most common congenital laryngeal anomaly which causes stridor in infants. It is usually benign and is a result of immaturity of the cartilages that result in collapse of supraglottic structures (arytenoids, epiglottis, and ary-epiglottic folds) inwards during inspiration and results in low-pitched inspiratory stridor which worsens with agitation, crying and feeding. The noisy breathing in infants with laryngomalaciaimprove with sleep or prone position.

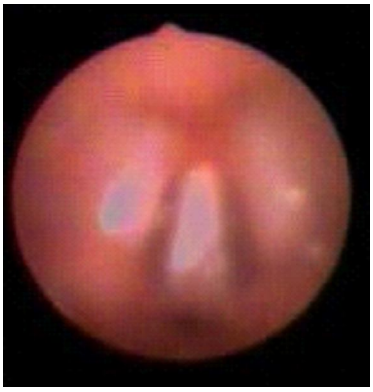


The symptoms usually become apparent by 4 weeks of age, worsen during first few months and then generally resolve by 12 to 18 months of age. If stridor presents earlier, or is associated with other associated symptoms like failure to thrive, recurrent respiratory infections, etc, anomalies other than laryngomalacia should be considered. Flexible laryngoscopy or bronchoscopy reveals a long, infantile epiglottis that may be omega shaped due to shortened aryepiglottic folds, and may fall backwards over the glottis. In severe cases the entire supraglottic structures may sink into the glotticopening with apparent life-threatening events. Depending on this, it has been classified into 5 types:

1. Inward collapse of aryepiglottic folds
2. Long tubular epiglottis
3. Antero-medial collapse of the arytenoid cartilages
4. Posterior displacement of the epiglottis
5. Short aryepiglottic folds.

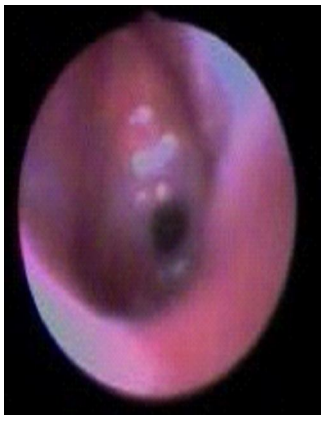
Laryngeal web

Fusion of the vocal cords by a web-like structure may be either congenital or acquired (synechiae). It is usually a result of prolonged or difficult intubation, leading to injury and inflammation of the vocal cords. These children present with hoarseness of voice, aphonia, strider and respiratory distress.



Subglottic stenosis

The subglottis extends from the lower surface of the true vocal cords to the lower surface of the cricoid cartilage. Subglottic stenosis may be classified as either congenital or acquired. Majority of subglottic stenoses are acquired

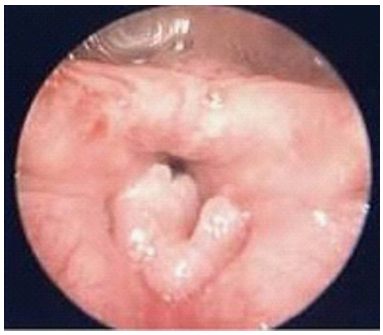


(95%) and the most common cause is difficult or prolonged endotracheal intubation or tracheostomy. The congenital subglottic stenosis is commonly membranous, but may also be cartilaginous. Depending on the severity of the constriction, it is classified into 5 types (Meyer):

1. Upto 50%
2. 51 - 70%
3. >71%
4. No detectable lumen.

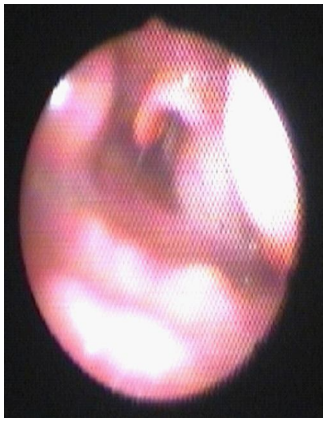
Laryngeal papillomatosis

This is the most common benign neoplasia of the larynx. It is viral in origin, caused by HPV types 6 & 11. The presenting symptoms are hoarseness of voice, stridor, respiratory distress and cough. They are usually multiple in number, irregular, friable and may be sessile or pedunculated. Treatment is by cryotherapy and they have a tendency to recur. They may occasionally also undergo spontaneous regression.



Laryngeal cyst

This rare anomaly may be again congenital or acquired, and appear like thin-walled submucosal masses.



Congenital laryngeal cysts are usually supraglottic in location. The subglottic cysts are acquired, and results from prolonged intubation. These children present with respiratory distress, stridor, hoarseness, aphonia and feeding difficulties.

Drug-induced sleep endoscopy (DISE)

Though more commonly used in adults, this is a rare use of the flexible bronchoscope in children with severe obstructive sleep apnea syndrome (OSA). It is used to identify the sites of obstruction in conditions that mimic sleep, and to look for hypertrophy of the lingual tonsils and occult laryngomalacia. The flexible laryngoscope is introduced just beyond the posterior nares and the patient is put to sleep using gradually increasing doses of propofol. The obstruction is graded using standard grading systems, like the Colorado DISE Grading Scale.

Thus, flexible bronchoscopy is a very useful, safe and a much under-utilised mode of investigation in the armamentarium of the Pediatric Pulmonologist.

Answer of quiz:

Dyskeratosis Congenita

(Zinsser-Engman -Cole syndrome)

Bone marrow failure with triad of reticulate skin hyperpigmentation, nail dystrophy and oral leukoplakia

A Rare Case of Failure to Thrive

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Abstract:

Abetalipoproteinemia(ABL) is a rare autosomal recessive disorder characterized by lack of lipids and apolipoproteins in plasma, fat malabsorption and various clinical manifestations secondary to it. ABL results from mutations in the gene encoding the large subunit of microsomal triglyceride transfer protein(MTP;OMIM 157147). We describe a 15 month old girl, born out of consanguineous marriage and presented with diarrhea,steatorrhoea,growth retardation. She was diagnosed to have ABL and managed with dietary modification and oral fat soluble vitamin replacement.

Key words: *Abetalipoproteinemia; Microsomal triglyceride transfer protein; Failure to thrive*

Introduction

Abetalipoproteinemia(ABL;OMIM 200100) is a rare metabolic disorder with a incidence rate of <1 in 100,000. In 1950 Bassen and Kornzweig first reported the clinical association of acanthocytosis in peripheral blood smear with retinitis pigmentosa and ataxia[1]. In 1958 Jampel and Falls observed low cholesterol level in affected individuals[2]. In 1960 Salt noticed absence of serum beta-lipoproteins in a patient with the syndrome. ABL caused by microsomal triglyceride transfer protein (MTTP;OMIM 157147) deficiency and characterized by absence of plasma apolipoprotein B and Apo-B containing lipoproteins. MTTP is a chaperone protein that facilitates the transfer of lipids onto Apo-B; and found in enterocytes and hepatocytes endoplasmic reticulum and includes three structural domains: N-terminal ß-barrel(residues 22-297),?-helix(residues 298-603) and C-terminal(residues 604-894) and three functional domains : transfer activity, membrane interaction and lipid binding. The N-terminal ß-barrel domain interacts with N terminus of Apo-B; Alfa-helical domain interacts with PDI and Apo-B, and the C-terminal mediates the lipid binding and transfer catalytic activity of MTTP[3.4].

Case report

A 15 months-old girl was referred to our hospital for evaluation of failure to thrive. She was born from third degree consanguineous parents.(Fig1) Her birth weight was 3.25kg but she failed to gain weight appropriately since two months of age. During admission her anthropometry was weight 3.8 kg; length 56cm; head circumference 39 cm; MUAC 9cm. on growth chart weight for age and head circumference for age was below 1st percentile; weight for height was between 1st and 3rd percentile. She also had developmental delay as neck holding was achieved at 6 months of age and she started to sit with support from 9 months of age. She used to

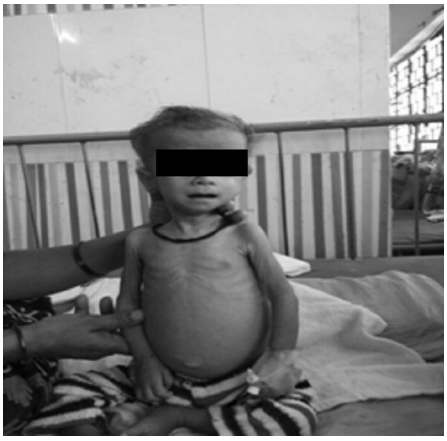

Figure 1. The child at presentation

have frequent defecation (10-12 times/day) often steatotic. She had no family history of similar problem. Physical examination did not reveal any abnormality.

Laboratory tests showed: Hb%-10.1,TLC-1300 N3OL64, SGPT-18U/L,SGOT-116U/L, Total protein-4.6gm/dl,albumin-3.1gm/dl, cholesterol-34mg/dl,triglyceride-18mg/dl. Stool examination showed presence of fat droplets(Fig 2). Thyroid function showed FT4-0.88ng/dl, TSH-3.4mIU/l. abdominal sonography demonstrated normal size liver and spleen. Screening for tuberculosis and HIV infection were negative.

In the presence of symptoms and with the initial laboratory reports our differential diagnosis was cystic fibrosis(CF) and pediatric Celiac Disease(CD).

Figure 2: Stool of the child showing steatorrhoea

Sweat chloride test was negative. Macroscopic findings in upper GI endoscopy included normal mucosa of oesophagus and stomach(microscopic examination was not possible as the parents did not give consent for it). IgG anti-Gliadin antibody was within normal limits. These reports ruled out CF and celiac disease.

The presence of severe hypocholesterolemia and hypotriglyceridemia suggested other conditions including ABL and homozygous familial hypobetalipoproteinemia(FHBL). The parents had absolutely normal lipid profile which ruled out FHBL.

Fundoscopy showed retinitis pigmentosa(Fig 3).Peripheral blood smear examination revealed presence of acanthocytes(Fig 4). Thus the diagnosis of abetalipoprotenemia was confirmed. Genetic studies could not be done because of lack of financial resources.

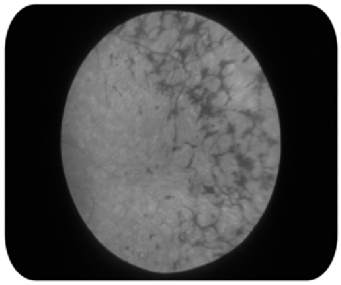

Figure 3 : Fundoscopic examination showing retinitis pigmentosa

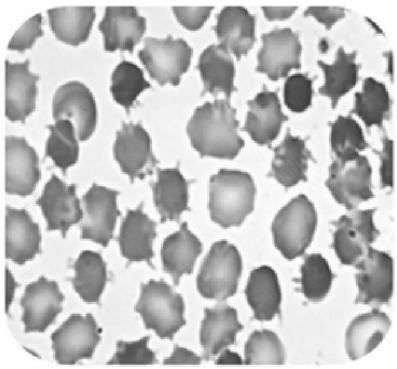

Figure 4: Blood smear showing acanthocytes

Treatment included dietary modification and high dose oral fat soluble vitamin supplementation. Our patient was treated with medium chain triglycerie(MCT oil @ 1ml/kg/

day), vitamin A @10000IU/day, vitamin E 200mg/kg/day, vitamin D 400IU/day, vitamin k injection 2 mg on every alternate day.

She was discharged when she showed adequate weight gain and followed up at regular interval. On her last visit she was 3 years old with weight of 13 kg and height of 90 cm(both around 50th percentile).

Discussion:

Abetalipoproteinemia is a rare autosomal recessive disorder characterized by fat malabsorption, acanthocytosis and hypocholesterolemia in infancy. Later in life deficiency of fat soluble vitamins is associated with development of atypical retinitis pigmentosa, coagulopathy, posterior column neuropathy and myopathy.

ABL is characterized by absent of plasma Apo-B containing lipoproteins that results from MTTP mutations[5]. To date atleast 33 mutations have been identified. Absorption of fat and fatsoluble vitamins are compromised, leading to failure to thrive and fat soluble vitamin deficiency[6]. Manifestations of posterior column neuropathy occurs secondary to vitamin E deficiency. Before the use of high dose oral fat soluble vitamin supplementation many ABL patient developed neurological complications before second decade and some did not survive the third decade. Muller et al reported in 1974 that high dose oral vitamin E(100IU/kg) could increase underdetectable serum vitamin levels in ABL patients.

Homozygous dysfunctional mutations in APOB leads to a clinically similar disorder called homozygous hypobetalipoproteinemia(HHBL; OMIM 107730). While obligate heterozygous parents of HHbl patients have half normal plasma levels of Apo-B and LDL cholesterol, obligate heterozygous parents of ABL patients have normal plasma lipoprotein profile. HHBL patients receive similar treatment advice as ABL patients.

Chylomicron retention disease is a rare recessive disorder characterized by defective chylomicron exocytosis from enterocytes. Sar1- guanosine triphosphate promotes the formation of endoplasmic reticulum to golgi transport carriers. These patients have severe intestinal symptoms with steatorrhea,chronic diarrhoea and failure to thrive.neurological manifestations are less severe than abetalipoproteinemia. Plasma cholesterol levels are moderately reduced and fasting triglycerides are normal but fat soluble vitamins are very low.

Gastrointestinal manifestations of ABL include diarrhea and fat soluble vitamin deficiency, which are consistent features in all reported cases. These manifestations usually develop during infancy and are worsened with a diet rich in fat. The diarrhea subsides later in part because patients learn to avoid fatty foods. However, the low serum levels of fat soluble vitamins continue, because the plasma transport and delivery of these vitamins to tissues depends almost exclusively (for vitamin E and beta-carotene) or in part (for vitamins A, D, and K) on intact synthesis and secretion of apo B-containing lipoproteins. Supplementation with high dose vitamin E results in increased serum vitamin levels to not more than 30% of the lower limit of normal. On the other hand, high doses of vitamin A therapy can normalize serum levels. This reflects the fact that despite impaired absorption and transport from the intestine,

subsequent transport of vitamin A in plasma by retinol-binding protein is not impaired in ABL.

Hematologic manifestations of ABL include acanthocytosis. These abnormal shaped cells comprise 50% or more of circulating erythrocytes and were among the earliest laboratory features of the disorder (see Figure 1). Their structure inhibits rouleaux formation, leading to extremely low erythrocyte sedimentation rates. Anemia has been reported in some cases of ABL . The likely cause was deficiencies of iron, folate, and other nutrients secondary to fat malabsorption. Hemolysis which appears to result from accelerated hydroperoxidation of fatty acids secondary to tocopherol deficiency may also contribute to anemia [7]. Elevated prothrombin time, and international normalized ratio due to vitamin K deficiency, was reported in several cases[7].

Neurological involvement in ABL may be the most serious clinical manifestation. In ABL both central and peripheral nervous systems are affected; patients can have either upper or lower motor neuron findings or both. The

primary driving pathology is demyelination [8]. The onset of neurologic disease usually begins in the first or second decade of life and in the past often progressed to catastrophic disability, although some patients inexplicably escaped serious affliction until much later in life [8]. The long-term clinical results of vitamin E therapy from multiple previous studies show improvement in neurologic

dysfunction with vitamin E treatment and early therapy before the age of 16 months prevents neurologic dysfunction.

Muscle involvement in ABL affecting both striated and smooth muscle has been reported in some patients, and furthermore was the cause of premature death cases among a few ABL patients . While the etiology of myopathy is unclear, myositis appeared to be related to ceroid pigment deposition, while muscle weakness could possibly be related to vitamin E deficiency and neuropathy.

Ophthalmic involvement in ABL is variable and appears to cover a wide range of symptoms and ophthalmic manifestations . The most prominent abnormality is pigmentary retinal degeneration. Most patients have loss of night vision early in the course of disease, while some patients also present with loss of color vision. The retinopathy often produces slowly enlarging annular scotomas with macular sparing, such that patients are relatively unaware of the progression of the disease. Complete loss of vision can ultimately occur [31]. Fundoscopic examination reveals an atypical pigmentation of the retina characterized by small, irregularly distributed, white spots.

It is of interest that reproductive system manifestations seem to be rather minimal in ABL, indicating that in the absence of LDL, there is sufficient capacity for synthesis. and secretion of steroid hormones, including sex steroids, provided by HDL. One study evaluating the endocrine function in a 37 year old female ABL patient of Greek origin who was diagnosed at age 5 years after instituting dietary modifications, found that serum progesterone and 17 (OH) progesterone are low at both exams as well as serum progesterone at day 21 of the menstrual cycle was below normal[9].

Conclusion

In summary, ABL is rare disease of lipoprotein metabolism. without treatment ABL is fatal. A high index of suspicion,timely diagnosis and early institution of therapy with fat soluble vitamin supplementation can reduce the potential severity of neuropathy and retinopathy.

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Vesiculobullous Lesion in Newborn – A Case report

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Abstract:

Incontinentia pigmenti (IP) is an X-linked dominant genodermatosis, involving skin, eyes, CNS, teeth and skeletal system. Skin manifestations are most common and occur in four distinctive phases. Here, we present a female neonate with vesiculobullous lesions and seizure, mimicking Congenital Herpes simplex infection. Skin biopsy and MRI Brain confirmed the diagnosis of Incontinentia pigmenti.

Keywords: *Incontinentia pigmenti, Vesiculobullous lesion, Herpes simplex*

Intrioduction

Incontinentia pigmenti (IP) is a rare X-linked dominant genodermatoses. [1] We report a case of IP in a female new-born, who presented with vesiculobullous lesions in trunk and extremities along with seizure since neonatal period.

Case report

A 3 day old appropriate for gestational age girl baby, born at term, out of non-consanguineous marriage, presented with vesiculobullous lesions in the trunk and extremities since birth. Mother's antenatal history was uneventful. There was no similar history in family. Mother sepsis screen done was negative and the baby was treated with topical antibiotics. On 6 th post-natal day, the baby had subtle seizure along with the involution if new skin lesions. The baby was active, feeding well and hemodynamically stable. Further enquiry revealed that there was no history of birth asphyxia or risk factors for sepsis. Her blood glucose, serum sodium, potassium, calcium were within normal limits. Immediate episode was controlled by IV Phenobarbitone. The baby was put on IV antibiotics and acyclovir keeping congenital herpes simplex infection as differential after drawing blood for culture. Repeat blood count revealed Hemoglobin of 15.2 g/ L , Total leukocyte count of 14.0 x109 /L with the differential count N29L45M3E25 and platelet count of 388 x 109/ L. CSF examination revealed 10 mononuclear cells, sugar57, protein 110. Examination of vesicle fluid showed white blood cells with 85 % eosinophils and 5% lymphocytes. Cultures of blood, urine and vesicle were negative for bacteria. Serum HSV-1 &2 IgM & IgG were negative. CT Brain revealed focal cerebral infarction in the left temporo-parietal region. Subsequently, it was found that the vesiculobullous lesions were arranged along Blaschko's line in fountain pattern(Fig 1). During the course of hospital stay, the lesions healed by hyperpigmentation to reappear at newer sites. So, our clinical diagnosis was Incontinentia pigmenti. Skin biopsy revealed eosinophilic spongiosis, neutrophilia and suprabasal vacuoles, findings supportive of IP. Hence, IV antibiotic and acyclovir were discontinued. Fusidic acid and Betamethasone cream were prescribed for skin lesions with oral Phenobarbitone. EEG showed left parieto-occipital sharp-wave activity. MRI Brain showed subacute infarcts in the bilateral frontal

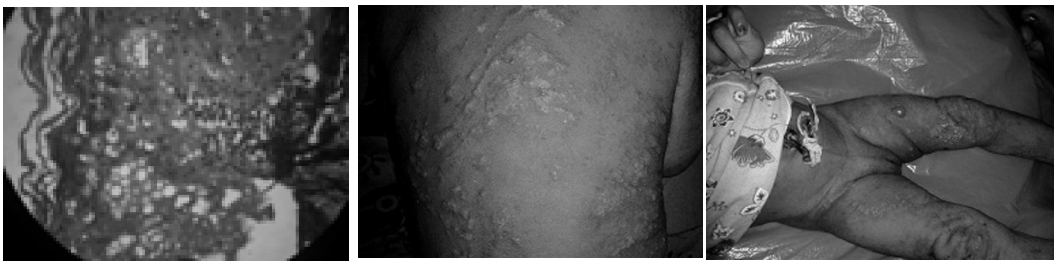

Fig 1. Vesiculobullous lesions were arranged along Blaschko's line

and left parieto-temporal watershed white matter. Ophthalmological examination at the age of one month was normal. Currently, the baby is being followed up by the multidisciplinary team on an outpatient basis.

Discussion

IP is a rare condition caused by mutation in the NF Kappa B essential modulator (NEMO) gene located in the q28 portion of the X chromosome.[2] Progression of skin manifestations occur in four phases , which may be concomitant or sequential. Initially, there is vesicular eruption, followed by hyperkeratotic, verrucous linear plaque. The third phase is characterized by the development of grayish blue hyperpigmentation along the Blaschko's lines or in swirling patterns. In the fourth phase, there are hypopigmented linear macules with no skin appendages. [3] CNS is involved in 10-40% of patients. Seizures are the most common neurologic complication, which usually develops within the first few weeks of life. Microcephaly, strokes, seizures, mental retardation, spasticity and ataxia are the other manifestations.MRI abnormalities include various cortical malformations and periventricular / white matter lesions [4]. HSV infection , herpes zoster, congenital syphilis , neonatal acne , staphylococcal infections, bullous impetigo, epidermolysis bullosa simplex, Letterer- Siwe disease, transient pustular melanosis, neonatal dermatitis herpetiformis and IP all have vesicopustular cutaneous manifestations[5]. Various literatures reveal many instances of erroneous diagnoses of vesiculopustular disorders in newborn, made as a result of suspicious findings.[6,7,8] Neonatal HSV infection can show up any time from as soon after birth till well beyond the neonatal period . 75 % to 90% of infants with neonatal HSV are born to women with no history or physical findings suggestive of genital herpes. Exposure to the virus occurs during passage through an infected birth canal or in utero. [9] Because of high mortality and morbidity of neonatal HSV infection, early initiation of acyclovir therapy in neonatal vesicular eruptions is very important, until a more thorough physical and laboratory evaluation can be done. In this case, HSV infection was the initial leading diagnosis on the basis of cutaneous blistering lesions and CNS manifestations. However, the MRI findings, eosinophilia and the skin biopsy confirmed the diagnosis.

Conclusion

This case report emphasizes that IP is a potential masquerader of HSV infection and should be included in the differential diagnosis of cutaneous blistering lesions and CNS involvement in neonates. Furthermore, this case highlights the importance of skin biopsies in vesicular lesions with CNS manifestation.

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Eating Disorder in Children

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Abstract:

Eating disorders have a high prevalence and are associated with morbidity and mortality. Eating disorders (EDs) continue to be underdiagnosed many adolescents go untreated, do not recover, or reach only partial recovery. EDs are also prevalent in younger children, boys, and minority groups. The complications of EDs affect every organ system. Neurobiological and genetic predispositions are emerging as important cause ofEDs. Recent treatment guidelines acknowledge that they are not caused by families or chosen by patients. EDs present differently in pediatric population and clinicians should have a high index of suspicion using new Diagnostic and Statistical Manual, 5th edition (DSM -5) diagnostic criteria because early intervention can affect prognosis. Outpatient family-based treatment , cognitive behavioral therapy and individual therapy should be provided. Pharmacotherapy is useful in specific contexts. Full weight restoration is very important , consists of high-calorie diets, and must allow for continued growth and development; weight maintenance is typically inappropriate in pediatric populations. Physical, nutritional, behavioral, and psychological health should be considered for full recovery and pediatric EDs have a good prognosis with appropriate care. ED prevention efforts should work toward aligning with families and understanding the impact of antiobesity efforts. Primary care providers can be key players in treatment success.

Keywords *– Eating Disorder (ED), Diagnostic and Statistical Manual , 5th edition (DSM-5)*

Introduction

EDs are disorders of eating behaviors , associated thoughts , attitudes and emotions, and their resulting physiological impairments . Anorexia nervosa (AN) and Bulimia nervosa (BN) based on two factors – Overvaluation of the presumed benefits of weight loss or shape change and fear of fat or somato – visceral discomfort associate with ingesting food that result in functional, medical, psychological and social impairment. Binge eating disorder(BED) are impulsive or compulsive rapid consumption of food and attended psychological and weight related consequences. They rarely present as a sole entity and are almost associated with comorbidities. Pediatric EDs are more common than type 2 diabetes, and the epidemiology is changing, with higher rates of EDs in younger children, boys, and minority groups.(1–3)

The prevalence of AN is around 0.5% to 2%(4) with a

peak age of onset of 13 to 18 years(5) AN has the highest mortality rate of any psychiatric disorder of at least 5% to 6% (6,7).The prevalence of BN is between 0.9% and 3%(9,10) with an older age of onset of 16 to 17 years(11) The risk of lifetime suicide attempts in BN are much higher(6) Although female patients account for most ED diagnoses, males have accounted for 10% of ED cases over the past years(4)with some studies reporting up to 25% of cases being male.(16) Furthermore, younger patients diagnosed with EDs are more likely to be boys, with a female to male ratio of 6 to 1, compared with a 10 to 1 ratio in adults.(3,17)Dieting behaviors are a risk factor for developing an ED and are highly prevalent; ~50% of girls and 25% of boys report dieting during the past year.(18)Moreover, 30% of girls and 15% of boys had disordered eating behaviors severe enough to warrant medical evaluation, and 9% of girls and 4% of boys reported daily self-induced vomiting.

Etiology

The exact etiology of EDs is not known; genetic, biological predispositions, environmental and sociocultural influences, and psychological traits contribute to EDs. Evidence continues to increase that EDs are heritable, with relatives of ED patients having 7 to 12 times greater risk of developing an ED.(20–22)Twin studies have shown heritability of AN between 33% and 84% and BN between 28% and 83%(4,22).There are also neurobiological factors being studied in EDs, but it is uncertain whether they contribute to the development of EDs or result from the physiologic alterations caused by EDs (23)

Clinical features

Most of the EDs develop during adolescence . It presents with weight loss, unexplained growth stunting or pubertal delay, restrictive or abnormal eating behaviors, recurrent vomiting, excessive exercise, trouble gaining weight, or body image concerns. Younger patients have atypical presentations; instead of rapidweightloss, they may present with failureto gainweight or height and may not endorse body image concerns or engage in binge eating or purging behaviors.(17,24) Obesity can delay the diagnosis and these population require more careful screening (3,25). Adolescents with chronic illnesses, especially insulin-dependent diabetes mellitus, are also at higher risk of developing ED behaviors and should be screened regularly. Emotional and behavioral signs of anorexia nervosa may include refusal to eat, denial of hunger, excessive exercise, adopting rigid meal or eating rituals . Behavioral symptoms of bulimia may include eating to the point of discomfort or pain followed by self induced vomiting, laxative use, excessive exercise.

Screeningtools, such asthe brief SCOFF questionnaire, are used in the primary care setting for ED screening in adolescents

The SCOFF questionnaire

1. Do you make yourself Sick because you feel uncomfortably full?
2. Do you worry you have lost Control over how much you eat?
3. Have you recently lost more than One stone (14 lb/ 6.3 kg) in a 3-month period?
4. Do you believe yourself to be Fat when others say you are too thin?
5. Would you say that Food dominates your life?

One point for every “yes”; a score of 2 indicates a likely case of anorexia nervosa or bulimia.

If an ED is suspected, it is important to obtain a comprehensive medical, family, and social history and a complete review of systems and to perform a thorough physical examination to evaluate for physical stigmata and medical complications of EDs .

History should include past medical history of Anorexia nervosa and other restrictive disorders , time course of weight loss, dietary habits including 24-hr recall, history of restricting, binge eating, and/or purging, exercise history, previous therapy. Pubertal/menstrual history - Timing of thelarche and pubarche, For males: history of

decreased erections or nocturnal emissions should be taken.

Family history of Eating disorders, obesity, depression, anxiety, alcoholism or drug abuse, bipolar affective disorder, schizophrenia , should be asked.Symptoms of systemic illnesses, such as inflammatory bowel disease, diabetes mellitus, celiac, lupus should be noted.

Physical examination findings- hypothermia, dry pale skin, facial wasting, thinning of scalp hair,parotid enlargement, dental carries, oral ulcers, hypotension, cardiac arrhythmias.

Diagnosis

New diagnostic criteria for EDs are published in the DSM-5, released in 2013.(33) Significant changes were made in order to improve the accuracy and precision of ED diagnoses, which will potentially allow for more targeted treatment. One major limitation of the fourth edition of the DSM was the diagnostic category of EDNOS, which accounted for the majority of ED diagnoses in most pediatric series.(34) EDNOS was a nonspecific diagnostic category that encompassed a wide spectrum of EDs, including subthreshold AN, subthreshold BN, and binge ED (BED).(14) This ambiguity led to misunderstandings of the clinical significance of the disorder and difficulty choosing the most effective therapy. To address these issues, the DSM-5 broadens the inclusion criteria for both AN and BN, BED is now a formal diagnosis, and other EDs have been further clarified.(35)

Adolescents with AN often present with dramatic weight loss or poor growth and may be preoccupied with food and weight. Restriction of entire food groups (ie, new-onset vegetarianism) or calories, andthe development offood rituals are commonplace. They commonly refuse to eat foods they once enjoyed, avoid meals with family and friends, and overexercise in a rigid manner. Pubertal milestones such as linear growth or menstrual cycles are often affected.(5,16,24)

DSM-5 criteria for AN consider expected weight and growth in children and adolescents versus comparisons to population norms. They describe,

1. A restriction of energy intake relative to requirements, leading to a lower than expected body weight.
2. Fear of weight gain to failure to gain weight in the face of low body weight or growth stunting.(5)
3. Disturbance in the way one's body weight or shape is experienced, undue influence of body shape,and weight on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight.Amenorrhea has been removed as a criterion because its use was never validated and excluded males, premenarchal females, and adolescents who remain eumenorrheic despite low body weight.(37)

Thehallmark of bulimia nervosa(BN) is recurrent episodes of binge eating accompanied by inappropriate compensatory behaviors. An objective binge episode involves eating more food in a discrete period of time than most people would eat, coupled with feeling a loss of control.

DSM-5 criteria for BN includes- objective binge episodesandsubsequentcompensatory behaviors at least once per week for 3 months. Patients with BN may be of any weight and often have frequent weight fluctuations fromfluid shifts. Caregivers or peers may notice the development of mood swings, surreptitious behaviors (ie, increasedtime inthe bathroom after meals, hiding food), or periods of fasting or excessive exercise.(9,33)

The distinguishing feature between binge eating disorder (BED) and BN is that episodes of binge eating are not associated with inappropriate compensatory behaviors. Patients with BED and BN display marked distress regarding binge eating and will often binge in secret.

Additional new categories in the DSM-5 with likely impact are avoidant restrictive food intake disorder, other specified feeding and EDs, and unspecified feeding and ED. "Avoidant restrictive food intake disorder is not

uncommon in children(35,39) and comprises a variety of restrictive eating behaviors (ie, swallowing phobias, textural aversions) that do not involve a fear of weight gain or distorted cognitions but lead to significant physical and emotional impairment. Other specified feeding and EDs refers to atypical AN (normalweight AN), subthreshold BN, purging disorder, and night eating syndrome. Unspecified feeding and ED comprises any other clinically significant EDs that do not fit the aforementioned categories.(33,39)

Complications

EDs can affect every organ system, and complications can occur at any weight.(16,24,40,41)

It is important for providers to act quickly and decisively when they suspect an ED in all patients to avoid complications and the potential for chronicity.

Cardiovascular system :

Cardiac complications are patients include bradycardia, hypotension, arrhythmias, and changes in heart rate variability.(15,40,) Hypotension and postural changes in heart rate and blood pressure can result from decreased cardiac mass leading to systolic dysfunction, in addition to volume depletion and autonomic dysfunction.(16,24,) .Associatedphysical symptoms may include headache, presyncope, syncope, and exercise intolerance, although patients are frequently asymptomatic even in the face of profound vital sign instability.(16,24) Patients with chronic purging are at risk for cardiomyopathy, and up to onethird of hospitalized patients with AN have mitral valve prolapse and pericardial effusion. Serious cardiac complications are not unique to AN but are also seen in other normalweight EDs, particularly atypical AN and BN.(15)

Gastrointestinal :

Gastrointestinal complications may occur secondary to malnutrition, vomiting, or binge eating. Complications secondary to malnutrition include delayed gastric emptying, constipation, mild transaminitis, dyslipidemias, and superior mesenteric artery syndrome.Patients who vomit risk esophagitis, and in severe cases, esophageal rupture and pneumomediastinum. They may present with reflux, hematemesis or parotid swelling. Patients with AN typically report abdominal bloating, nausea, and postprandial fullness. Patients with binge eating behaviors are at risk for gastric dilation or rarely gastric rupture and pancreatitis. Electrolytes Electrolyte disturbances occur in patients who engage in vomiting, laxative abuse, or diuretic use, with hypokalemia and hypophosphatemia being the most common.(49)Hypochloremic metabolic alkalosis may develop in patients who vomit, and hyperchloremic metabolic acidosis may develop in those who abuse laxatives. Patients with malnutrition are at risk for refeeding syndrome during treatment.

Endocrine disorders :

Hyperthyroidism or hypothyroidism, Diabetes mellitus,Hypercortisolism Adrenal insufficiency .. Girls and boys may present with decelerated linear growth, pubertal delay, or pubertal regression, and menstrual dysfunction is common in females. Low insulin-like growth factor-I and low to low-normal thyroxine and triiodothyronine levels are seen.(40,48) Sick euthyroid syndrome can be seen in severely malnourished patients and resolves with reversal of the malnourished state. ED adolescents also risk reduced bone mineral density primarily due to poor nutritional intake, low BMI, and reduced fat mass(.45)Leptin plays a key role in energy homeostasis, and levels are low in malnourished states. A recent study demonstrated that if leptin levels are normalized, menstrual function and thyroid and bone markers improve in hypothalamic amenorrhea.(49)

Psychiatric disorders :

Depression Obsessive compulsive disorder/anxiety, Substance abuse.

Renal :

ED Patients can develop dehydration and renal insufficiency due to severe fluid restrictionor vomiting. Other renal abnormalities include pyuria and, less commonly, proteinuria and hematuria, which both clear

with hydration and reversal of malnutrition.(40) Patients with AN may lose renal concentrating ability, which can result in high urine output and inaccurate specific gravity measurements on urinalyses.(44.45)

Hematologic :

Bone marrow hypoplasia is seen in lowweight EDs, primarily leukopenia and anemia, with rare cases of thrombocytopenia. Leukopenia is not thought to increase infection risk, and all dyscrasias resolve with the reversal of malnutrition. It is important to evaluate for iron and vitamin B12 deficiency in anemic patients because these are easily reversed with supplementation.

Neurologic :

Malnutrition significantly affects the brain in children and adolescents because of the dynamic changes that are occurring in cognitive and structural braindevelopmentduringthisperiod.(33,34) Severely ill patients with AN have been shown to have reduced brain tissue volume and impaired neuropsychological functioning.

Treatment modalities

In 1995, the Society for Adolescent Medicine issued a statement that the treatment threshold for ED adolescents should be low because of potentially irreversible effects of EDs on growth and development, their mortality risk, and evidence that early treatment improves outcomes.(49)

Children and adolescents are triaged to outpatient treatment, partial hospitalization, residential programs, and inpatient hospitalization based on severity of illness, duration of disease, safety considerations, and familial preferences. Treating patients in a home setting is preferred, but other models of care may be necessary and appropriate.

A paradigm shift in EDs is evident in newer treatment modalities. In older paradigms, patients with thought to develop maladaptive eating behaviors in part because of overly controlling caregivers. This approach focuses on developing insight into the etiology of the disorder or cognitive behavioral therapy (CBT). These therapies focus on the patient's distorted body image and undue influence of weight and shape with a drive for thinness.

A newer paradigm takes into account the biological and genetic contributions to EDs and views caregivers as critical allies in treatment.(50) In this approach, nutritional rehabilitation is considered an important factor in improving cognitions and is the primary initial focus of treatment rather than causation, with age-appropriate insight developing over time. This corresponds with the tenets of family-based treatment (FBT).Evidence for effective treatments in EDs in children and adolescents is growing but remains limited. FBT progresses through 3 phases that target the goals of treatment in children and adolescents with EDs: physical, behavioral and psychological recovery. Phase I of FBT focuses on coaching the caregivers to refeed their child to recovery through specific therapeutic interventions. Food exposures are commonly used to target anxieties and aversions to certain foods or food groups; caregivers are encouraged to incorporate foods their children used to enjoy before the ED rather than to practice avoidance. Once the child is weight restored, FBT progresses to Phase II, which focuses on gradually transferring developmentally appropriate control of eating back to the child or adolescent. Phase III works on relapse prevention and any other remaining developmental considerations, and then treatment termination. FBT typically is conducted over a 6- to 12-month time period. Whereas in traditional treatments, fewer than half of AN patients fully recover within 2 to 5 years, a third partially recover, and 20% develop chronic illness, 50% to 60% of patients in FBT achieve full remission within 1 year, another 25% to 35% partially recover (showing improvement but not full remission), and only 15% are nonresponsive to treatment. Thus, FBT is emerging as a first-line treatment in pediatric EDs.

Finally, translational research is underway targeting known deficits in neurocognitive processes, neurotransmitters affected in EDs, and neuroanatomic changes found on imaging studies to tailor treatment and

improve treatment response in patients with EDs.(48,49,50)

Pharmacotherapy :

Pharmacologic agents are often used in patients with EDs, despite few studies demonstrating efficacy. There have been no published randomized controlled trials (RCTs) for antidepressant treatment in AN conducted in children and adolescents, and selective serotonin reuptake inhibitors and tricyclic antidepressants have not been shown to be better than placebo in weight gain or improvement in ED symptoms in adults. There is no evidence to suggest that pharmacotherapy in AN should be first line, but it may play a role in individual patients resistant to treatment or with premorbid psychiatric conditions. In BN, several RCTs in adults have found that antidepressants are effective in decreasing binge eating and purging symptoms. Specifically, fluoxetine has a strong evidence base and is approved by the Food and Drug Administration for use in adults with BN; thus far there is some evidence that the effects are similar in adolescents. Other medications such as topiramate and ondansetron are currently being studied for use in adults with BN but are not routinely used. In adults with BED, selective serotonin reuptake inhibitors seem to be effective in short-term reduction of binge eating but do not seem to be superior to CBT alone.Although different metrics for recovery exist in the literature, most agree that behavioral recovery includes normalizing eating patterns and the return of flexibility in eating. Psychological recovery includes improved self-esteem and age-appropriate interpersonal, psychosocial, and occupational functioning. Weight and body shape should no longer have an undue influence on self-evaluation, and normal growth and pubertal patterns are restored.

Physical recovery includes full weight restoration, return of menses and/or pubertal progression, linear growth if expected, and reversal of most or all organ damage. Nutritional restoration involves reaching a goal weight and the ability to eat a varied and balanced diet, but it is important to remember that a "maintenance weight" is often inappropriate in pediatric populations. Children and adolescents continue to grow and develop throughout puberty and into young adulthood(43,44) Body composition and activity changes will mandate changes in weight even if a final adult linear height has been achieved. This is an important concept to highlight for parents and patients when working toward recovery. The determination of goal weight in this population is complex: the provider typically works with a registered dietician experienced in treating EDs and must consider previous weight and linear growth trajectories if previously normal, geneticpotentialwiththeuse of midparental height, and the median body weight using standardized Centers for Disease Control and Prevention BMI growth curves for height, age, and gender.

Conclusion

EDs in children and adolescents are prevalent and have serious medical and psychological consequences. Children and adolescents have increased potential for long-term complications, thus it is imperative that providers recognize the risk factors and screen for EDs in their patients. Early recognition and aggressive treatment is needed to prevent complications and chronicity. Treatment efforts that focus on weight restoration, reducing blame, and actively incorporating caregivers and families have emerged as particularly effective. The evidence base for ED treatment modalities continues to grow, but to be successful, the treatment team, the family and the PCP must work in collaboration to promote remission and to prevent relapse in this population. Future research is needed to refine treatment in pediatric ED patients and to clarify the role of pharmacotherapy in the treatment of these disorders. Primary and secondary prevention of EDs are also important in improving the health of children, adolescents, and their families.

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