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FROM THE EDITOR'S DESK

Greetings from the Journal Committee of IJPP! In this issue we focus on some of the common as well as interesting topics in the field of Neonatology. This issue is compiled and edited Dr.Durai Arasan, Dr.V.Lakshmi and Dr.S.Lakshmi. They have carefully chosen the topics and authors for this issue, with the concurrence of the Journal Committee of IJPP.

'Birth asphyxia - Definition and concepts in the management' is written by Dr.Vishnu Bhat, et al. They have given a detailed account on this topic and also mentioned that prevention of asphyxia is important in bringing down neonatal mortality and morbidity. Respiratory distress in newborn is a symptom complex consisting of various clinical entities. Dr.Arvind Saili has given a vivid picture on the 'Approach to respiratory distress in newborn'. We hope this article will benefit both postgraduates and pediatricians while dealing with neonatal problems. Surfactant deficiency is the main contributor for respiratory distress in newborn. The introduction of 'Surfactant therapy' in infants with low birth weight and prematurity has been cost effective in developing countries. Dr.Namasivayam Ambalavanan stressed that surfactant should be administered early and more than one dose is occasionally required in neonates with RDS.

The article on 'Necrotizing enterocolitis' (NEC), which is one of the most common medico surgical emergencies in neonates is contributed by Dr.Arvind Shenoi, et al. He has discussed the pathophysiology, management and outcome of NEC in NICU in Indian scenario. Inborn errors of metabolism, though a rare disorder is still posing a problem in the diagnosis and management. Dr.Mamta Muranjan discusses an overview on this complex subject in detail. Hope this article will be an academic feast to all postgraduates and neonatologists. Dr.Muralinath focuses the role of plain X-ray in neonatal chest diseases. With years of experience in the field of pediatric radiology, he has emphasized how the plain x-ray plays a vital and key role in the evaluation of RDS in infants with illustrative chest skiagrams. We hope the FAQs in neonatal office practice will be useful for the practitioners. Dr.S.Criton has discussed in detail the 'Cutaneous viral infections in children' and highlighted the common viral exanthems in children. Dr.Panna Choudhury, et al in their article on 'Prevention of adult diseases in children: Nutrition perspective', stressed the crucial role of pediatricians in identification of children at risk of obesity. In the 'Radiologist talks to you' column, Dr.Vijayalakshmi, et al have discussed the role of ultrasonogram in the diagnosis of renal cystic disease. Persistent cough in children is well narrated by Dr. Paramesh. They conclude that ultrasonogram is the only investigation necessary to diagnose and follow-up polycystic kidney disease. We thank all the contributors for the column on 'Case study'. The Journal Committee of IJPP once again thank all the contributors in this issue. The next issue will also cover some more interesting topics related to neonatology.

Dr. A.Balachandran
Editor-in-Chief

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Print the manuscript on one side of standard size A4, white bond paper, with margins of at least 2.5 cm (1") in double space typescript on each side.
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(of which one could be in the form of clinical photographs / specimen photographs / investigations)

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NEONATOLOGY

BIRTH ASPHYXIA – DEFINITION AND CURRENT CONCEPTS IN MANAGEMENT

**** Vishnu Bhat B***
***** Narayanan P***

Abstract*: Birth asphyxia is an important cause of mortality and morbidity in India. Improved antenatal care will definitely bring down its incidence. Once the cerebral injury has occurred, the management is mainly supportive. Newer cerebroprotective therapies are being tried. The outcome depends on various factors. Most of the severely affected babies do not survive and the ones who do not have multisystem involvement usually do well with excellent outcome.*

Key words*: Birth asphyxia, definition, management, outcome.*

Perinatal asphyxia is defined as an insult to the fetus or newborn due to lack of oxygen and or perfusion to various organs. It is characterized by presence of profound metabolic or mixed acidemia with a pH of less than 7.1 on an umbilical cord arterial blood sample, persistence of an Apgar score of 0-3 for more than 5 minutes, presence of clinical and neurologic sequelae in the immediate neonatal period and evidence of multi organ system dysfunction[1].

The two working definitions of the National Neonatal and Perinatal Database network are as follows: [2]

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Birth asphyxia: Apgar score of less than 7 at one minute of age

Moderate asphyxia: Apgar score between 4 to 6 at one minute of age or slow gasping breathing at one minute of age

Severe asphyxia: Apgar score of 3 or less at one minute of age or no breathing at one minute of age.

The overall incidence of perinatal asphyxia is around 0.5 to 2 % but is significantly more when the gestational age is below 36 weeks[3]. It is the leading cause of neonatal mortality in India.

Ninety percent of insults due to asphyxia occur in the antepartum or intrapartum period and the rest occur in the immediate postpartum period[4]. Antepartum causes include impaired maternal oxygenation (maternal hypertension, diabetes, vascular disease, drug use or other systemic disease), decreased blood flow from the mother to the fetus (placental infarction or fibrosis, placental abruption and cord accidents), impaired gas exchange across the placenta and increased fetal oxygen requirement, other causes include birth trauma, failure to initiate respiration, severe respiratory diseases and congenital heart diseases etc. The response to mild and moderate asphyxia differs from that to severe asphyxia. The fetus and the neonate are more resistant to asphyxia than an adult because of a lower rate of metabolism and presence of more glycogen reserves[5].

An increase in the PCO_2 and a fall in the PO_2 produces a diving reflex wherein there is a shunting of blood towards vital organs i.e. the

brain, heart and adrenals due to vasodilatation in these organs and flow of blood away from the viscera, bone, muscle and skin due to vasoconstriction caused by an increased chemoreceptor and sympathetic activity.[6] Hypoxia also results in energy being produced by anaerobic glycolysis which leads to metabolic acidosis due to accumulation of pyruvate and lactate. There is an overall reduction in body movements to minimize oxygen consumption. When severe asphyxia occurs (defined as a reduction of oxygen content of the blood to less than 1 nmol/L) all the adaptive and protective mechanisms mentioned above are completely overwhelmed; there is a failure of the cerebral auto regulation and hence the cerebral blood flow decreases, there is a drastic fall in the cardiac output and in the blood pressure and ultimately mechanical asystole and cardiac electro-mechanical dissociation and renal tubular necrosis occurs.

Investigations

Blood

Serum glucose, electrolytes, Ca, Mg, ammonia, lactate, pyruvate. Serial acid base study will help in close monitoring of these sick babies.

CSF

Lumbar puncture is also done to rule out infection as chorioamnionitis in the fetus can result in asphyxia.

EEG

Electroencephalography changes provide valuable information regarding the severity. The role of EEG in assessing brain death is not clear. An isoelectric EEG can be seen in patients with neuronal necrosis. Conversely persistent EEG activity has been recorded even with other evidence of brain death.

Indications for EEG: 1. Documenting subclinical seizures, 2. Diagnosing seizures in paralysed child, 3. Decision on stopping anticonvulsants and 4.Predicting long term neurological outcome.

Limitations: 1.Subtle seizures arising from sub cortical focus are not associated with EEG changes and 2. Technically difficult to obtain EEG in newborns due to movement artefacts.

Neuroimaging

USG: The anterior fontanelle approach is used to detect injury to the basal ganglia, thalamus and periventricular leukomalacia. The characteristic evolution of echo densities of periventricular leukomalacia is the initial formation of small echolucent cysts to final swiss cheese appearance.

CT scan: It provides important information in the diagnosis of diffuse cortical injury in severe selective neuronal necrosis. The value in assessment is evident only several weeks after the injury.

MRI: Selective cortical neuronal necrosis is shown by hyper intensity of cortex on weighted images followed by development of selective neuronal necrosis. Parasagital injury is best seen on MRI[7].

Magnetic resonance spectroscopy: Helps in early delineation of impaired energy metabolism and identification of infants who are candidates for therapy that interrupt events leading to cell death[7].

Technetium scan: It is based on an uptake of technetium which crosses a damaged blood brain barrier. This is detected by an external array of gamma detectors thereby giving a coarse image of topographic injury. A technetium scan is valuable in the evaluation of full term infants. The optimal postnatal age for the study is 7 days. Abnormalities usually disappear within 3-4 weeks[8].

Other investigations

Creatinine kinase (brain specific);

Hypoxanthine, Aspartate aminotransferase, Erythropoietin, Endorphin, Lactate, Ascorbic acid and neuron specific enolase may be helpful in evaluating hypoxic damage[9].

Management

1. Oxygen levels

Oxygen levels have to be kept in normal range by monitoring transcutaneous or arterial PO_2. Hypoxia should be treated by oxygen and / or ventilation. Only minimal handling is recommended. Hyperoxia also causes problems due to free radical production and decrease in cerebral blood flow. Now there is evidence to support the theory that resuscitation of asphyxiated newborn with room air is as effective as using 100% oxygen. Neurologically the infants did not differ from each other[10].

2. Carbon dioxide levels

CO_2 should be kept in normal range. Hypercapnia causes tissue acidosis and increased cerebral blood flow. More blood flow to uninjured areas with relative ischemia to damaged areas (Steal phenomenon) causes extension of infarct size. Hypocapnia decreases cerebral blood flow.

3. Perfusion

Cerebral perfusion pressure (CPP) = Mean blood pressure (MBP) - Intra cranial tension (ICT)

Cerebral Perfusion Pressure (CPP) should be maintained within narrow range. Too little can cause ischemic injury and too much can cause hemorrhage in damaged areas. In asphyxia, cerebral auto regulation is lost. So cerebral perfusion entirely reflects systemic BP in a pressure passive fashion.

In asphyxia as CPP is equal to MBP, central venous pressure (CVP) and MBP should be monitored and maintained as shown in table 1. Crystalloids, colloids and vasopressors have to be used judiciously to maintain CVP, MBP and CPP. Conversely if hypertension develops and persists despite discontinuation of pressors and adequate sedation, the systemic BP should not be further lowered since it may be required to maintain CPP in the face of elevated ICT.

Table 1. Normal CVP and MBP

Maturity	CVP	MBP
Term	5-8 mm Hg	45-50 mm Hg
Preterm		
<1000g	3-5 mm Hg	30-35 mm Hg
1000-2000g		35-40 mm Hg

4. Glucose levels

Blood glucose level should be kept at 75-100 mg/dL range to provide adequate substrate for the brain. Both hyperglycemia and hypoglycemia have been shown to be harmful to brain in asphyxia by different studies. Normal glucose infusion rates of 5-8 mg/kg/ min may not be enough to maintain normoglycemia and rates as high as 9-15 mg/kg/min may be needed. Glucose infusions should be discontinued slowly to avoid rebound hypoglycemia. In seizures hypoglycemia should be corrected before giving anticonvulsants. Such seizures should not be used for Sarnat staging.

5. Calcium levels

Calcium level should be maintained in normal range by monitoring serum level. All infants with asphyxia should have the S.calcium levels monitored.

6. Temperature

The temperature of the newborn should be kept in normal range. Though deep hypothermia has shown to be neuroprotective in animals this has not been proved in humans.

7. Cerebral edema and fluid management

A simple bedside estimate of ICT can be made in infants by measuring the vertical distance between the anterior fontanelle and heart, measured at the point that the midportion of the fontanelle flattens as the baby is tilted up. Devices applied to the anterior fontanelle provide noninvasive methods for measuring ICT. Normal will be 50 mm H_2O or 5 mm Hg.

Management of ICT is not important in asphyxia because of following reasons:

Cerebral edema and raised ICT are uncommon accompaniments of asphyxia. It is especially unusual in preterms unless complicated by intracranial hemorrhage.

When present, ICT reflects extensive cerebral necrosis rather than swelling of intact cells. It has uniformly poor prognosis. It peaks at 36-72 hrs after the insult. It is more properly regarded as an effect rather than cause of brain damage.

MBP, not intracranial pressure primarily affects cerebral perfusion. Also there is no deterioration in neurological function by EEG or clinical examination at the time of maximum ICT recordings.

Infant's patent sutures and open fontanelles are protective to some extent of any acute increase in ICT that might occur. So, current treatment of ICT is restricted to fluid therapy. Avoiding fluid overload can minimize cerebral edema.

8. Control of convulsions

Prophylactic Vs therapeutic anticonvulsants

1. Prophylactic Phenobarbital at 2 hour to newborn infants with birth asphyxia showed that seizures occurred in 75 percent of both test and control groups with similar neurological outcome and mortality. The only difference was higher incidence of hypotension requiring inotropic support in prophylactic group[11].

Concurrent study by another group showed 3-fold increase in incidence of subsequent seizures and trend towards increased mortality in pretreated infants. So at present anticonvulsants are recommended only at onset of symptoms and not prophylactically. Similarly only clinical seizures or changes in blood pressure and heart rate in paralyzed infants need to be treated. Asymptomatic electrical seizures need not be treated as they are brief, not known to cause damage and the need for high doses of anticonvulsants to abolish such activity, which can cause various adverse effects[12].

Phenobarbitone: It is the drug of choice. It enters the CSF and brain rapidly with high efficiency. Blood level is predictable following intravenous dose. Protein binding is lower in newborns and so free levels are higher. The drug has been reported to have some cerebroprotective effect[13].

Phenytoin: Phenytoin in high doses in adults has been shown to cause irreversible injury to purkinje cells of cerebellum though not proved in newborns. The main advantage is that it does not cause respiratory depression and sedation in the usual dose.

Diazepam: It is not a preferable drug for maintenance because of extremely rapid redistribution out of brain. When used with phenobarbitone, it carries an increased risk of severe circulatory collapse and respiratory failure. Therapeutic levels are variable and not always less than toxic dose. Vehicle for diazepam is sodium benzoate, which can displace bilirubin from albumin predisposing to kernicterus.

Suggested protocol for acute seizures[10]: After treating hypoglycemia and hypocalcemia, Phenobarbital is given IV in a loading dose of 15-20 mg/kg in 10-15 minutes with careful

monitoring of blood pressure and respiration. A dose of 20 mg/kg achieves a blood level of 20 µg/ml which is needed to achieve anticonvulsant effect. If seizures are not controlled, administer additional doses of 5 mg/kg every 15 minutes till seizures are controlled or a total dose of 40 mg /kg is reached. Total dose in excess of 40 mg/ kg does not provide additional anticonvulsant effect. In severely asphyxiated infants with hepatic or renal dysfunction, higher blood levels are reached and last longer with 40mg/kg dose resulting in sedation and hypotension for several days. Hence after first 20mg/kg dose, some clinicians go for 20mg/kg phenytoin with cardiac monitoring. If still there is no response, i.v. Lorazepam is given at dose of 0.05- 0.1 mg / kg as often as needed. It is better to use phenytoin when the baby is comatosed or has respiratory depression. A combination of phenytoin with phenobarbitone often controls convulsions better with lesser side effects. Other drugs used for acute seizures are primidone, lidocaine, thiopentone, paraldehyde and valproate where experience in newborns is lacking. Once levels of conventional anticonvulsants are maximized to 40 µg/ml for phenobarbitone and 20 µg/ml for phenytoin, there is little reason to eliminate every twitch[11].

Maintenance therapy is with phenobarbitone at dose of 3-5 mg / kg day in 2 divided doses IV or orally and / or phenytoin at 5-8 mg/kg/day in 2 divided doses IV. Oral absorption of phenytoin is poor. When infant's condition is stable for 3-4 days, anticonvulsants arc weaned of gradually.

Duration of treatment and indications for stopping anticonvulsant: Optimum duration of therapy relates to the likelihood of recurrence of seizures if the drugs are discontinued. The three main determinants include neurological status, cause of seizures and EEG. If neurological examination is abnormal, 50% will have recurrence, while if interictal EEG is abnormal it is 40%. The recurrence is 20-30% with asphyxia and 100% corticol dysgenesis. Metabolic seizures have the lowest recurrence rates.

9. Other system management

A. Management of cardiac effects: Adequate ventilation with correction of hypoxemia, acidosis and hypoglycemia can reduce myocardial damage. Volume overload must be avoided. Diuretics may be ineffective if there is concomitant renal failure. If there is cardiac collapse, inotropic drugs like dopamine and dobutamine have to be started. Epinephrine should be avoided as it causes vasoconstriction and fall in perfusion and acidosis. Some infants in great distress may require afterload reduction with a peripheral beta agonist like Isoproterenol or peripheral alpha-blocker like phentolamine, tolazoline or nitroprusside[10].

B. Management of renal effects: Two main problems are Acute tubular necrosis (ATN) and Syndrome of inappropriate anti diuretic hormone secretion (SIADH), which are managed mainly by fluid restriction. Oliguria must not be attributed to SIADH or ATN unless prerenal etiologies such as hypovolemia or vasodilation have been ruled out. Dopamine at 1.25-2.5 µg/kg/min may aid renal blood flow. Dialysis is the treatment for severe cases, but not offered to many babies because of high mortality associated with such cases[10].

C. Gastrointestinal effects: There is increased risk for bowel ischemia and necrotizing enterocolitis. So infants with asphyxia must not be fed for 2-3 days or till good bowel sounds are heard and stools are negative for blood or reducing substance[10].

D. Hepatic effects: Since there may be bleeding due to hepatic dysfunction clotting factors and fresh frozen plasma may be given. Blood sugar should be maintained at 75-100 mg/dL and drugs metabolized by liver should be avoided[10].

E. Pulmonary effects: Adequate oxygenation and ventilation with possibly mild alkalinisation may be helpful. Method of ventilation is different if the primary problem is hyaline membrane disease, primary pulmonary hypertension of newborn or meconium aspiration syndrome. High frequency ventilation and ECMO can be tried in selected cases[6].

Potential new therapies of cerebroprotection[7]: It is very difficult to predict during the neonatal period which neonates will suffer the most profound damage after an insult to the central nervous system, since more than 30 percent of neonates presenting with moderate encephalopathy have normal outcome.

1. Oxygen free radical inhibitors and scavengers: Anti-oxidant enzymes, superoxide dismutase and catalase conjugated to polyethylene glycol have prolonged half life and improved penetration into blood brain barrier, but protective only if administered many hours before hypoxic insult.

Xanthine oxidase inhibitors – allopurinol and oxypurinol protect immature rats from hypoxic damage even when administered early during the recovery phase after resuscitation. In hypoxia ATP is degraded forming adenosine which is metabolised with the help of xanthine oxidase to uric acid releasing superoxide and hydrogen peroxide as side products. So inhibition of xanthine oxidase decreases free radical production.[13,14]

Elimination of free iron: Iron has the ability to transfer electrons and catalyze formation of more reactive species – hydroxyl radicals and other iron- oxygen compounds like ferryl and perferryl ions. So depletion of dietary iron or chelation with desferrioxamine is tried in experimental animals[15].

Prevention of excess Nitric Oxide formation: NO is produced by endothelial cells and microglial cells in response to asphyxia. Superoxide and NO combine to form Peroxynitrite which decomposes releasing oxidants. Inhibition of NO synthesis with L-NAME - (Nitro L arginine methyl ester) has been tried. It prevents secondary brain injury by suppression of NO production during recovery. But inhibition during hypoxic insult could be deleterious.

Vitamin E (alpha-tocopherol) - membrane bound chain breaking anti oxidant prevents chain elongation in free radical damage.

Lazeroids-non-glucocorticoid 21 aminosteroid prevents iron dependent lipid peroxidation by scavenging peroxyl radicals[16].

Indomethacin-cyclooxygenase and phospholipase inhibitors ameliorate ischemic brain damage atleast in adult animals and substantially reduces free radical generation during reperfusion.

Excitatory amino acid antagonists: Agents that would inhibit glutamate release from nerve terminal (e.g. baclofen) or block its postsynaptic action (NMDA and AMPA receptors or ion channels e.g. phencyclidine, Ketamine, Mk-801)[17] reduce hypoxic damage in adult animals even when administered upto 24 hours after the metabolic insult. NMDA and AMPA receptor antagonists are the most potent drugs available to ameliorate the devastating effects of hypoxia.

Magnesium sulphate: Retrospective study has suggested that premature babies whose mothers received magnesium sulphate for the treatment of pre eclampsia or as tocolytic agents are less likely to develop cerebral palsy compared with those not exposed to the drug. Divalent magnesium ion is glutamate receptor antagonist, which blocks neuronal influx of calcium ions.

Calcium channel blockers: Calcium is an intracellular second messenger, which causes

hypoxic damage by multiple mechanisms. Calcium channel blockers, which cross the blood brain barrier like flunarizine and nimodipine are tried. But the neuroprotective effect is not impressive.

Platelet-activating factor antagonist BN 52021 attenuates hypoxic damage.

2. Other drugs

Monosialogangliosides are important constituent of nerve cell membrane. It gives neuroprotection by incorporation into cell membrane.

Growth factors: Nerve Growth Factor has been shown to reduce severity of hypoxic damage in immature rat. The neuroprotective effect of exogenously administered erythropoietin has received much attention for ischemic disease, and promising data are emerging for the newborn.

Glucocorticoids: Dexamethasone given immediately before hypoxic insult does not give protection. But if administered > 24 hrs before insult, there is improved neuronal outcome.

3. Non-pharmacological interventions

Hypo / Hyperglycemia : Blood glucose level of >600 mg/dL is shown to protect the brain. Similarily prolonged fasting induced hypoglycemia (>12 hrs) has been shown to be neuroprotective.

Carbondioxide: Premature babies ventilated for RDS are at increased risk for hypoxic damage if they develop hypocapnia.

Hypothermia: Preliminary results of two randomized clinical trials of either systemic cooling or selective head cooling in encephalopathic neonates suggest that moderate hypothermia is safe in the high risk newborn. In at least one study, newborns with moderate encephalopathy had better neurodevelopmental outcomes at 18 months than did newborns in the normothermic group[18].

Hypoxic Preconditioning: Immature rats subjected to cerebral hypoxia sustain less damage if exposed to hypoxia alone compared to animals not exposed previously to hypoxia. The mechanism is by induction of genes or proteins that influence metabolic events during insult or reperfusion.

Prognosis of perinatal asphyxia

The degree of asphyxia necessary to cause permanent brain damage in experimental animals is quite close to that which causes death (> 25 minutes of total asphyxia). Survival with brain damage is actually uncommon in this model. The extremes of death or intact survival are the most likely outcome. Likewise in humans, birth asphyxia severe enough to damage fetal brain usually kills before or soon after birth, the remainder survive and are normal. The only groups with significant neurological impairment are those who were severely asphyxiated yet narrowly escaped death. Any infant severely asphyxiated to result in neurological sequelae would have other organ system severely affected. Full term asphyxiated infants have mortality of 10-20% and neurological sequelae in survivors will be 20-45 % (40% mild 60% severe) (Table 2).

Within the first two weeks, it is very difficult to offer a prognosis because the present methods of prognostication are very unreliable. Unfavorable signs are:

1) Severe prolonged asphyxia, 2) Sarnat Stage III encephalopathy, 3) Multiorgan system involvement, 4) Elevated intracranial pressure more than 10 mm Hg, 5) Persistence of abnormal neurological signs at discharge especially absence of Moro reflex., 6) Persistence of extensive hypo densities (cystic encephalomalacia) on CT scan

Table 2. Sarnat staging and outcome

Stage	Outcome
1	100 % normal neurological outcome
I1	80 % normal (if symptoms persist for <5 days)
111	50% die; 50 % have severe sequelae (mental retardation, epilepsy, microcephaly)

at least 4 weeks after the insult, 7) Abnormalities on brain scan and 8) Persistent oliguria less than 1 ml/kg/hour for the first 36 hours of life[19].

Points to remember

1. ***Birth asphyxia is an important cause of neonatal mortality and morbidity***
2. ***Severe asphyxia results in death and most of the survivors may be normal.***
3. ***Persisting neurological abnormality and abnormal brain scan indicate poor outcome.***
4. ***Prevention of asphyxia is important.***

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NEWS AND NOTES

CLINICAL FELLOWSHIP IN PEDIATRIC INTENSIVE CARE

Kanchi Kamakoti CHILDS Trust Hospital, a 200 bedded superspecialty children's hospital in Chennai, is a recognized teaching center for training postgraduates in both the DNB and PhD in Pediatrics and Pediatric Surgery. KKCTH is a referral center for seriously ill children from Chennai and the neighbouring states. The hospital has a newly renovated PICU with 10 ICU and 7 step-down beds. There are about 450 admissions to the PICU annually (not including step-down admissions)

The hospital invites applicants for a Clinical Fellowship in Pediatric Intensive Care. The duration of the Fellowship is 2 years. This Fellowship is accredited by the Indian Academy of Pediatrics Critical Care Chapter and the Indian Society of Critical Care Medicine Pediatric Section. Upon completion of the Fellowship, candidates can appear for the Fellowship examination conducted by the IAP-Critical Care Chapter. Candidates must have completed either MD or DNB in Pediatrics. Fellows will be paid a stipend on par with hospital Registrars.

Interested candidates may apply to the Medical Director with a copy of their CV.

For further information, please contact Dr. B. Ramachandran (e-mail: mdpicu@hotmail.com, mobile: 098401 34245).

SHALINI RAKESH FELLOWSHIP IN PEDIATRIC NEPHROLOGY - 2006

Applications are invited for the Shalini Rakesh Fellowship in Pediatric Nephrology. The applicant should be a postgraduate in Pediatrics and below 40 years old. Preference will be given to those working on a permanent position in a hospital. The trainee would spend 3 months at a center recognized for training in pediatric nephrology in the country. A training grant will be provided.

Application forms may be obtained from Dr. Pankaj Hari, Department of Pediatrics, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029. Email: pankajhari@hotmail.com.

The last date of sending the completed application is 31 October 2005.

NEONATOLOGY

APPROACH TO RESPIRATORY DISTRESS IN NEWBORNS

**** Arvind Saili***

Abstract: *Acute respiratory distress is a common morbidity in neonates. This symptom complex consists of rapid breathing, retractions, nasal flaring, grunting, cyanosis and apneic spells. The etiology is predominantly of respiratory tract origin but also includes cardiovascular, metabolic, CNS and surgical causes. A detailed history and physical examination leads to the precise diagnosis. The degree of distress can be assessed by respiratory scores. The management includes hemodynamic stabilisation, adequate oxygenation and treatment of specific underlying disorder. Respiratory failure diagnosed by an arterial blood gas analysis needs to be managed by proper ventilation.*

Keywords: *Respiratory distress, oxygenation, ventilation.*

Respiratory problems constitute a major proportion of neonatal illnesses. It is the commonest cause of morbidity and mortality in this segment of population. The attending pediatrician must diagnose the condition promptly and initiate appropriate therapy to curtail the mortality ensuing from this disorder of the respiratory tract.[1]

Definition

Respiratory distress is a symptom complex which may present with tachypnoea (respiratory rate more than 60/min), chest indrawing or retractions, nasal flaring, grunting, central cyanosis and occasionally it may be associated with apneic spells.[2]

Etiology

The aetiology of respiratory distress may be due to medical or surgical conditions. It could be a symptom of a pathological condition of any organ system. The causes for respiratory distress can be classified based on the time of onset of distress (Table 1).[3,4]

Table 1. Causes of respiratory distress

Onset	Causes
At birth	Transient tachypnea of newborn, meconium aspiration syndrome, asphyxia, choanal artresia, congenital diaphragmatic hernia, pulmonary hypoplasia
1-6 hrs.	Hyaline membrane disease, Tracheo esophageal fistula
1st day	Polycythemia, congenital penumonia
1st week	Persistent pulmonary hypertension, pulmonary hemorrhage, pneumonia, Wilson Mikity Syndrome, Congenital heart disease
2-3 weeks	Chronic lung disease, patent ductus arteriosus
Variable presentation	Inborn Errors of Metabolism

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History and physical examination

A detailed history often gives a clue to the diagnosis in a case of respiratory disorder in a neonate. The time of onset of the respiratory distress is also important as it may point to certain clinical conditions which present early in life in contrast to others which may present late.

Specific history provides a clue to the diagnosis of specific disorders (Table 2).[3] Although any respiratory illness can present at any time, surfactant deficient respiratory distress syndrome (RDS) always presents within the first 4 hours. The other conditions presenting during this period include congenital malformation, congenital pneumonia, transient tachypnea of newborn (TTNB) and persistent fetal circulation.

After 4 hours of age, the respiratory conditions presenting in a neonate may include pneumonia, congenital malformation, acidemia, congenital heart disease, etc.

Physical examination

The history and time of onset of disease give a clue to the diagnosis but the physical examination is important to reach a conclusive diagnosis. The physical examination helps to establish the gestation, confirm historical data and guide therapy.

Establish gestation with a Ballard or Dubowitz method[5] or any of the standard modifications. This helps to narrow down the possible causes of respiratory distress.

Some of the conditions diagnosed on a physical examination are given in Table-3.[3]

The degree of respiratory distress can be assessed by various scores. The commonly used ones are Silverman Anderson score and the Downe's score (Table 4).

Investigations

A complete blood count, hematocrit, chest x-ray and arterial blood gas must be done in all cases. Blood glucose is done to rule out hypoglycemia. Blood culture to determine the specific microbes involved in the illness is important. Chest x-ray is instrumental in diagnosing and differentiating between medical and surgical causes of respiratory distress. ABG can help to decide the degree of hypoxia and strategy to manage if the child is in respiratory failure (Table 5).

In addition, cranial USG to determine intracranial hemorrhage and ECHO in suspected cases of CHD and PPHN are mandatory.

Table 2. Clinical history suggesting probable diagnosis

Clinical history	Probable diagnosis
Prematurity, diabetes in mother, antepartum hemorrhage	Hyaline membrane disease
Prolonged rupture of membranes, foul smelling liquor, maternal fever, UTI, diarrhoea, unclean vaginal examination	Pneumonia
Prolonged labor, meconium stained amniotic fluid, fetal distress	Meconium aspiration syndrome
Polyhydramnios	Esophageal atresia
Oligohydramnios	Pulmonary hypoplasia
Post maturity, cord prolapse, fetal distress	Perinatal asphyxia
Delayed cord clamping	Polycythemia

Table 3. Signs and symptoms as a guide to diagnosis in neonates with respiratory distress

Signs and symptoms	Most likely neonatal conditions
· Scaphoid abdomen and shift of apical impulse; gurgling sounds on chest auscultation	· Diaphragmatic hernia
· Shift of apex beat to contralateral side	· Air leak / Pneumothorax
· Shrill cry / abnormal tone	· Central nervous system disorder
· Persistent frothing at mouth	· Tracheo esophageal fistula
· Increased antero posterior diameter of chest, Meconium staining of cord / skin	· Meconium aspiration syndrome
· Decreased breath sounds	· Pneumothorax, hyaline membrane disease, pneumonia, pulmonary hypoplasia
· Cyanosis in quiet baby which disappears on crying	· Choanal atresia
· Blood stained froth from larynx	· Pulmonary hemorrhage

Table 4. Downe's score[6]

	0	1	2
Respiratory rate	< 60	60 – 80	> 80
Cyanosis	None	In room air	In 40% FiO_2
Retractions	None	Mild	Severe
Grunting	None	Audible with stethoscope	Audible without stethoscope
Air entry	Clear	Bilaterally decreased	Barely audible

Score 1-3 : Mild respiratory distress; 4-7 : Moderate distress - prepare to transfer / intubate if baby is worsening; >7 : Impending respiratory failure - intubate

Management

1. **Warmth and humidity :** The temperature of the baby should be maintained between 36.5^{0}C to 37.5^{0}C and the humidity should be above 60%. The baby can be nursed in the incubator or under a radiant warmer. Safe measures to keep the baby warm must be used.
2. **Oxygenation :** The neonate must be well oxygenated. Hypoxemia can lead to acidemia, patency of the ductus arteriosus, decrease in surfactant synthesis and increased risk of persistent pulmonary hypertension. The oxygen tension should be between 60-90 mm Hg and the oxygen saturation on pulse oxymetry between 90-95%. Cyanosis is not an early clinical sign for hypoxemia since it appears very late in the course of illness due to presence of fetal hemoglobin in neonates which has high affinity to oxygen.[7]

Table 5. Interpretation of ABG in neonates

	Normal	Respiratory Failure
pH	7.30-7.40	< 7.2
$PaCo_2$	30-35 mm Hg	55-60 mm Hg
PaO_2	> 60mm Hg in room air	< 60 mm Hg FiO_2 0.4 – 0.5
Base deficit	-5 to 0 m Eq/L	
O_2 saturation	>90 – 92%	< 85%

• Oxygen hood : Oxygen can be administered by the oxygen hood in spontaneously breathing babies. The FiO_2 can be adjusted to keep normal levels of SaO_2. A blender system is the most reliable way to administer a fixed concentration of oxygen via a hood.

• Nasal oxygen : For prolonged oxygen requirements e.g. neonates with chronic lung disease the administration of oxygen by nasal cannula is practical and easy as it allows the baby to be picked up for feeding. It is difficult to monitor oxygen concentration in such cases.[8]

• CPAP : If the neonate is unable to maintain oxygenation with the head box then continuous positive airway pressure (CPAP) is required. The indication for CPAP would be : 1. PaO_2 <60 mm of Hg in FiO_2 > 0.6 and 2. recurrent apneic spells

• Mechanical Ventilation : Failure of CPAP is an indication for mechanical ventilation. Mechanical ventilation is indicated if any two of the following are present :

1) Moderate to severe retraction, 2) Respiratory rate >70/min, 3) Cyanosis in FiO_2 >0.4, 4) Intractable apneic spells, 5) PaO_2 <50 mm of Hg in FiO_2 >0.8 with CPAP, 6) $PaCO_2$ >60 mm Hg and 7) PH <7.25

3. **Fluid and electrolytes :** The sick baby in respiratory distress should be on intravenous fluids initially. 10% dextrose 60-80 ml/kg on the first day should be initiated. The blood sugar should be maintained above 60 mg/dl. After 48 hours of age the neonate can be switched over to Isolyte 'P' fluid therapy. The fluid requirement can be tailored by assessing the urine output, specific gravity, osmolality, S.electrolytes and weight of the neonate. Trophic feeds can be initiated early through nasogastric tube to maintain intestinal cell turnover and integrity. Then these feeds can be gradually changed over to oral feeds.

4. **Maintain perfusion:** Maintaining the normal perfusion of the child is of critical importance. The features reflecting normal perfusion are normal blood pressure, capillary refill time of less than 2 seconds, adequate urine output and normal metabolic status. Blood pressure must be monitored frequently. Hypotension may result from hypovolemia or through a cascade triggered by hypoxemia and metabolic acidemia. The mean BP must be kept above 35 mm of Hg. The neonate can be infused bolus doses of normal saline or Ringers lactate in a dose of 10 ml/kg if hypovolemia is diagnosed. The PCV should be kept above 40%. If hypotension persists despite correction of hypovolemia then the neonate should be administered inotropes like dopamine as an infusion at 5-20 μg/kg/min.[9]

5. **Hematocrit :** Neonates on ventilatory support must have the hematocrit above 40%. Polycythemia if present must be treated since it may lead to hyperviscosity leading to adverse cardiopulmonary consequences.

Venous hematocrit should be maintained below 65% and close to 55%.

6. Antibiotic therapy

If the respiratory distress is of infective origin and the neonate has positive sepsis screen or cultures, then antibiotic therapy should be initiated. Appropriate and rational antibiotic therapy is necessary.

7. Surgical intervention

Surgical causes of respiratory distress should be treated with surgical intervention after the neonate has been suitably stabilized hemodynamically.

Prompt management of respiratory distress has a direct impact on the morbidity and mortality in these vulnerable neonates.

Points to remember

1. ***Acute respiratory distress is a common cause of morbidity and mortality in newborn babies.***
2. ***Detailed history and examination lead to precise diagnosis which can be confirmed by investigations.***
3. ***Respiratory score for assessing severity of distress is important for monitoring the course of illness.***
4. ***Adequate oxygenation is the cornerstone of management, and can be achieved by different methods of oxygen administration.***
5. ***Respiratory failure must be diagnosed early and should be managed aggressively to curtail mortality.***

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NEONATOLOGY

SURFACTANT THERAPY

**** Namasivayam Ambalavanan***

Abstract*: Surfactant is a complex mixture of phospholipids, proteins, and neutral lipids produced by alveolar type II cells. Surfactant deficiency contributes to the pathophysiology of respiratory distress syndrome (RDS) in premature infants. Surfactant therapy reduces death and bronchopulmonary dysplasia in premature infants with RDS. In infants requiring mechanical ventilation for RDS, surfactant should be administered early, and more than one dose is occasionally required. Surfactant is cost-effective in developing countries, but it is also essential to optimize the use of antenatal steroids, continuous positive airway pressure (CPAP) / ventilatory management, and overall supportive care in order to observe the benefits of surfactant and improve outcomes.*

Key Words: *Surfactant, Neonate, Respiratory Distress Syndrome*

Introduction

Fifty years ago, in 1955, Pattle observed that bubbles in pulmonary edema fluid were remarkably stable, and hypothesized that the bubbles contained "a protein layer that abolished the tension of the alveolar surface".[1] In 1956, Clements observed that extracts from the lung, but not from other tissues or serum, had surface tension lowering effects.[2] Avery and Mead subsequently observed that lungs of infants who died of respiratory distress syndrome (RDS; then called hyaline membrane disease) did not have surfactant.[3] It was later discovered that alveolar type II cells produce surfactant which is a complex mixture of phospholipids (80%), proteins (10%), and neutral lipids (10%). The principal phospholipid is phosphatidylcholine (80% of phospholipids), which is the major surface active agent. The proteins consist of four surfactant-specific proteins: SP-A, B,C and D of which SP-B is necessary for the surface-tension lowering activity.

After the discovery that surfactant deficiency was responsible for the pathophysiology of RDS, research focussed on surfactant replacement as a possible therapy. In 1980, Fujiwara reported on the successful use of a modified bovine surfactant extract.[4] Multiple randomized controlled trials on different surfactants and dosing regimens have since then been conducted on premature infants with (or at risk for) RDS. The use of surfactant in term infants and in older children for various indications has also been investigated, although not as thoroughly as for preterm infants with RDS.

Types of surfactants

Natural surfactants are those derived from animal lungs. Surfactant TA and Survanta are lipid extracts of minced bovine lung, while Infasurf and Alveofact are chloroform/methanol extractions of bovine lung washes. Curosurf is derived from minced porcine lung followed by chloroform/methanol extraction and then purified

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by liquid-gel chromatography.[5] Artificial surfactants include Exosurf and Pumactant 7 (ALEC), which are not marketed currently in the USA or Europe, and the newer synthetic surfactants Sinapultide (KL4) and Venticute (rSPC).[5]

Surfactant in premature infants

Benefits

Surfactant use is associated with short-term as well as longer-term benefits. Short term benefits include improvements in oxygenation, reductions in air leaks (pneumothorax and pulmonary interstitial emphysema), and lower mortality.[5,6] Overall, a review of multiple publications indicates that natural surfactants reduce death by about 30%, BPD/death by 25%, and pneumothorax by more than 50%.[5-8] Long-term follow-up have shown neither beneficial nor adverse effects of surfactant use on growth and/or neurodevelopmental parameters.[6]

Which surfactant is best – Natural or Synthetic?

Natural surfactants are associated with a lower incidence of pneumothorax (Odds ratio 0.60; 95% CI 0.49-0.73) and mortality (Odds ratio 0.83; 95% CI 0.70-0.99) as compared to synthetic surfactants, although no significant differences were noted in bronchopulmonary dysplasia (BPD) or the combined outcome of BPD/death.[7] Natural surfactants may also improve oxygenation and lung compliance more rapidly. However, it is possible that these differences may be diminished with the newer synthetic surfactants (KL4 and rSPC), as described near the end of this review. A few studies have been done to demonstrate that one synthetic surfactant is better than other synthetic surfactant, or that one natural surfactant is better than the other. Speer et al, demonstrated that Curosurf resulted in a more rapid improvement in oxygenation than Survanta, and was associated with a trend towards reduced pneumothorax, severe intraventricular hemorrhage, and mortality.[9] In a recent large multicenter trial, treatment with Curosurf (200 mg/kg initial dose) resulted in rapid reduction in FiO_2 with fewer additional doses of surfactant versus treatment with Survanta in infants <35 weeks gestation with RDS, and significantly reduced mortality than either Survanta or Curosurf (100 mg/kg dose) in neonates <32 weeks gestation with RDS.[10] Bloom et al in a multicenter randomized controlled trial observed that Infasurf had a modest benefit in the acute phase of RDS, and produced a longer duration of effect than Survanta.[11]

Prophylaxis versus Rescue?

Prophylactic surfactant is surfactant administered immediately after birth or soon after birth before RDS is clinically evident, while rescue surfactant indicates surfactant therapy for established RDS. Prophylactic surfactant has the theoretical advantages of replacing surfactant before the onset of RDS and thereby reducing effects of volutrauma on atelectatic lung, and possibly a more homogeneous distribution of surfactant when given immediately after birth. Current clinical evidence indicates that prophylactic surfactant reduces airleaks (pneumothorax, pulmonary interstitial emphysema), mortality, and bronchopulmonary dysplasia / death, without significant adverse effects.[12] However, it is currently unclear which infants would benefit most from prophylactic administration. Administration of prophylactic surfactant to all very low birth weight infants would result in over-treatment, as many will not develop RDS severe enough to require surfactant. There are also logistical issues with surfactant administration soon after birth to large numbers of premature infants, many of whom may not be born at referral centers. In addition,

administration of surfactant in the delivery room may result in unilateral administration (if there is endotracheal tube displacement into a main bronchus) or in pharyngeal/esophageal administration (if endotracheal tube dislodgement occurs).

Early selective use of surfactant (neonates < 2 hours of age, intubated for RDS) is better than delayed selective use of surfactant as it may reduce pneumothorax (RR 0.70, 95%CI 0.59, 0.82), pulmonary interstitial emphysema (RR 0.63, 95%CI 0.43, 0.93), neonatal mortality (RR 0.87, 95%CI 0.77, 0.99), chronic lung disease (RR 0.70, 95%CI 0. 55, 0.88), and chronic lung disease or death at 36 weeks (RR 0.84, 95%CI 0.75, 0.93).[13] Therefore, the current clinical practice in many referral centers is to administer rescue surfactant early, once it is clear that the infant has RDS and requires intubation for mechanical ventilation.

Indications for surfactant

Different studies have used different criteria as indications for administration of surfactant.

Infants on CPAP: Verder et al, evaluated early versus late treatment of RDS in preterm babies <30 weeks gestation receiving nasal CPAP.[14] Early-treated neonates (arterial to alveolar oxygen tension ratio or a/APO_2 of 0.22 to 0.35; mean, 0.26) had a lower incidence of mechanical ventilation (main indications for mechanical ventilation being a/A PO_2 <0.15 or severe apnea) or death (21%) than did late-treated neonates (63%), who did not receive surfactant treatment (Curosurf) until the a/APO_2 was <0.22 (0.15 to 0.21; mean, 0.16). This study demonstrates that although half the neonates <30 weeks' gestation with RDS can be treated with nasal CPAP alone, early treatment with surfactant when the a/APO_2 is 0.22 to 0.36 may reduce the need for mechanical ventilation.[14]

Infants on the ventilator: Kendig et al, administered rescue surfactant if the fractional inspiratory oxygen concentration (FiO_2) was at least 0.40 or if the mean airway pressure was at least 0.686 kPa (7 cm H_2O), or both.[15] Dunn et al, used chest radiographs consistent with RDS, as well as supplemental oxygen with a mean airway pressure of at least 7 cm H_2O.[16] Egberts et al, used a FiO_2 of > 0.60 while on mechanical ventilation as an indication for surfactant.[17] There have been no studies comparing the effectiveness of surfactant administration at each of these thresholds.

In neonates with (or at risk for) RDS, early surfactant replacement therapy with extubation to nasal CPAP is associated with a reduced need for mechanical ventilation and increased utilization of exogenous surfactant therapy, when compared with later selective surfactant replacement and continued mechanical ventilation.[18] Before administration of surfactant, it probably does not matter whether nasal CPAP is initiated in a prophylactic (immediately after birth regardless of clinical status) or in a rescue manner (requiring FiO_2 > 0.40).[19]

Method of administration

Surfactant is administered by bolus administration through the endotracheal tube. It is important not to shake the vial and cause frothing. Each dose is often given over a few minutes as two to four aliquots into the endotracheal tube. These doses may be given either directly with a syringe into the endotracheal tube, or via a side-port adapter. Changes in position of the baby to ensure adequate spreading has not been shown to be useful. Slow administration by an infusion pump through an endotracheal catheter has also not shown to improve results.[20] Opened vials can be kept in the refrigerator at 2-8°C for up to 12 hours, and should not be frozen. It is necessary to rapidly

wean off from the ventilator if the clinical response is quick.

Pilot trials have examined the feasibility of the laryngeal mask airway (LMA) for surfactant administration[21] and of intrapartum nasopharyngeal instillation of surfactant after delivery of the head but before delivery of the shoulders[22], but the effectiveness of these techniques has not yet been determined. The administration of surfactant by nebulization does not appear to have any advantages, and may not be as effective as direct endotracheal instillation.

When do we give additional doses?

Kattwinkel et al, compared the relative efficacy of administering second and subsequent doses of Infasurf surfactant (not the initial dose) at a low threshold (FiO_2 >30%, still requiring endotracheal intubation) versus a high threshold (FiO_2 >40%, mean airway pressure >7 cm H_2O) of respiratory support.[23] There was no difference in the number receiving mechanical ventilation at 72 hours or in the secondary respiratory outcomes (BPD at 28 days or 36 weeks). However, there was a significantly higher mortality for infants with complicated RDS (with perinatal compromise or sepsis) who had received retreatment according to the high-threshold strategy.[23] The dosing interval usually ranges from 6-12 hours between doses, and varies with the characteristics of the surfactant. The usual dosing frequency of Survanta is 4 mL/kg at least six hours apart. For Curosurf, the initial dose is 2.5 ml/kg, with up to two subsequent doses of 1.25 mL/kg at 12-hour intervals. Each dose of Infasurf is 3 mL/kg, which can be given every 12 hours for a total of up to 3 doses. The older synthetic surfactant Exosurf was given at 5 mL/kg every 12 hours.

How many doses?

As stated in the previous paragraph, the indications for re-dosing are variable. In general, most of the benefit occurs with the first dose, with declining benefit from subsequent doses. Most infants do not need more than two doses. Infants with very severe RDS or a persistently high oxygen requirement may occasionally receive up to four doses.

In neonates of 30-36 weeks gestation with RDS, Dunn et al, showed that surfactant improved oxygenation by 10 minutes postinstillation, and better oxygenation with lower ventilatory parameters was maintained over the first 24 hours, despite deterioration in oxygenation and ventilatory requirements starting 6 to 12 hours after the first dose.[24] The deterioration in oxygenation could be minimized by the use of multiple doses; however, extra doses had no effect on diminishing ventilatory requirements or time to extubation. Multiple doses of surfactant may have a greater effect on sustaining improvements in oxygenation than on ventilatory requirements.[24]

Speer et al, evaluated in a randomized European multicenter trial whether the beneficial effects of a single large dose of Curosurf in babies with severe RDS could be enhanced by using multiple doses of surfactant. Both the single dose and multiple dose groups had a rapid improvement in oxygenation and a decline in ventilatory requirements, but diminished ventilatory requirements were noted in the multiple dose group 2-4 days after randomization.[25]

Surfactant in term infants and older children

Surfactant therapy has been used in situations other than the premature infant with RDS, such as in term infants with meconium aspiration syndrome.[26] A multicenter randomized, double-blind, placebo-controlled trial was conducted on term infants (>2000g, >36

weeks) with respiratory failure at high risk for requiring ECMO. Infants were randomly assigned to receive four doses of beractant, 100 mg/kg (n = 167), or air placebo (n = 161) before ECMO treatment and four additional doses during ECMO, if ECMO was required. It was noted that surfactant, particularly in early respiratory failure, significantly decreased the need for ECMO (29.3 % in surfactant group vs. 40.4 % in the control group, $p<0.05$), without increasing the risk of complications.[27] Surfactant therapy in meconium aspiration syndrome may be administered as a routine bolus administration or as diluted surfactant lavage.[28,29] Surfactant therapy benefits term and preterm infants with pneumonia and respiratory failure, although the response may be slower and multiple doses needed.[30] Surfactant therapy has not been shown to benefit infants with congenital diaphragmatic hernia.[31]

Surfactant may be beneficial in infants and older children with Acute Lung Injury (ALI), in which surfactant dysfunction is known to occur. A recent multicenter, randomized, blinded trial compared a natural lung surfactant to placebo in 153 infants, children, and adolescents with respiratory failure from ALI.[32] Entry criteria included age 1 week to 21 years, enrollment within 48 hours of endotracheal intubation, radiological evidence of bilateral lung disease, and an oxygenation index higher than 7. The intervention consisted of 2 doses of 80 ml/m^2 calfactant or an equal volume of air placebo administered 12 hours apart. Natural lung surfactant acutely improved oxygenation and significantly decreased mortality although no significant decrease in the course of respiratory failure measured by duration of ventilator therapy, intensive care unit, or hospital stay was observed.[32] Small clinical trials indicate that surfactant may improve oxygenation and reduce the duration of mechanical ventilation in infants with bronchiolitis.[33]

New developments

Surfactant can be used as the vehicle to carry other therapeutic agents. One such agent is recombinant human superoxide dismutase (rhSOD), which when given intra tracheally within two hours of surfactant reduces injury markers in tracheal aspirates.[34] rhSOD also improves respiratory outcome (reduction in hospitalizations and asthma medications) in premature infants followed-up at one year of age.[35]

Lucinactant is a synthetic surfactant containing sinapultide, a surfactant-associated protein B mimic. Recent randomized clinical trials indicate that this compound is a safe and effective treatment for respiratory distress syndrome in preterm infants, with efficacy superior to, or at least comparable to Curosurf and Survanta.[36,37]

Surfactant in developing countries

Surfactants are expensive medications and are therefore considered by some physicians as not suitable for widespread use in developing countries due to their cost and the relative lack of emphasis placed on high risk neonatal intensive care. However, the expanding middle class in many developing countries with an increased awareness of what is available elsewhere in the world now seeks higher quality care. Individuals who have sought coronary bypass grafts or MRI scans for their elderly relatives now request neonatal intensive care, hoping for survival of their children. With smaller families, they are better able to allocate scarce resources to their children. Surfactant may not only reduce mortality, but may also reduce overall costs by reducing the length of hospital stay and morbidities.[38] Cost-effectiveness studies in developing countries have demonstrated that surfactant use is cost effective and that quality adjusted life years (QALY) for NICU care

compares favourably with cost per QALY of several forms of adult health interventions.[39]

Natural surfactants improve oxygenation faster and lead to slightly better outcomes as compared to the older synthetic surfactants, although even these synthetic surfactants show marked improvement in clinical outcomes compared to no surfactant. In many developing countries, the natural surfactants may be more expensive and harder to obtain as compared to locally produced synthetic surfactants. Clinicians have to weigh the relative benefits and disadvantages and individualize their approach.[40]

With increasing use of surfactant in developing countries, an increase in the prevalence of bronchopulmonary dysplasia[41] as well as associated morbidities such as retinopathy of prematurity and long-term handicap may be observed in infants who may otherwise have died without the use of surfactant. Surfactant alone will not prevent or treat RDS. Skilled nursing care and physician intervention is essential, with close emphasis placed on minimizing mechanical ventilation, improving nutrition, and preventing infection. Therefore, surfactant should only be used in referral centers and by personnel with expertise in the care of critically ill neonates. It is necessary to remember that antenatal steroids are probably more important in developing countries – they are far cheaper, safer, and more effective in reducing mortality and morbidity due to RDS and other illnesses in premature infants. The use of antenatal steroids must be optimized before surfactant is used extensively. The benefits of surfactant will not be observed unless optimal CPAP/ventilatory management is used, and overall supportive care is excellent.

Recommendations

The Committee of the Fetus and Newborn of the American Academy of Pediatrics has made the following recommendations[6] and these recommendations appear relevant to most institutions around the world:

1. Surfactant replacement therapy should be directed by physicians qualified and trained in its use and administration. Qualifications should include experience in management of the respiratory care of low birth weight neonates, particularly those on mechanical ventilation.
2. Nursing and respiratory therapy personnel experienced in the management of low birth weight neonates, including mechanical ventilation, should be available within the unit at the bedside when surfactant therapy is administered.
3. Equipment necessary for managing and monitoring the condition of low birth weight neonates, including that needed for mechanical ventilation, should be available on-site when surfactant therapy is administered. Radiology and laboratory support to manage a broad range of needs of these neonates should be available.
4. More important, surfactant therapy should be used only in institutions in which facilities and personnel are available for the management of multisystem disorders and low birth weight neonates.
5. An institutionally approved surfactant therapy protocol, which is a mandatory component of the quality assurance program for neonates, should exist.
6. In the institutions not satisfying recommendations 2 through 5, and when timely transfer to an appropriate institution cannot be achieved, surfactant therapy may be given, but only by a physician skilled in endotracheal intubation. Under these circumstances, consultation with a subspecialty center should be obtained.

Neonates should be transferred from such institutions if appropriate and when feasible to a center with appropriate facilities and staff trained to care for multisystem morbidity in low birth weight neonates.

Points to remember:

1. ***Surfactant reduces death and death/ bronchopulmonary dysplasia in premature neonates with respiratory distress syndrome.***
2. ***In neonates requiring mechanical ventilation for respiratory distress syndrome, surfactant should be administered early, and more than one dose is occasionally required.***
3. ***The use of surfactant is cost-effective in developing countries, but it is also essential to optimize the use of antenatal steroids, CPAP/ventilatory management, and overall supportive care in order to observe the benefits of surfactant and improve outcomes.***

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NEWS AND NOTES

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NEONATOLOGY

NECROTIZING ENTEROCOLITIS

**** Manoj Peter Menezes***
***** Arvind Shenoi***

Abstract: *Necrotising enterocolitis(NEC) is the commonest gastrointestinal emergency in the newborn. It is a medico-surgical emergency. The etiology includes possible ischemia, hypovolemia, shock and vasospasm on a premature gut. Thus LBW, VLBW neonates are at greatest risk for it. Clinical features range from increased gastric residuals and abdominal distension, to signs of frank gut perforation with shock in severe NEC. Laboratory studies show hyponatremia, acidosis, hematologic derangement. Radiologic imaging along with clinical features help to stage the disease into mild, moderate or severe. Staging helps to plan treatment and prognosticate.Inspite of intensive care, the mortality in severe NEC is >50%. The key to managing NEC is early detection and instituition of prompt medical and surgical care with nutrition support.*

Keywords: *Necrotising enterocolitis, Infant newborn,*

Necrotizing enterocolitis (NEC) is the most common surgical emergency occurring in neonates. Population studies indicate an incidence ranging from 0.23 - 2.4 cases per 1000 live births[1]. Though it may be observed in term babies, it is much more common in premature infants, and as more premature babies survive, expecting an increase in the overall incidence is reasonable. The reported mortality is about 22%[1].

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Pathophysiology

Although the exact etiology remains elusive, ischemia and reperfusion mucosal injury may play a role. Some factors implicated in the occurrence of NEC include -

1. Perinatal asphyxia, hypovolemia and shock causing mesenteric vasospasm.

2. Large volume of intragastric feeds, rapid advancement in the volume of feeds or the use of hyperosmolar feeds including formula feeds[2]. Babies who are breastfed have a lower incidence of NEC than formula fed babies. Mortality is significantly lower in predominantly breast fed neonates than those predominantly fed formula and this is particularly evident in neonates above 30 weeks gestation[3,4].

3. Translocation of intestinal flora across an incompetent mucosa may play a role in spreading disease and systemic involvement. Inflammation of the intestinal tissues and the release of inflammatory mediators (e.g. leucotrienes, tumor necrosis factor and the platelet activating factor) lead to variable degrees of intestinal damage.

4. Outbreaks of NEC seem to follow an epidemic pattern within nurseries suggesting an infectious etiology even though a specific pathogen has not been identified.

There are also reports of preterm infants developing NEC following the use of mydriatic eye drops during ophthalmologic examinations[5].

Race/Sex: Most studies show no difference in the incidence based on race. Male and female babies are affected equally.

Gestational age: The incidence of NEC varies inversely in relation to birth weight and gestational age. The attack rates are as high as 40% in those weighing less than 1000g at birth, falling dramatically to just 3.8 per 1000 lives births for infants weighing between 1501 and 2500g at birth. The average age of onset is related to the post-conceptional age, with those more premature developing NEC at a later date.

Clinical features

NEC is more common in the preterm infants and there is a significant difference in the antecedent history between term and preterm infants. The affected term baby has a median age of onset between 1-3 days of life and is usually systemically ill with asphyxia, respiratory distress and sepsis or has a history of intrauterine growth retardation. Maternal cocaine abuse is a significant risk factor for the term baby.

Preterm babies have usually achieved full-volume feeds or are advancing on enteral feeds when symptoms develop.

Gastrointestinal symptoms include: 1.Feed intolerance characterized by abdominal distention and vomiting, 2. Increased abdominal girth, 3. Gastric residuals, 4. Decreased bowel sounds, 5. Visible intestinal loops or a palpable abdominal mass, 6. Blood-streaked stools (the presence of occult blood in stools is not a specific marker of NEC) and 7. Erythema of the abdominal wall.

Systemic signs and symptoms include:1.Lethargy and temperature instability, 2. Apnea and bradycardia, 3. Poor peripheral perfusion and shock, 4. Bleeding diathesis and 5.Cardiovascular collapse.

Published data from Chandigarh suggests that prefeed residue, abdominal distension, lethargy were the commonest presenting signs[6].

Early surgical consultation is mandatory, especially if abdominal signs are present as transfer to a tertiary care facility for appropriate surgical care may be required.

Laboratory investigations

1. Complete Blood count, 2. Blood culture - to rule out sepsis mimicking NEC, 3.Serum electrolytes and 4. Serum bicarbonate.

An extremely ill baby may also need an arterial blood gas to rule out impending respiratory failure.

Characteristic abnormalities include.

1. **Thrombocytopenia** (<100,000/ cu.mm) is usually associated with NEC. It may be worsened by a consumption coagulopathy (raised PT, raised aPTT, low fibrinogen, elevated fibrin degradation products).
2. **Hyponatremia** due to a developing capillary leak.
3. **Metabolic acidosis:** Persistently low platelet counts and sodium levels, and persistent metabolic acidosis despite treatment may be an indication for laparotomy in an ill infant, even in the absence of signs of perforation.

Imaging studies: Antero-posterior and left lateral decubitus radiographs are essential for the initial evaluation and for monitoring any baby with abdominal signs, and may be needed as frequently as every 6 hours. The abdominal radiograph may reveal an abnormal gas pattern, dilated loops and thickened bowel walls. A fixed dilated loop that does not change position on serial radiographs may indicate a gangrenous loop. “Pneumatosis intestinalis” is pathognomoic of NEC and represents intramural air extravasated

from the intestinal lumen. It appears as a characteristic train track lucency within the bowel wall. "Portal gas", is air present in the portal venous system, appears as hypodense branching areas over the liver shadow. Abdominal free air indicates a perforation and it mandates immediate surgical intervention. The "football sign" represents the oblong lucency over the liver shadow due to intraperitoneal free air on a supine film.

Abdominal ultrasonography may reveal (a) Ascites (b) Portal air ('**Champagne flute**') sign (c) A doppler of the orientation of the superior mesenteric artery to the superior mesenteric vein may help rule out a malrotation and volvulus. (d) Recent studies demonstrate a markedly increased peak flow velocity in the celiac and superior mesenteric arteries in early NEC.

An upper GI barium study with a small bowel follow through and a water-soluble contrast enema may definitely rule out volvulus and Hirschsprungs disease.

Based on the systemic, gastrointestinal and radiological signs NEC has been staged according to the Modified Bell's criteria (Table 1).

Treatment

Early or suspected NEC is often difficult to diagnose as the clinical signs and symptoms are often non-specific, as are the radiological and laboratory findings. All babies with definite NEC should be transferred to a level III unit.

Management varies according to the stage of NEC

1. Cease all enteral feeds.
2. Secure intravenous access. Central venous access through percutaneously inserted central venous catheters or surgically placed central lines may be required for parenteral nutrition. Parenteral nutrition may be needed till enteral feeds can be restarted. At our unit, we have found a combination of lipids and amino acids infused through an aseptically placed peripheral venous canula and changed every three days, to be adequate for intravenous alimentation.
3. Broad spectrum parenteral antibiotic therapy, after collection of blood and urine cultures, should be initiated without delay. At our unit we use a combination which provides coverage for gram-positive, gram-negative and anaerobic organisms, till cultures become available.
4. Extremely ill babies in impending respiratory failure require endotracheal intubation and ventilation.
5. Immediately consult a pediatric surgeon and organize a laparotomy if indicated. Abdominal decompression with a large bore catheter, paracentesis to drain an ascites causing respiratory embarrassment, and placing an intra-abdominal drain are alternatives to laparotomy in babies who are too sick for surgery.

Complications

Complications are related to the disease or the therapy. To name a few

1. Intestinal strictures, short-gut syndrome and malabsorbtion following extensive surgery and resection, 2. Centrally placed catheters are a risk factor for staphylococcal and fungal sepsis and 3. Prolonged parenteral nutrition may be associated with cholestasis and direct hyperbilirubinemia.

Mortality

It ranges from 10-44% in infants weighing less than 1500g compared to 0-20% in those more than 2500g.

Table 1. Modified Bell's Staging Criteria for Necrotizing Enterocolitis

Stage	Systemic signs	Intestinal signs	Radiologic signs	Treatment
I. Suspected				
A	Temperature instability, apnea, bradycardia	Elevated pregavage residuals, mild abdominal distension, occult blood in stool	Normal or mild ileus	NPO, antibiotics x 3 days
B	Same as IA	Same as IA, plus gross blood in stool	Same as IA	Same as IA
II. Definite				
A: Mildly ill	Same as IA	Same as I, plus absent bowel sounds, abdominal tenderness	Ileus, pneumatosis intestinalis	NPO, antibiotics x 7 to 10 days
B: Moderately ill	Same as I, plus mild metabolic acidosis, mild thrombocytopenia	Same as I, plus absent bowel sounds, definite abdominal tenderness, abdomina cellulitis, right lower quadrant mass	Same as IIA, plus portal vein gas, with or without ascites	NPO, antibiotics x 14 days
III Advanced				
A: Severely ill, bowel intact	Same as IIB, plus hypotension, bradycardia, respiratory acidosis,metabolic disseminated intravascular coagulation, neutropenia	Same as I and II, plus signs of generalized peritonitis, marked tenderness and distension of acidosis,	Same as IIB, plus definite ,ascites abdomen .	NPO, antibiotics x 14 days, fluid resuscitation, inotropic support, ventilator therapy, paracentesis
B: Severely ill: bowel perforated	Same as IIIA	Same as IIIA	Same as IIB, plus pneumoperitoneum	Same as IIIA, plus surgery

The outcome *mortality and morbidity* is directly related to severity of the disease with worse outcome associated with advanced staging.

Prevention

1. Breast fed babies have a lower incidence of NEC compared to formula fed babies.
2. Systematic review published by the Cochrane Collaboration in 1999 reported no effect on NEC of rapid feeding advancement for low birth weight infants.
3. High clinical suspicion of NEC in premature

babies and early surgical consultation do help reduce the morbidity and mortality.

4. In pregnancies at risk for fetal growth restriction, abnormal antenatal doppler velocimetry in the form of Absent or Reverse End Diastolic Frequencies (A/R EDF) in the umbilical arteries is a useful guide to predict NEC and mortality in the early neonatal period[7].

Points to Remember

1. ***NEC is the most common GI emergency in neonates.***
2. ***NEC can present late in the smallest babies.***
3. ***Early NEC is difficult to diagnose – if in doubt treat early and conservatively (cease feeds and start broad spectrum antibiotics).***
4. ***Early surgical consultation is a must, and babies with 'definite' NEC should be referred to a NICU.***

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XXVI UP PEDICON 2005

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NEONATOLOGY

INBORN ERRORS OF METABOLISM IN NEONATES: AN OVERVIEW

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Abstract: *Inborn errors of metabolism (IEM) are perceived as rare disorders, but in reality affect 1 – 2% of newborns. They are monogenic disorders resulting from deficiency of a critical enzyme functioning in intermediary metabolic pathways. Two categories are identified in the neonate: a)dramatic onset and b) insidious onset. The metabolic deficiency in IEM is present from conception and some disorders manifest antenatally, or at birth with malformations. The usual presentation after birth is deterioration after a variable symptom-free interval or sudden death. The commonest patterns of disease are acid-base disturbances, neurological deterioration (encephalopathy), liver disease, cardiac disease and hypoglycemia. The illness resembles neonatal medical or surgical crisis, especially sepsis. Suspected IEM must be investigated rapidly and systematically. Screening tests are performed first followed by confirmatory tests. Diagnostic accuracy depends on method of sample collection, storage and transport. Therapy has to begin immediately when IEM is suspected and relies on correction of fluid and acid-base imbalance, preventing catabolism, neutralization and removal of toxic metabolites and administration of cofactors.*

Keywords: *Inborn errors of metabolism, neonatal period, diagnosis, management*

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Introduction

"Guérir parfois, soulager souvent, consoler toujours" (Cure sometimes, relieve often, always sympathize) – the words of Ambroise Paré sum up the responsibility of a physician caring for a child with an inborn error of metabolism (IEM). However successful management depends on prompt diagnosis. Due to the large number of disorders, diverse manifestations and lack of distinctive symptoms, diagnosis can be difficult. Moreover, IEM are perceived as rare disorders. In reality, the frequency is as high as 1 – 2% of newborns [1]. The estimated incidence of IEM that are detected by newborn screening is 1: 3400 to 1: 4700 [2]. Unlike countries of North America, Europe, Australia and some Southeast Asian countries there is no program for newborn screening on a mass scale in India. As a consequence, barring limited data from Hyderabad where the frequency of aminoacid disorders and galactosemia was 1:3660 and 1: 10300 respectively, the incidence and prevalence for most IEM in India is unknown [3]. In India these disorders are misunderstood, misdiagnosed or largely ignored. The likely reason is that many physicians are not aware of the signs and symptoms that are excellent clues to diagnosis and consequently do not perform comprehensive evaluation. Limited facilities for investigations also limit the scope

of diagnosis. It must be appreciated that diagnosis does not require extensive knowledge of biochemical pathways or individual metabolic disease. An understanding of the broad clinical manifestations of IEM provides the basis for knowing when to consider the diagnosis. Even in untreatable conditions it is crucial to reach a diagnosis, so that genetic counselling and prenatal diagnosis can be offered to the family.

Since the signs and symptoms are usually non-specific, there is a need to develop an approach to identify neonates with metabolic disorders. The scope of this article is to enable a physician to be familiar with the clinical context in which IEM should be suspected; to use simple screening tests to identify the likely disease; to collect, store and transport specimens appropriately; and institute immediate and emergency care for the affected infant. It must be emphasized that such neonates are best managed at adequately equipped centers with an experienced team.

Pathophysiology

IEM are single gene disorders. The primary defect is a mutation of a gene controlling synthesis of an enzyme functioning in an intermediary metabolic pathway which results in deficient activity of that enzyme (Fig 1.). Lack of enzyme function produces secondary derangements: either lack of product (D) (e.g. hypoglycemia due to lack of glucose resulting from glucose – 6- phosphatase deficiency in glycogen storage disease type I), accumulation of immediate precursor (C) (ketoacid derivatives of valine, leucine and isoleucine in maple syrup urine disease) or remote precursors (A, B) or activation of alternative pathways (E) forming toxic byproducts (e.g. production of galactitol by alternate metabolic pathway in galactosemia). The diverse clinical presentations reflect the detrimental effects of this metabolic block on various organs. Sometimes deficiency of a co-factor which is responsible for activation of an apoenzyme produces a metabolic block (e.g. deficiency of pyridoxine, which is a cofactor for the neuronal enzyme glutamic acid decarboxylase blocks GABA synthesis resulting in seizures). Thus manifestations of the disease are either because of the accumulation of toxic metabolites proximal to the block, "intoxication type" (maple syrup urine disease [MSUD], urea cycle defects [UCD], organic acidemias), or because of inability to generate or utilize energy, "energy deficiency type" (fatty acid oxidation [FAO] defects, glycogen storage disease, primary lactic acidosis and mitochondrial respiratory chain disorders) or excessive storage of substrate "storage disorders" (lysosomal storage disorders)[4]. (Fig. 1).

The metabolic deficiency in IEM is present from the time of conception. Yet, most of the diseases have no adverse effects on the developing fetus. This is due to the placental barrier which functions as a dialysis system for removal of toxic metabolites[5]. It is only after separation of the placenta that the detrimental effects of toxic metabolites give rise to symptoms. Most IEM presenting in the neonate like galactosemia, UCD and organic acidemias manifest only after the specific substrate (galactose or proteins) becomes available from feeds.

Clinical presentations of IEM

The diverse nature of the metabolic disease in the newborn is reflected in the modes of presentation. Two broad phenotypes are identified: dramatic onset of intoxication type and some energy-deficiency type of IEM and insidious onset of storage disorders. The distinguishing features of these phenotypes are summarized in Table 1. Disorders with acute manifestations far outnumber chronic diseases

and the focus of this paper is on diagnosis and management of acute neonatal IEM.

Often, the first hint of an IEM is a family history of neonatal deaths, similarly affected siblings or sudden infant death syndrome (SIDS); though most newborns with inborn errors have no family history. Affected males on the mother's side of the family should raise suspicion of X-linked recessive disorder. Parental consanguinity is a risk for autosomal recessive disorders.

The onset of symptoms depends on nature of the molecular defect, environmental factors and possibly other genetic factors[6]. An environmental trigger provoking acute metabolic crisis can often be identified (Table 2)[7]. Mutations leading to complete lack of enzyme synthesis produce severe disease with early onset. An example is methylmalonic acidemia with a Mut^0 phenotype. The mutation causes near complete deficiency of methylmalonyl-CoA mutase. On the other hand Mut-phenotype has residual enzyme activity. Mut^0 causes severe neonatal disease with 80% developing symptoms in the first week of life [8].

Modes of presentation

A. During pregnancy: Some metabolic diseases cause maternal complications during pregnancy carrying affected fetuses. Acute fatty liver of pregnancy (AFLP) and hemolysis elevated liver enzymes and low platelets (HELLP) syndrome are known to be associated with fetal long chain acyl Co-A dehydrogenase (LCHAD) deficiency, an inborn error of fatty acid oxidation.[7,9,10] A fetus affected by non-ketotic hyperglycinemia or pyridoxine dependency could develop intrauterine seizures in late pregnancy perceived by the mother as abnormal fetal movements [6]. Non-immune fetal hydrops is a presenting feature of IEM like Gaucher's disease type II, sialidosis type II, galactosialidosis, mucolipidosis type II, GM_1 gangliosidosis, MPS Type IV and VII, Farber's disease, red cell enzymopathies (glucose-6-phosphate dehydrogenase deficiency, pyruvate kinase deficiency), congenital disorders of glycosylation, neonatal hemochromatosis and glycogen storage disorder type IV. Development of cardiac failure or arrhythmias in respiratory chain disorders can also result in hydrops. [5,11]

B. At birth: IEM like energy deficiency disorders cause in-utero metabolic derangements leading to disruption of normal fetal development. Consequently, dysmorphisms and malformations are characteristically noted in such disorders. The manifestations and differential diagnosis of disorders presenting at birth are described in Table 3.[5,6,11,12]

C. After birth

i. Sudden death: Death in a neonate without a previous illness, following a disproportionately mild illness or in a family with a history of unexpected deaths should raise the suspicion of an IEM. Defects of FAO and respiratory chain disorders lead to sudden death. Medium chain acyl CoA dehydrogenase (MCAD) deficiency typically presents with sudden death and has been proved by post-mortem investigations in 1% of infants with SIDS [13]. Respiratory arrest or cardiac arrhythmia is usually responsible for sudden death in such cases[11]. Other disorders causing apparently sudden death like UCD, organic acidemias, biotinidase deficiency or pyruvate dehydrogenase (PDH) deficiency usually cause acute illness with obvious clinical symptoms that precede death by hours to days [7].

Any unexpected death should be probed by autopsy. Autopsy should be performed within 4 to 6 hours of death [14]. Unfortunately, in India such deaths are seldom investigated, not even in

Table 1. Modes of presentation

Acute	Chronic
Intoxication/ Energy deficiency type	Storage disorders
Dramatic onset	Insidious onset
Rapid progression	Static or slowly progressive
Signs of encephalopathy: Lethargy, vomiting, abnormality of tone, seizures, coma, death	White or grey matter signs: Mental retardation, seizures, psychomotor regression, spasticity, visual or auditory abnormalities
Lack of energy: Failure to thrive, weakness	Organomegaly
Respiratory symptoms: Tachypnea, apnea	Skeletal abnormalities Dysmorphisms
Therapy: Diet plays a major role	No role of diet, therapy by enzyme replacement or organ transplant

Table 2. Factors provoking symptoms of IEM

Provocative factor	Examples	Clinical implication
Diet	Hereditary fructose intolerance, fructose diphosphatase deficiency	Manifests only when fructose is introduced in the diet (honey, cane sugar). Honey customarily offered as prelacteal feeds.
Dietary protein intake	Urea cycle defects, organic acidemias	Though protein content of breast milk is relatively low, it should be avoided. Not advisable to give colostrum. Manifestations can coincide with weaning
Weaning	Disorders of gluconeogenesis, glycogen storage disorders, fatty acid oxidation defects.	Increased interval between feeds or overnight starvation provokes symptoms .
Infections, fever, starvation, surgery, anesthesia, constipation	Organic acidemias, fatty acid oxidation defects, urea cycle defects	Frequency of infections can be reduced by preventing anemia and immunizations
Drugs	Glucose-6-phosphate dehydrogenase deficiency Porphyria	Avoidance of precipitating drugs

Table 3. IEM manifesting immediately after birth

Manifestation	Disorder	Description
Seizures	Pyridoxine dependency	Myoclonic seizures, early and prominent, often intractable
	Non-ketotic hyperglycinemia	Hiccups (non-ketotic hyperglycinemia)
	Primary lactic acidosis	Lens dislocation (Molybdenum cofactor or sulfite oxidase deficiency)
Hypotonia	Peroxisomal disorders Mitochondrial/ respiratory chain disorders Congenital lactic acidosis	Typical dysmorphisms and or malformations are often present
Dysmorphisms and malformations	Primary lactic acidosis – pyruvate dehydrogenase (PDH) deficiency	Facial features resemble fetal alcohol syndrome Agenesis of corpus callosum
	Glutaric aciduria type II	Abdominal wall defects, renal cysts, hypospadias, rocker bottom feet
	Non-ketotic hyperglycinemia	Agenesis of corpus callosum, gyral malformations
	Zellweger syndrome	Hypotonia, facies resemble Down syndrome, liver disease, renal cysts
	Propionic or methylmalonic acidemia	Abnormal facies, hypoplastic or inverted nipples
	Smith-Lemli-Opitz syndrome	Microcephaly, hypospadias, syndactyly, polydactyly
	Mucopolysaccharidosis, mucolipidosis, GM_1 gangliosidosis	Coarse facies, dysostosis, hepatosplenomegaly
Symptomatic hyperammonemia	Glutaric aciduria type II Pyruvate carboxylase deficiency	Distinguished from urea cycle defects by absence of symptom free interval
	THAN (Transient hyperammonemia of newborn)	

teaching institutions. Physicians are disinclined to motivate the family and parents refuse consent for autopsy. Thus, an opportunity for establishing diagnosis and offering genetic counseling is lost until the next affected child is born.

In the rare event of autopsy being performed, findings that should raise suspicion of an IEM are cardiomyopathy, dilatation of the heart (especially if endocardial thickening is detected), pale flabby muscles, enlarged

Table 4. Biochemical autopsy for suspected or undiagnosed IEM

Sample	Collection	Storage
Plasma	3-5 ml heparinized sample from which plasma is separated	Plasma is frozen at -70° C
Serum	Serum separated from 5 ml blood collected without anticoagulant	Frozen at -70° C
Whole blood Leucocyte separation Cytogenetics DNA analysis	 5 ml heparinized sample 5 ml heparinized sample 3-5 ml of EDTA sample	 On wet ice, 4° C Overnight refrigeration at 4° C Refrigerated, (not to be frozen). If facilities for DNA extraction are available, DNA can be stored at – 20° C
Urine	Suprapubic tap, swab from posterior bladder wall, squeeze from bladder wall at autopsy or from diaper if uncontaminated with feces, on filter paper (Whatman 3MM)	Refrigerated at 2 – 8° C for months or immediately frozen & stored at -70° C Specimen on filter paper should be dried at room temperature for 4 hours.
Blood for acylcarnitine analysis	Newborn screening card or any thick filter paper Should be completely dried at room temperature for 4 hours	Can be stored at room temperature for days or refrigerated indefinitely. DNA can be extracted from dried blood if required in future.
CSF or vitreous humor		Frozen and stored at -70° C
Skin biopsy for fibroblast culture (can be collected up to 4 days after death), 3 x 2 mm segment including dermis (Enzyme assay, radioisotope study, cytogenetics)	Tissue culture medium, sterile Ringers lactate or normal saline	Site is cleaned with alcohol containing fluid; avoid use of iodine containing solutions. If prolonged storage required, store at -70 °C.
Liver, muscle, heart, kidney, brain (collect within 2 hours of death)	1 cm^3 pieces 5 cm cubes 1 mm cube preserved in glutaraldehyde	Collect in aluminium foil or double plastic bag, freeze immediately in liquid nitrogen or dry ice For enzyme assay For electron microscopy
Bone marrow	Smears	

liver or spleen, microvesicular fatty liver, fibrosis or cirrhosis of the liver and edema of the brain [13]. In most cases there is dearth of gross findings, but if IEM is suspected gross autopsy must be complemented by biochemical investigations (Table 4) [5,11,12,13,14]

ii. Deterioration after a symptom-free interval: Most neonates with IEM are typically born healthy. They deteriorate after a variable symptom-free interval ranging from hours to weeks after feeds are commenced. However, catabolism occurs even in the absence of oral feeds. Progressive accumulation of toxic metabolites results in symptoms. Physical signs like cataracts and unusual odours immediately raise suspicion of an IEM. Most symptoms however are relatively non-specific and do not discriminate metabolic disorders from other insults as manifestations in neonates are stereotypic. Therefore high index of suspicion, clinical acumen and experience are the keys to correct diagnosis. Clues to suspect IEM are mysterious onset of illness after a variable interval in a previously healthy full term baby born without antenatal or perinatal risk factors. The usual course is to investigate and treat for sepsis, but when investigations for sepsis yields no result and the baby relentlessly deteriorates despite ongoing therapy, an alternative diagnosis is suspected. This strategy delays onset of therapy to a stage where death is imminent or significant neurological damage has set in which predicts permanent neuro-developmental disability. It is therefore prudent to perform screening tests for IEM simultaneously with investigations for sepsis [11]. It must be remembered that documentation of sepsis does not exclude IEM as such infants rapidly become debilitated and develop sepsis. Neutropenia and thrombocytopenia which are markers of neonatal sepsis are also seen with diseases like propionic and methylmalonic acidemia[7,8]. Furthermore, disorders like galactosemia predispose to gram-negative sepsis [12]. Ostensible illnesses like pneumonia, adrenal crisis, shock, dehydration, congestive heart failure, bowel obstruction, intracranial bleed and neonatal diabetes should raise doubt of an IEM [7,15]. In fact, a respiratory disease with tachypnea in absence of cough, retractions and auscultatory signs is likely to be an IEM.

Patterns of deterioration

1) **Acid-base disturbances**: An IEM is suspected in a neonate with metabolic acidosis when it is persistent or unexplained despite normal tissue perfusion, associated with increased anion gap and not easily corrected by sodium bicarbonate administration. Another disturbance that arouses suspicion of IEM is respiratory alkalosis which is an early finding in UCD. Both will be clinically apparent as tachypnea. Blood gas analysis will identify the nature of defect and should be performed in any tachypneic baby with paucity of respiratory findings. However, blood gas analysis may not reflect presence of lactic acidosis. Significant lactic acidosis can be present with a normal pH, as the lactate level should exceed 5 mM/L before blood pH is altered[7]. It is therefore essential to measure serum lactate and pyruvate when congenital lactic acidosis is suspected. IEM associated with lactic acidosis are disorders of pyruvate metabolism, FAO defects, mitochondrial diseases, organic acidurias and UCD. Technique of sample collection for lactate estimation is of utmost importance as applying tourniquet, squeezing the extremity, crying or breath holding elevate

Table 5. Investigations in a suspected IEM

Blood	Urine	CSF
Screening tests		
Complete blood count Glucose Calcium Electrolytes (anion gap) Liver enzymes Smear for vacuolated lymphocytes Blood gas Ammonia Lactate, pyruvate Ketones	pH, odour Ferric chloride (Phenylpyruvic acid) Dinitrophenylhydrazine (Ketoacids) Cyanide-nitroprusside (Sulphur-containing amino acids) Rotheras (Ketonuria) Benedicts test (Reducing sugars)	
Confirmatory tests		
Amino acids Free carnitine Acylcarnitines Biotinidase assay Very long chain fatty acids Transferrin isoelectric focusing Leukocyte enzymes DNA study	Amino acids Organic acids by GC-MS Sulfitest Mucopolysaccharide electrophoresis Oligosaccharides	Proteins Lactate Glycine Alanine

lactate level. Lactic acidosis is significant when associated with ketosis and in the absence of shock, infections and seizures, as all these cause secondary lactic acidosis [5]. Estimation of ketones in blood or urine should always accompany determination of acid-base status.

2) **Metabolic encephalopathy**: The pointers to a metabolic cause of neurologic symptoms are altered neurologic status disproportionate to systemic signs and symptoms. Early symptoms are poor feeding, vomiting, lethargy, irritability, breathlessness and abnormalities of tone. Abnormality of tone, especially generalized hypertonic episodes and opisthotonus are characteristic, whereas non-metabolic causes of coma usually cause hypotonia. Abnormal limb movements like boxing, pedaling, slow limb elevations and large amplitude tremors may be noted. Seizures, apnea, stupor and coma occur late in the course of the disease [7,11]. When seizures occur, neonates are usually comatose. Seizures may be associated with hypoglycemia. Cerebral edema with signs of raised intracranial pressure can be present, especially in disorders like galactosemia which is known to give rise to pseudotumor cerebri[11,12]. The manifestations of some of the disorders causing metabolic encephalopathy are summarized below.

MSUD: Opisthotonus, abnormal limb movements, abnormal urine odor (burnt sugar or curry-like), DNPH positive

UCD: Reye-like disease, hypotonia, coma, anicteric hepatomegaly, hyperammonemia,

respiratory alkalosis, elevated hepatic transaminases.[7]

Organic acidemia: Acutely ill, dehydration, coma, abnormal urine odor, tone abnormality, hematological abnormalities (neutropenia, thrombocytopenia), ketotic hyperglycinemia, candida infection.

FAO Defects: Reye-like illness, hypoglycemia, hepatomegaly, elevated transaminases, cardiomyopathy, SIDS.[7]

Non-ketotic hyperglycinemia: No symptom-free interval, myoclonus, hiccups, hypotonia, stupor, apnea, EEG – burst suppression pattern, elevated CSF glycine.[6]

Sulfite oxidase / molybdenum cofactor deficiency: Refractory seizures, severe hypotonia, lens dislocation, low plasma uric acid.[6,7]

3) **Liver parenchymal disease**: Usual type of jaundice in neonates is unconjugated hyperbilirubinemia. When direct hyperbilirubinemia is detected IEM are an important differential diagnosis if anatomical obstructions are ruled out[12]. Occasionally, indirect hyperbilirubinemia is noted in galactosemia due to hemolysis from high red cell galactose-1-phosphate level[12]. Hepatomegaly and coagulopathies are seen with these disorders. IEM with liver parenchymal injury can be differentiated on the basis of associated clinical examination and laboratory tests:

Cataracts: Galactosemia, respiratory chain disorders[11]

Renal tubular acidosis with Fanconi syndrome: Tyrosinemia type I, fructosemia, galactosemia[7,11]

Dysmorphism: Peroxisomal disorders

Hypotonia: Respiratory chain disorders

4) **Cardiac disease**: Presence of cardiomyopathy may suggest a mitochondrial respiratory chain defect, a long chain fatty acid oxidation disorder, defects of carnitine metabolism or Pompe's disease (GSD-II). Congenital disorders of glycosylation (CDG) can present in the neonatal period with cardiomyopathy and / or pericardial effusion. Other features of CDG include failure to thrive, facial dysmorphism, inverted nipples and supragluteal fat distribution. Cardiac rhythm disturbances are manifestations of conditions like mitochondrial disorders. [7, 11]

5) **Hypoglycemia**: Hypoglycemia in a preterm or small for gestation infants, infant of diabetic mothers and following perinatal complications is unlikely to have a metabolic basis. But a well grown term infant with hypoglycemia that is persistent, recurrent, and severe or unexplained must be thoroughly investigated[7,11,12]. The differential diagnosis is presented in Figure 2.

Investigations for suspected IEM[4,5,6,7,12]

Once an IEM is suspected, the dictum is to investigate rapidly and systematically. Investigations for chronic disorders can be selectively chosen based on clinical evaluation. However, for acutely symptomatic infants an array of screening tests give useful information before resorting to expensive confirmatory tests (Table 5, 6 and 7). It is advisable not to delay investigations for IEM in a neonate with sepsis. Diagnostic yield and accuracy depends on collection of samples during the acute symptomatic period. Samples should be collected, stored and dispatched to the laboratory appropriately (Table 8). The laboratory should be provided a list of possible differential diagnoses. The feeds and drugs administered must be communicated to the laboratory. Results

Table 6. Interpretation of urinary screening tests

Disease	Ferric chloride	Dinitrophenyl hydrazine	Cyanide - nitroprusside	Rotheras test	Benedicts test
Phenylketonuria	+	+	-	-	-
Galactosemia	-	-	-	-	+
Organic acidemia	+	+	-	+	-
Homocystinuria	-	-	+	-	-
MSUD	-	+	-	+	-

Table 7. Diagnosis based on initial screening tests

Acidosis	Ketosis	Lactate	Ammonia	Diagnosis
-	+++	-	-	MSUD
+++	++	+	+	Organic acidemia
++	-	+	+	Fatty acid oxidation defect
+	+	+++	±	Primary lactic acidosis
-	-	-	+++	Urea cycle defects
-	-	-	-	Non-ketotic hyperglycinemia, sulfite oxidase/ molybdenum cofactor deficiency, peroxisomal disorders

can be confounded by incorrect technique of collection, inadequate amount, improper storage and transport. Results should be interpreted within the clinical context. It is not uncommon to get referral with reports incompatible with clinical features. Caution must be exercised in interpreting results when multiple tests show positive results.

Genetic counseling is a crucial aspect of management. Almost all IEM are autosomal recessive with few exceptions like ornithine transcarbamylase (OTC) deficiency, pyruvate dehydrogenase (PDH) deficiency, Hunter disease (MPS type II) and Menkes disease which are X-linked recessive. Counselling must be offered in a non-directive manner, explaining therapeutic options, prognosis, inheritance, recurrence risk and options for reproductive decision making.

Principles of treatment[5,11,12]

Initial management of IEM: If a metabolic disease is suspected, it is desirable to discuss therapeutic options with a physician conversant in the management of metabolic disease. It is ideal to transfer the baby to a tertiary care centre. In an at risk pregnancy in-utero transport is preferred. If the infant is critical, transfer can be deferred till the condition is stabilized, but immediate vigorous measures should be commenced as outlined below.

General measures: Milk (both breast and animal milk) is the source of toxic metabolites in many metabolic diseases. Feeds are discontinued immediately when IEM is suspected. Adequacy of respiration must be assessed and mechanical ventilation instituted early if required. Encephalopathy or apnea call for use of

Table 8. Sample collection for IEM

Test	Sample	Comments
MPS screen	15 ml urine 50 ml aliquot of 24 hour sample	Fresh Transport on dry ice, within 24 hrs
MPS electrophoresis	Urine 10 ml	Fresh
Urine amino acids	Urine 24 hours	Room temp, within 24 hrs
Sugar chromatography	Urine 5 ml	2 hours after milk feed
TLC for oligosaccharides	Urine 10 ml	Fresh
Plasma amino acids Qualitative Quantitative	2ml heparinised blood 2 heparinised capillary tubes Blood 3 ml heparinised Plasma 1 ml deproteinised	Preferably fasting On ice
Serum ammonia	Blood 2 ml	Collect without applying tourniquet, transported on ice and analyze immediately within 15 minutes
Serum lactate	Blood 2 ml in fluoride	Arterial sample, collected as above, transport within 30 minutes on ice,
Serum pyruvate	Blood 2 ml in perchlorate	As for serum lactate
Lysosomal enzymes	Blood 7 ml heparinised In EDTA WBC pellet	4°C, within 6 hrs Within 48 hours -20°C, on dry ice
Beutler test	Blood 0.5 ml heparinised or heparinised capillary tube	Can be stored at room temperature for a week
Biotinidase assay	2 ml plasma heparinised,	
Carnitine	Blood 3 ml heparinised	
Very long chain fatty acids	Plasma 5 ml EDTA	
Urine organic acids	10 – 15 ml 5 ml on a thick filter paper	Fresh, without preservative in an airtight container Air-dry thoroughly
Plasma acylcarnitines	Newborn screening card	Free flowing blood, without squeezing, spreading uniformly and soaking to the reverse side of the paper, allowed to air dry for 4 hours

mechanical ventilation. Infants with organic acidemia are dehydrated and require fluid replacement with volumes one and a half to twice the maintenance with an electrolyte solution in 10% dextrose. Dextrose is infused at the rate of at least 5 mg/kg/min (3 ml/kg/hr of 10% dextrose)[16]. Infusion through an umbilical venous catheter is necessary if concentration to maintain

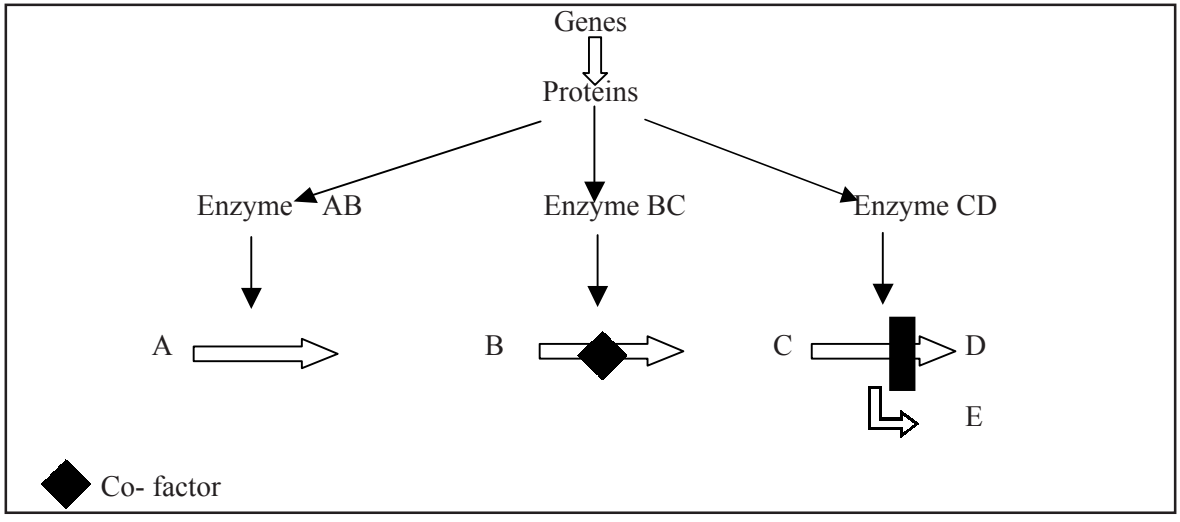

Fig. 1 Pathophysiology of IEM

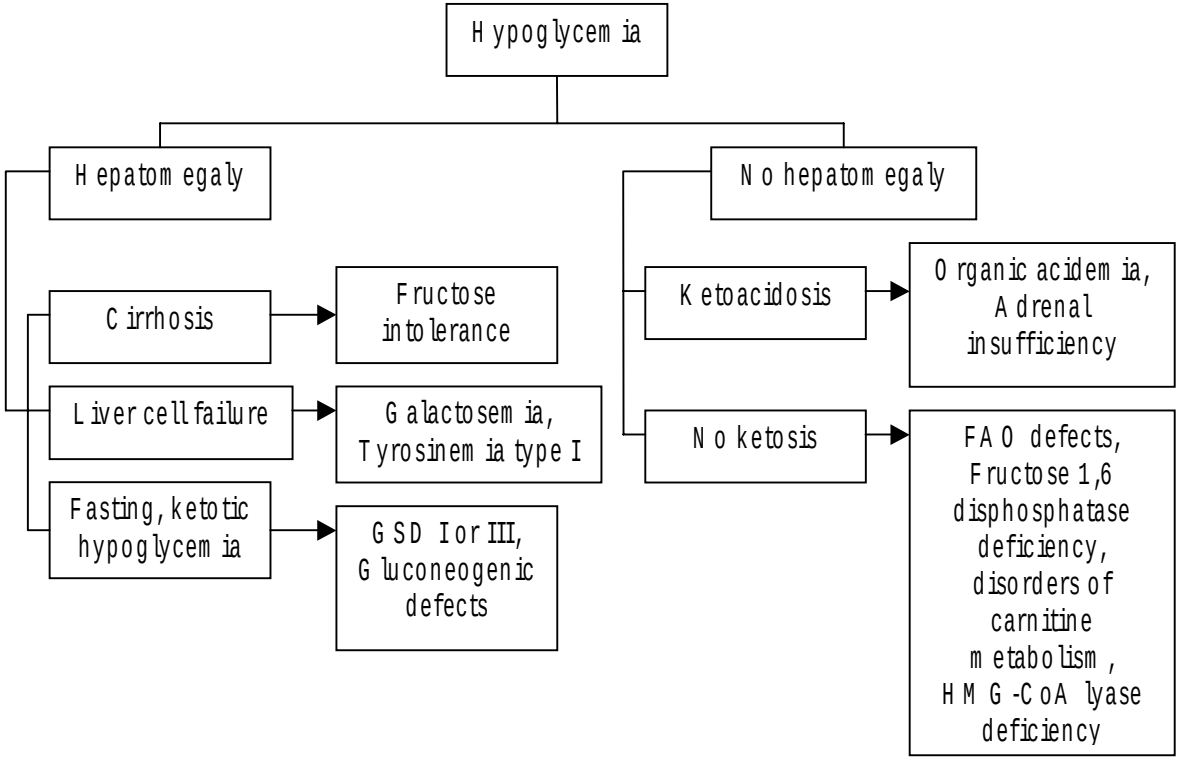

Fig. 2. Differential diagnosis of neonatal hypoglycemia due to IEM

euglycemia exceeds 10%. Blood sugar is maintained at 120 mg/dL. Overhydration is avoided as it would aggravate cerebral edema which is often present. Inotropes are used if circulatory shock is not corrected by intravascular volume expansion. Insulin in doses of 0.05 IU/kg/hr is recommended to prevent tissue catabolism. As many metabolic diseases are aggravated by tissue catabolism, higher rate of dextrose infusion may be required beyond 24 hours along with intravenous lipids. Acidosis is corrected using sodium bicarbonate in doses up to 20 – 30 mmol/kg. For scavenging ammonia, sodium benzoate is the only option easily available in India. It is given as an initial loading dose of 250 mg/kg through nasogastric tube followed by 250 mg/kg/day in divided doses. Medications alone are often inadequate and hemodialysis or peritoneal dialysis is required to remove accumulated toxic metabolites (MSUD, UCD and organic acidemias). Dialysis must be commenced without delay in neonates requiring mechanical ventilation, those who are comatosed, having cerebral edema or if ketoacidosis and/or hyperammonemia are not easily corrected. Seizures are promptly terminated with anticonvulsant therapy. Pyridoxine should be administered for intractable seizures where a cause is not evident. Carnitine (100 mg/kg/day), biotin (10 mg per day), hydroxycobalamin (1mg, intramuscular) and thiamine (600 mg/day) can be empirically administered whilst awaiting results.

The long term management of these patients involves dietary modification and avoidance of precipitating factors, special care during periods of stress, long term vitamin therapy and use of drugs like ammonia scavenging drugs for patients with hyperammonemia. Special dietary products are available from various manufacturers [Ross Metabolics (Abbott Laboratories, U.S.A), Mead Johnson (U.S.A.) and Scientific Hospital Supplies (UK)]

Points to remember

1. ***IEM manifests in the neonate as acid-base disturbance, hypoglycemia, liver disease, acute encephalopathy or cardiac disease***
2. ***Symptoms resemble sepsis and other medical and surgical illnesses and screening tests for IEM must be performed as part of initial evaluation for such disorders.***
3. ***Prompt therapy to eliminate source of toxic metabolite, correction of acid-base derangement and fluid deficit, removal of toxins and promoting anabolism must be instituted on suspicion of IEM***

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NEWS AND NOTES

12TH ANNUAL CONFERENCE OF THE INDIAN SOCIETY OF CRITICAL CARE MEDICINE

Date : 8-12th February 2006

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3. Oncology issues in ICU, transfusion therapy
4. Infectious Diseases: Newer antibiotics, minimizing resistance, complicated malaria, HIV
5. Neurology: coma, seizures, head trauma
6. Metabolic & renal issues: Dyselectrolytemias, renal failure, renal replacement therapies
7. Ethics in PICU: Management in the Indian scenario.

For details contact: Dr. A. S. Arun Kumar, Organising Secretary, Criticare, Chennai 2006, Medical Director's Office, Sri Ramachandra Medical Hospital and Research Institute, Porur, Chennai – 600 116, Tel : 044-2476 5519, Email :criticarechennai@yahoo.co.in

NEONATOLOGY

X-RAY CHEST AND THE NEONATE

**** Muralinath***

Abstract*: This article is about the role of plain x-ray in the evaluation of neonatal chest. Essential features to note in an x-ray chest along with an interpretative approach are dealt with. The focus is on the evaluation of the respiratory distress in the newborn, where plain x-ray plays a vital and key role. Basic pathology is emphasized, and how, the x-ray findings are but a reflection of the basic structural changes ensuing from the pathology is stressed and stated.*

Key words*:Neonate, X-ray chest, Interpretative approach, Respiratory distress.*

Plain x-ray of the chest plays a pivotal role in the evaluation of the newborn chest. Swischuk (1979) calls the neonatal radiograph "the right arm of the clinician". Hence it is mandatory that a clinician caring for the newborn has a basic understanding of this vital tool – x-ray chest – which will provide the clinician with a wealth of information. It is a simple and cost-effective imaging modality and above all the examination can be conducted at the bedside without altering the conditioned environment of the critically ill newborn in whom examination is often required.

In reading the x-ray of the chest, it is essential that one develops a rational and interpretative approach. The approach should be meticulous and systematic. One such approach to the neonatal chest radiograph is listed in Table 1.

Table I. Interpretative approach to Neonatal chest x-ray

Technique
Penetration
Rotation
Inspiration
Motion
Systematic approach
Extrathoracic
Abdomen
Neck
Tubes, catheters
Soft tissues
Bony thorax
Mediastinum
Thymus
Trachea and bronchi
Great vessels
Heart
Diaphragm
Lungs

To begin with, evaluate the technical adequacy of the chest radiograph. It should be adequately penetrated so that the pulmonary details are well brought out; which is essentially the vascular markings. When the penetration is adequate, the intervertebral disc spaces and the vessels posterior to the heart are seen well. The

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Table 2. Features to assess on x-ray chest in infant with suspected cardiac disease

Feature	Comment
Quality of film	Adequate inspiration
	Normal penetration
	Centred on mid chest
	Not rotated
Abdominal situs Bronchial situs	Normal/inverted/ambiguous
Aortic arch side	Left or right
Heart	Side
	Direction of apex
	Size
	Contour
Lung vasculature	Plethora
	Oligaemia
	Pulmonary venous engorgement
Diaphragm	Distinct
	Side of apex should be more caudal
Lung fields	Any pathology
Musculoskeletal	Vertebral / rib abnormalities
	Fractures

degree of rotation is evaluated by noting the distance between the centre of the vertebral bodies and the lateral aspect of the ribs – thereby evaluating the bilateral symmetry. Classically, aeration or volume of the lungs is assessed by noting the level of the diaphragm; in an adequate inspiration the diaphragm should be at the level of the 6th rib anteriorly or the 8th rib posteriorly. [Evaluation of the degree of inspiration in infants often is more a matter of experience than science]. Motion artefacts creep in if the exposure time is not short enough; either patient or respiratory motion will cause blurring of the diaphragmatic contour and pulmonary vascular markings. Each anatomic portion of the chest radiograph should then be thoroughly evaluated. Various tubes and catheters when present should be scrutinized for their appropriateness. For example endotracheal tube when present should be 1 to 2 cms above the carina or approximately at the level of T1-T2.

The routine view is the supine (AP) view of the chest. Lateral views are taken when required (eg. anterior pneumothorax).

X-ray of the chest is excellent for the evaluation of lungs, bones and soft tissues. When it comes to the heart per se its role is rather limited. As far as imaging of the heart is concerned, fetal and neonatal echocardiography are the mainstay in the antenatal detection and postnatal evaluation of cardiac disease.

However, the plain x-ray is excellent in the evaluation of the pulmonary status in cardiac disease. An approach to the evaluation of the chest x-ray in cardiac disease is appended in Table 2. Through the Plain x-ray the common observations made are:

1. The cardiac size through the CT ratio (55 to 60%). This is not very precise; the subjective evaluation through experience is a better option.
2. Gross cardiac anatomy.
3. Pulmonary status.
4. Situs.

Respiratory distress

Respiratory distress is a symptom, not a disease. Respiratory symptoms of tachypnea, retractions, nasal flaring, grunting and cyanosis in a neonate can be caused by diverse diseases such as sepsis, acidosis, anemia, central nervous system and cardiac diseases, short rib skeletal dysplasias and thoracic anomalies. The first chest radiograph is crucial for defining whether the lesion is of pulmonary, nonpulmonary

intrathoracic or extrathoracic in nature. A systematic approach to the examination (ABC'S: Abdomen, Bones, Chest, Soft tissues) is paramount.

Chest x-ray more often than not pin-points the diagnosis, and at the least, usually tells one whether pulmonary pathology is present. In this regard, it is most unlikely that significant pulmonary disease, other than lung hypoplasia with persistent fetal circulation (PFC), is present if the chest radiograph is normal. It is essential to have basic clinical information to draw the right conclusion from the chest radiograph. One of the fundamental aims in the evaluation of respiratory distress in the newborn is to establish whether the underlying cause requires medical management or surgical intervention. Radiology more often than not makes that distinction quite clear. A neonate with respiratory distress may suffer from hyaline membrane disease – HMD (a medical condition) or have a diaphragmatic hernia (a surgical entity). A simple radiograph of the chest and abdomen will bring to light, the underlying problem in a graphic manner. X-rays faithfully reproduce the structural changes; an understanding of the basic pathologic process of the disease that leads to these structural changes is the key to x-ray diagnosis. Pathology predicates radiology and radiology predicts pathology.

Some of the common medical and surgical causes of respiratory distress are discussed herewith. The aim is to highlight the basic essential facts that make the diagnosis possible on radiographic grounds with clinico-radiographic correlation.

Medical causes of respiratory distress

Hyaline Membrane Disease (HMD): This is the most common cause of respiratory distress in premature infants. The risk factors are diminished gestational age (lower the birth weight; greater the incidence), perinatal asphyxia and hypoxia and maternal diabetes. The basic pathology is lack or deficiency of surfactant. Surfactant reduces surface tension; its lack leads to difficulty in alveolar expansion. The result is poorly aerated lungs. The airway up to the periphery is distended with air. The distal airway (terminal, respiratory bronchiole and alveolar duct) is distended.

The resultant radiographic features are 1. Small volume lungs (diminished/ no air in the alveoli), 2. Granular appearance of the lungs (distended distal airway contrasted against the collapsed air spaces) and 3. Air bronchogram running to the periphery (Fig 1).

These are the basic radiographic findings that reflect the underlying pathology which results in the diagnosis. A common situation encountered is pulmonary white-out, where the lungs appear opaque. This could be due to poor aeration or pulmonary haemorrhage. In poor aeration the air bronchograms are diminished while it is not so in pulmonary haemorrhage. But what clinches the diagnosis in case of pulmonary haemorrhage is of course the froathy hemorrhagic fluid emanating from the endotracheal tube.

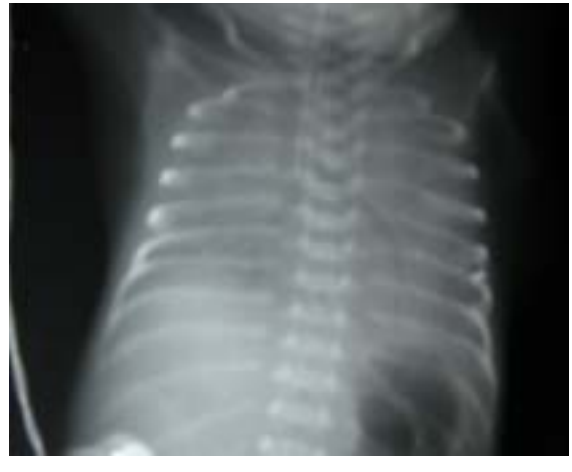

Fig 1. X-ray chest of a neonate with hyaline membrane disease

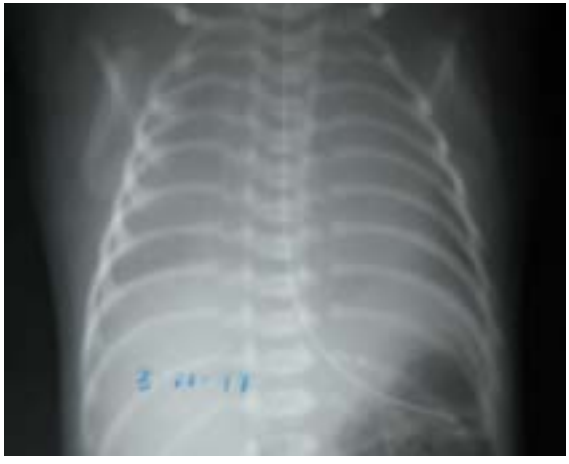

Fig 2. Transient tachypnoea of newborn

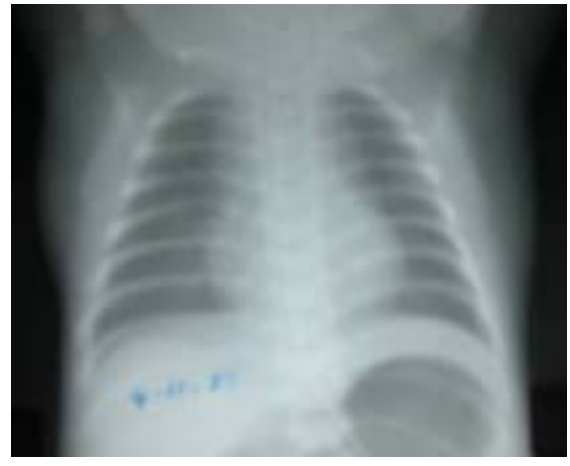

Fig 3. TTN: Clear lungs after 24 hours

Transient Tachypnea of the Newborn (TTN): TTN is the most common cause of respiratory distress in the newborn. Basic pathology is delayed clearance of pulmonic fluid. This leads to normal or large volume lungs. The fluid is drained through lymphatics and venous channels in the interstitium giving raise to stiff / less compliant lungs with streaky interstitial / vascular densities.

The radiographic features are: 1. Normal / large volume lungs, 2. Parahilar / perihilar radiating streaky densities and 3. Minimal fluid in pleural space / fissures (Fig 2). These changes usually resolve in 24-72 hrs (Fig 3).

Meconium Aspiration Syndrome (MAS): Meconium aspiration is the most common cause of neonatal respiratory distress in mature / postmature infants. This is essentially due to aspiration of meconium in to the airway and its attendant sequelae. The effect will depend on the nature of the matter (large or small particles) and the extent of involvement; which will depend on the amount and particle size - large volume, small particles will produce marked damage as they can impact distal airways to a greater extent. The result will be hyperaeration (due to compromised and narrow airway), uneven aeration (depending upon site and nature of obstruction - complete or incomplete). Because of distal airway obstruction air trapping and airleak are common. Meconium in addition to the mechanical obstruction also produces chemical inflammation (pneumonitis) and tends to inactivate surfactant. This further complicates the issue; the resulting ventilatory and vascular alterations and airleak result in hypoxaemia and acidosis. This leads to persistent pulmonary hypertension (PPHN). There are no specific imaging findings for PPHN. Since the severity of PPHN is the major prognostic determinant, it is no surprise that the radiographic severity of the disease may not correlate with the clinical picture.

The radiographic picture in MAS is 1.Bilateral hyperaeration, 2. Uneven aeration (because of atelectasis and focal hyperaeration) leading to heterogeneous opacities (Fig 4) and 3. Airleak (Commonly – pneumothorax).

Neonatal pneumonia

Here a high index of clinical suspicion is the key to the diagnosis. The radiographic findings are quite varied and often non-specific. The radiographic signs of neonatal pneumonia are quite non-specific and tend to mimic or blend

in with other diseases of the neonate. They may produce strand-like opacities from the hilum, resembling TTN or aspiration syndromes. They may produce patchy infiltrates or diffuse reticulonodular densities throughout the lungs. Group B streptococcal (GBS) is the most common offending organism in neonatal pneumonia. GBS pneumonia has a propensity to resemble HMD. The only difference is, HMD has small volume lungs as opposed to GBS pneumonia which has normal or large volume lungs. A peculiar complication of GBS pneumonia is delayed right sided diaphragmatic hernia. The pathophysiology of this association is not known. As stated earlier a high index of suspicion and corroboration through other laboratory parameters is required to draw the right inference.

The advent of mechanical ventilation brought about a sea-change in the management of respiratory distress in the new born. Mechanical ventilation is certainly a blessing but the curse is airleak and chronic lung injury. It is again the X-ray chest that documents and brings it to light.

Airleak: The pathophysiology is that the amount of pressure needed to adequately ventilate the lungs may lead to rupture of alveoli and terminal bronchioles. The air then moves into the interstitium pulmonary interstitial emphysema (PIE). It may then track along the bronchovascular sheath and lead to pneumomediastinum when it tracks medially and pneumothorax when it tracks peripherally. This air may also track along the vascular sheaths medially to produce pneumopericardium. Pneumomediastinum may track cranially to become subcutaneous emphysema or it may track caudally to become retroperitoneal and then intraperitoneal – pneumoperitoneum. Air may enter the vascular channels to produce air embolism. All these manifestations can be

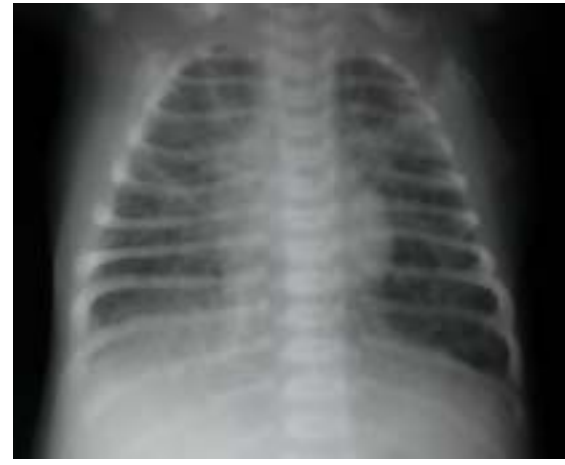

Fig. 4. Meconium aspiration syndrome

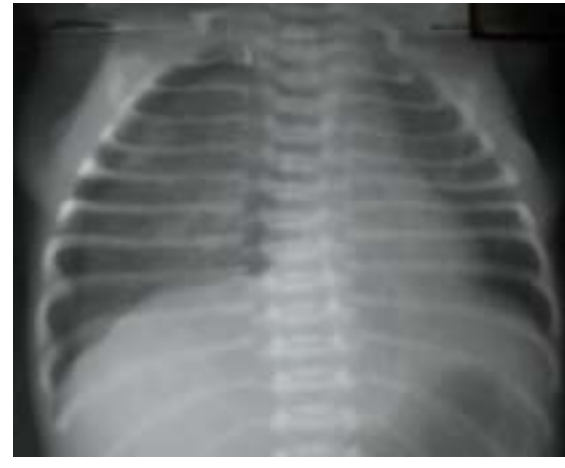

Fig. 5. MAS / Pneumothorax right

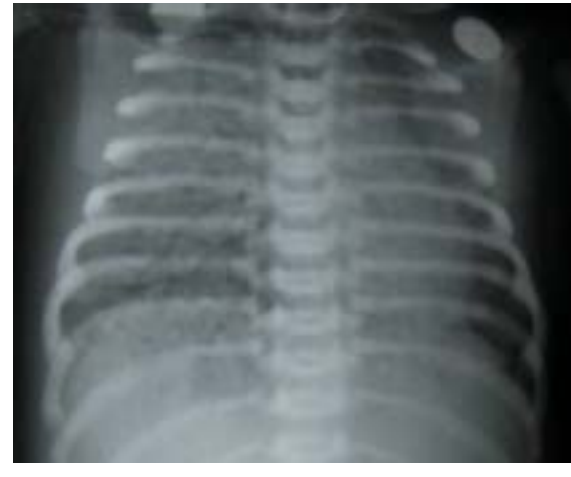

Fig.6. Pulmonary interstitial emphysema

detected by the plain x-ray study.

Pulmonary Interstitial Emphysema (PIE): This appears like tortuous, wormy, beaded or nodular lucencies and they tend to radiate from the hilar region. This is air tracking along the bronchovascular sheath of the lung (Fig 6).

Pneumomediastinum: Mediastinal air lifts the thymus away from the heart. When it is beneath the heart, the "continuous diaphragm sign" is seen. Extension into the neck produces subcutaneous emphysema (Fig. 7).

Pneumothorax: On the affected side the distinct lateral margin of the collapsed lung is seen. Black air-filled space devoid of lung markings is seen lateral to that. Anterior pneumothorax is diagnosed by noting subtle hyperlucency on the affected side and the sharp delienation of the cardiac and mediastinal silhouette on that side.

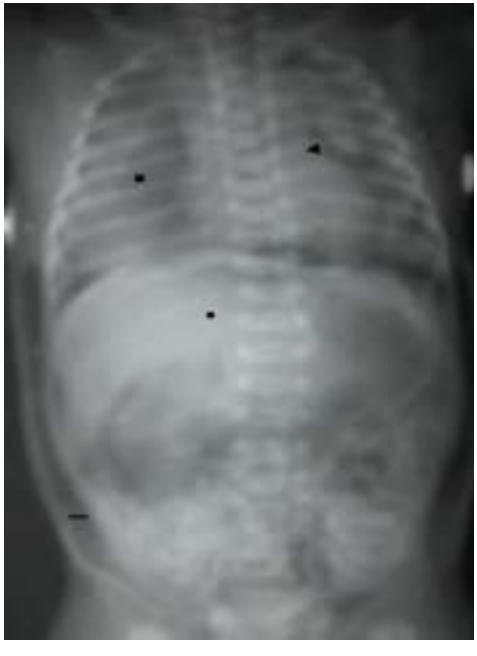

Fig. 7. Air leak in C & R
◢ Pneumomediastinum, ■ pneumothorax,
● pneumoperitoneum and
– subcutaneous emphysema

Pneumopericardium: Defined by air surrounding the heart and delimited by the surrounding pericardium.

Pneumoperitoneum: Air in the peritoneal cavity increases the transradiancy of the abdomen, diminishes the hepatic density and outlines the falciform ligament – "foot ball sign".

Chronic lung disease (CLD)/
Bronchopulmonary Dysplasia (BPD)

CLD in infancy is a consequence of the improved survival of both preterm and term neonates with diseases that require prolonged ventilation. The most encompassing and generally accepted definition of CLD is that of a neonate with radiographic evidence of lung damage (disease) and a need for oxygen at 36 post conceptional weeks. The paradox one has to face in this situation is that the events that cause lung damage increase the need for ventilation and prolonged ventilation increases the lung damage. The classic radiographic picture of CLD is bilateral hyperaeration with scattered, coarse linear densities and cyst like lucencies. These findings represent air trapping, interstitial fibrosis, atelectasis and emphysema (Fig 8).

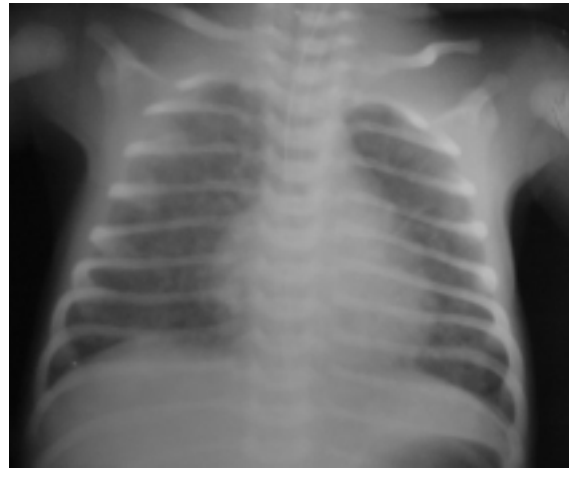

Fig. 8. Chronic lung disease / BPD

Surgical causes of Respiratory distress

With the advent of antenatal ultrasound many of these established pathologies will be detected before hand. However, in most cases the diagnosis will be confirmed (or made) after birth because of respiratory distress.

Diaphragmatic hernia

Types: 1. Postero lateral – hernia of Bochdalek.
2. Anterior – hernia of Morgagni.
3. Central tendon defect.

Present discussion is confined to the hernia of Bochdalek which is commonest type, presenting in the neonatal period causing respiratory distress.

The radiographic picture is but a reflection of the underlying pathology - herniated bowel in the thorax, through the defect in the diaphragm. Left side is commonly affected. The radiographic findings are cyst like lucencies (bowel) in the hemithorax, contralateral shift of the mediastinum and paucity of bowel gas in the abdomen. The placement of an NG tube will help in localizing the stomach (Fig 9). This is of immense value in the differential diagnosis from eventration of diaphram.

It is worthwhile to remember that diaphragmatic hernia is a syndrome – a syndrome of hernia, pulmonary hypoplasia, lung immaturity, left heart hypoplasia and persistent pulmonary hypertension. Consider this fact in the evaluation and management of diaphragmatic hernia.

Eventration: This condition is made out by delineating the elevated (eventrated) dome and the viscera lying subjacent to it. On the left side, the stomach will be seen immediately beneath and on the right side, the liver. Placement of an NG tube helps in the localization of the stomach (Fig 10).

Congenital Cystic Adenomatoid Malformation (CCAM): Three types of CCAM are described radiographically.

a) Type I (50%) Single or multiple large cysts.

b) Type II (40%) Multiple small cysts. Has congenital anomalies and has associated malignancies.

c) Type III (10%) Appears solid with microscopic cysts. Of the three types Type I has the best prognosis.

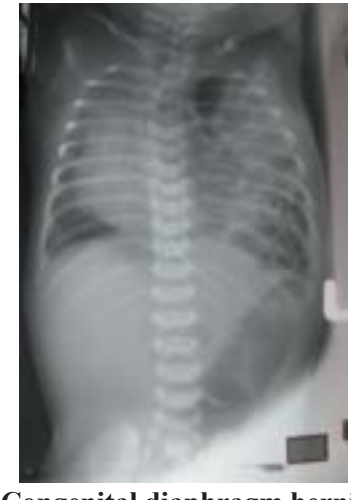

Fig. 9. Congenital diaphragm hernia

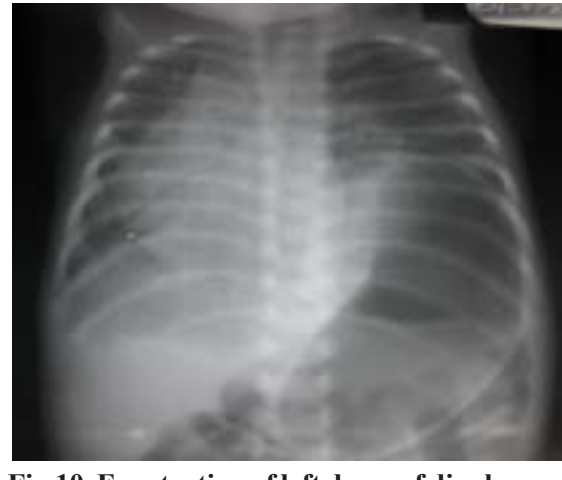

Fig.10. Eventration of left dome of diaphragm

The radiographic picture is that of cystic lucencies in the hemithorax. Radiographic findings in CCAM are cystic mass (90%), single lobe and unilateral (>95%). It is rare in right middle lobe. When CCAM is large it produces contra lateral shift of medaistinum. This may mimic a diaphragmatic hernia. The differentiating feature is defined diaphragm and normal complement of bowel loops / gas in the abdomen (Fig 11). Type III may present as opaque hemithorax.

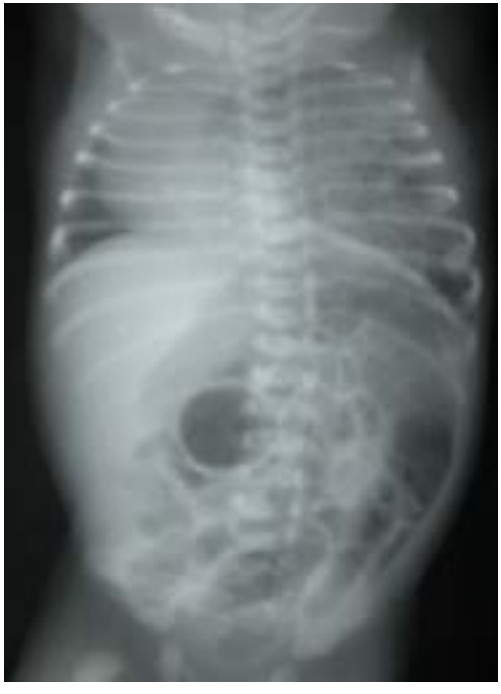

Fig.11. Congenital cystic adenamatoid malformation

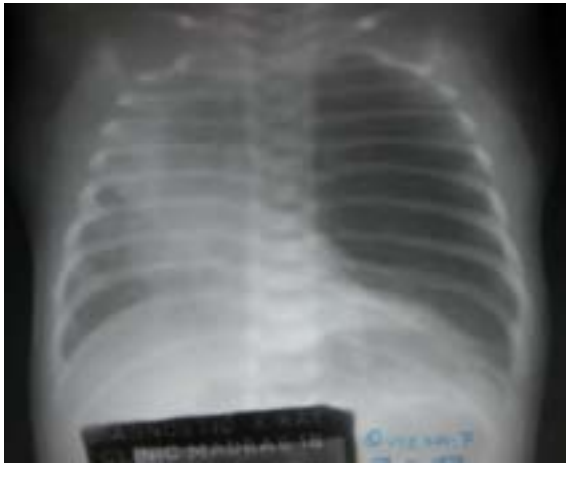

Fig.12. Congenital lobar emphysema

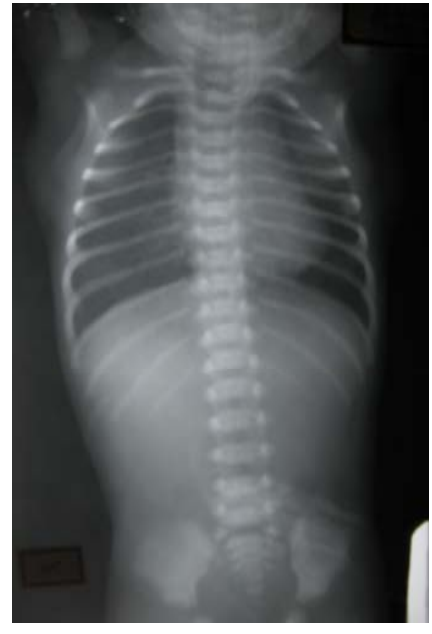

Fig 13. Oesophageal atresia

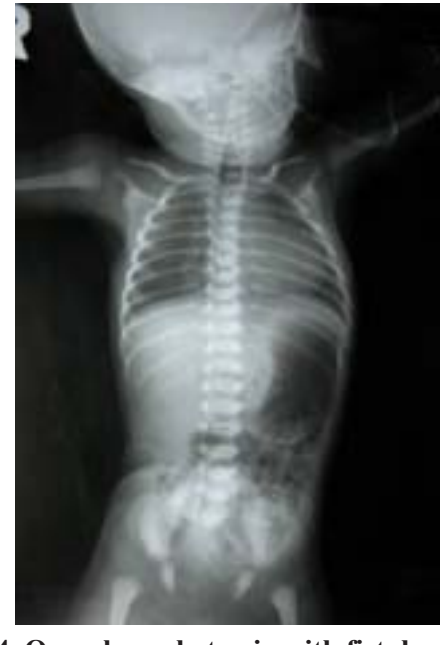

Fig.14. Oesophageal atresia with fistula

Congenital Lobar Emphysema (CLE): CLE is a constellation of clinical findings in a neonate with specific imaging characteristic. It is a symptom complex and not a specific disease. An etiology is identified in only 50% of cases. The lobes commonly affected are the left upper lobe, right middle lobe and the right upper lobe – in that order. Occasionally two lobes may be involved (left upper lobe and right middle lobe).

The radiographic picture of the affected lobe will depend upon when the film was taken. When taken early – before the pulmonic fluid is expelled – the affected lobe will appear like an opaque mass; after the expulsion of the fluid the classic emphysematous picture evolves.

The findings consist of : 1.Enlarged fluid or air filled lobe of the lung – all become air filled within days, 2. Compressive collapse of adjacent lobes, 3. The lucent area shows spaced out thin pulmonary vessels, 4.Contralateral shift of mediastinum and / or herniation of the lobe across the midline (Fig 12).

Oesophageal Atresia with or without fistula

Radiographic picture will depend upon the type. In oesophageal atresia without fistula a gasless abdomen is seen with the upper blind pouch filled with air. NG tube will be seen to coil in this pouch (Fig 13). In oesophageal atresia with fistula (the commonest type where the lower pouch communicates with the trachea) gas filled bowel loops will be seen along with the coiled tube in the upper pouch (Fig 14).

Evaulation of tubes and catheters

The study can be utilized for the evaluation of catheters and tubes placed (Fig 15a, 15b, 16 & 17).

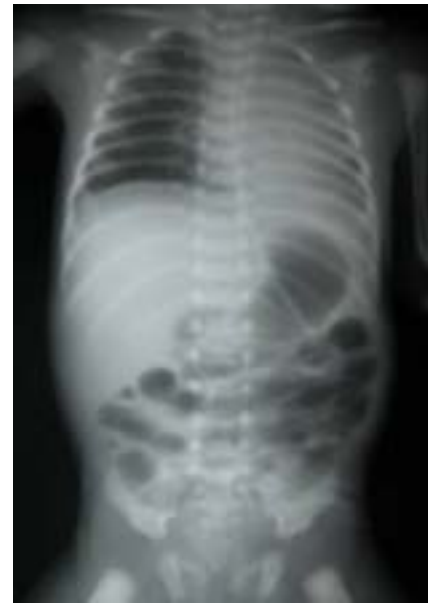

Fig.15a. ET tube low – underaeration left

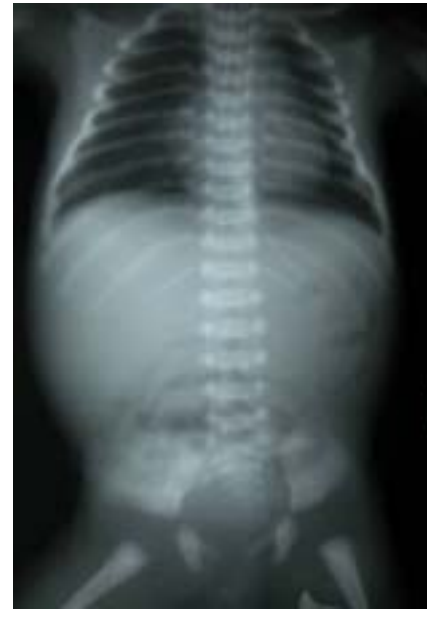

Fig 15b. Tube repositioned - even aeration

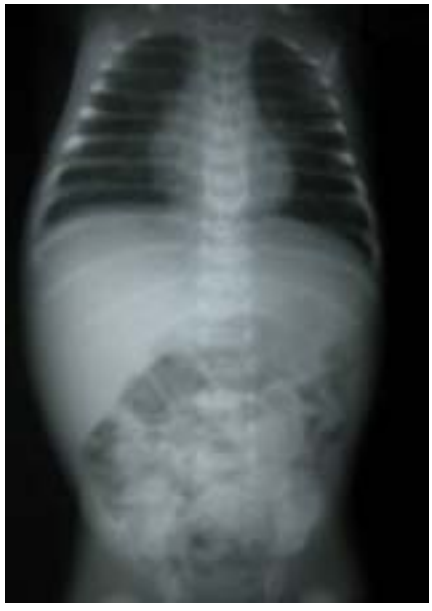

Fig.16. Coiled NG tube in oesophagus

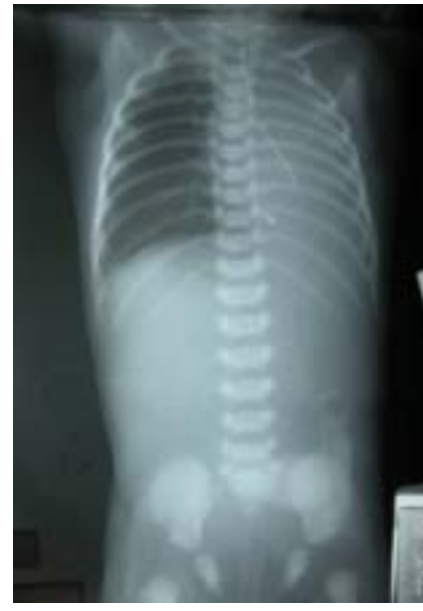

Fig.17. NG Tube in left main bronchus

Key points to remember

1. ***A systematic approach to x-ray interpretation is essential.***
2. ***An understanding of the basic pathology (which leads to the structural changes) of the disease is the key to Roentgen diagnosis.***
3. ***The first and mandatory imaging study to be done in the evaluation of respiratory distress is the x-ray of the chest.***

NEWS AND NOTES

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ADOLESCENT PEDIATRIC CHAPTER OF IAP AT KOLKATA (ADOLECON 2005) ON
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Correspondence: **Dr.Sukanta Chatterjee**, HOD Ped. CMC Kolkata, Organizing Secretary, Adolecon 2005, 889A, Lake Town, Kolkata – 700 089. Tel-fax 033-22198118(O), 25345909 ®, 09830275685 (M). Email: adolecon2005@rediffmail.com

NEONATOLOGY

FREQUENTLY ASKED QUESTIONS IN NEONATAL OFFICE PRACTICE

1. What is the normal pattern of urination and passage of stools in the newborn?

Babies pass urine immediately after birth and a little urine in the next 24-36 hours. Thereafter they pass 40-60 ml of urine/kg/day or a minimum of 6 times per day.

Babies usually pass meconium immediately after birth, which is dark, sticky green material composed of bile, intestinal secretions and amniotic debri. Most of them pass meconium within 24 hours (but this may be delayed in preterm babies). By 2-3 days transitional stools, which is a mixture of meconium and normal stools are passed. Once breast feeding is established they pass golden yellow, soft stools with every feed.

2. How long can a newborn sleep? Can he recognize the mother when awake?

Baby has irregular sleep wake cycles and sleeps for up to 18 hours in a day with 50-60% of sleep being REM sleep. Circadian rhythm is detectable in heart rate and body temperature by 1 month of age.

A neonate prefers familiar face of a human being to scrambled shapes or structure. He recognises his mother using the sense of hearing and smell.

3. How to assess the adequacy of weight gain in the newborn?

All babies should be weighed at birth. The baby loses weight for the first few days. Weight loss is usually 4-7% and should not exceed 10-12% of the birth weight. From 1 week of age a normal baby should gain weight at the rate of 20-30 g/day in the initial three months.

4. What is the best advice for mother regarding feeding ?

Mother is motivated and encouraged to give exclusive breast-feeding only. She is also advised not to give pre-lacteal feeds, pacifiers, bottles or other indigenous preparations and to exclusively breast feed on demand for 6 months. Successful breast-feeding prevents hypoglycemia and other metabolic problems in the babies

5. How frequently should a baby be fed?

Generally newborns have to be fed on demand. Healthy neonates feed 10 or more times in a day. Two or three hourly feeding schedule should not be imposed. Topping with other feeds before the next feeding time will result in failed lactation.

6. How long should the baby be fed?

Baby should be put to the breast until he has completed and is satisfied. This usually takes 7-10 minutes. Once lactation is established a baby gets most of the milk in the first 4-6 minutes. Sucking longer than this is therefore is of non-nutritive value. The baby should be offered the other breast once a breast is completely empty

7. How do we assess if the baby is getting sufficient milk?

A baby who sleeps for 2 hours at a stretch, has well formed golden yellow semisolid stools, voids urine at least 6 times a day, appears content and gains adequate weight is considered to have adequate breast milk. Babies on breast milk judge their own intake and only if the weight gain is unsatisfactory should some assessment of intake be attempted.

8. What are the reasons for a baby not feeding well?

If the baby is well, the common causes are prematurity, difficult delivery, sedated due to intrapartum or postnatal sedation. It may also be due to poor attachment (Latching) at breast and due to poor positioning.

9. What are the common causes for frequent crying in the newborn?

Persistent crying in the neonate is usually due to hunger but can also be due to pain, boredom and discomfort. Painful conditions include otitis media, intussusception, bone and joint infection and incarcerated hernia. The common myth of 'wind' or insufficient milk should not be accepted.

10. Does passing of wind indicate colic?

The bottle fed baby will always swallow some air with each feed compared to the breast fed baby. Positioning the baby upright helps to burp the baby.

Infantile colic occurs in the late neonatal period. Its etiology remains a mystery although food allergy, lactose intolerance and GERD are thought to be predisposing factors. Maternal stress may play a role. Switching over to bottle feeds will not help. Reassuring the mother regarding the benign nature of the condition is helpful.

Relaxed mother, proper positioning of the baby, prokinetics and antispasmodics have been advocated.

11. Whydo babies have hiccups?

It occurs due to rhythmic clonic contraction of the diaphragm. It usually occurs immediately after a feed due to distension of stomach and irritation of diaphragm. Faulty feeding technique and aerophagy often produce hiccup. Burping the baby and proper advice regarding feeding must be imparted to all mothers.

12. When does the umbilical cord fall? How do you take care of the umbilicus of a baby?

The umbilical cord usually falls in one week and epithelializes by 2 weeks. The umbilical stup should be kept clean and dry without any local applications either indigenous or commercial. Scanty bloody discharge for a day or two is common. Persistent bleeding should be evaluated for coagulation disorders, while persistent discharge should be evaluated for patent vitello intestinal duct or urachus. If a granuloma is present, it can be cauterized by topical coppersulphate crystals or the commonly available rock salt.

13. When a baby feels warm, does it mean he is febrile? What is the approach to a febrile neonate?

If the body feels warm it need not be fever, however if the measured body temperature shows a rise, it could be either due to infection or dehydration secondary to environmental causes. Inadequate intake with a weight loss of more than 10% resulting in dehydration may result in fever.

If dehydration is the cause, serum osmolality, is increased to 310 mOsm/L. This should be managed by increasing oral feeds and nursing the baby in a cool environment.

14. Is vaginal bleed in the newborn normal?

Vaginal bleeding is common and it occurs in 25% of female neonates and macroscopically visible in 3.3% of babies. It is due to maternal hormonal withdrawal and needs to be investigated when persistent.

15. What are the common eye changes seen in the newborn following vaginal delivery?

Retinal and subconjunctival hemorrhages are commonly seen after vaginal delivery. They result from increased venous congestion and pressure during delivery. Retinal hemorrhages usually resolve within 1-5 days. Subconjunctival hemorrhages resolve within 1-2 weeks.

16. What is the management for the watering of eyes in the Newborn?

It is enough to instruct the mother to massage the duct by firm pressure (several times a day) over the medial angle of eye (Lacrimal duct area). If infection occurs, it can be kept under control by antibiotic eye drops or ointment.

17. How to treat noisy nasal breathing in newborn?

Snuffles (makes sniffing sounds / breaths noisily). A nasal discharge following a spell of crying is common in early infancy. For unknown reasons, some babies in the first 2 to 3 months have a mucoid nasal discharge, which, although unpleasant to see, is harmless. It is apparently non infective and non allergic. No treatment is required as it clears up spontaneously.

18. How to manage enlargement of breast in neonates?

Breast enlargement of varying degrees is seen in 80% or more of full term infants of both sexes, starting 2 or 3 days after birth and reaching a peak in the second week. It may be asymmetrical. Milk secretion may occur by 7 days of age. The breast enlargement is presumably related to the estrogen received from the mother via the placenta. No treatment is indicated and massage of the breast should be avoided. Prolonged enlargement could be due to exposure to estrogenic substances.

NEWS AND NOTES

MAHA NEOCON 2005, AURANGABAD

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DERMATOLOGY

CUTANEOUS MANIFESTATIONS OF VIRAL INFECTIONS IN CHILDREN

**** Criton***

Abstract*: Viral infections in children are seen frequently. The significance lies mainly in differentiating a viral exanthem from a drug rash. Many viral infections challenge all forms of therapy.*

Key words*: Viral infections, children*

Prompt diagnosis of viral infections of children is important in many ways; 1.It prevents morbidity and mortality and can avoid unnecessary investigations and treatments 2. It helps in preventing spread of the infection in the community 3. It helps to introduce prompt and appropriate treatment at least in some of the serious infections. So a working knowledge of various viral infections is essential for those who are engaged in patient care. Moreover the skin lesions that are formed during the course of illness or in the beginning of infection may be specific at certain situations so that a proper diagnosis may be made by the examination of skin lesions alone.

Viral infection may affect the skin by three different routes; direct inoculation, systemic infection or local spread from an internal source.

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Viral exanthems

In majority of situations the viral exanthems are self limiting and no aggressive treatment is required. However, knowing these diseases are important to anticipate complications, to decide when and where to intervene and prognosticate. Childhood exanthems are non-specific and cannot be accurately ascribed to an etiological agent. Exanthems may be morphologically classified into erythematous, vesicular and papular types; occasionally there may be pustules and petechial lesions. The erythematous exanthems are the most common. This is distributed diffusely on the trunk and extremities. They can occur any time and in general, those occurring during winter months are caused by respiratory virus and those occurring in summer months are caused by enteroviruses.

Measles(Rubeola)

Measles starts with a prodrome of fever, nasal congestion, cough and rhino conjunctivitis. Photophobia is more common with adolescents. A transient macular or urticarial rash has also been described early in the prodrome. The Koplik's spot, the characteristic enanthem usually presents in the prodromal phase and appears as punctate white-gray papules on a red background. They begin on the buccal mucosa, opposite lower molar teeth and often spread to involve other parts of mucosa[1]. The exanthem occurs over 2-4 days after the prodrome. It begins at the hairline and behind ears and spread centrifugally and in a cephalo caudal direction. Lesions begin as discrete erythematous macules and papules and gradually coalesce. By the third day of rash, the

entire body is involved. Pruritus is not a prominent symptom. Usually by 4th day the rash begins to fade, in the same order as it appeared. Fever persists through the second or third day of the rash and then falls. Persistence of fever after the onset of exanthem may suggest complications[1]. Associated with these findings generalized lymphadenopathy and splenomegaly can occur.

Modified measles occurs in individuals with pre existing partial immunity. This is usually seen in infants less than 1 year who possess maternal antibody to measles and those who have received exogenous immunoglobulin. The symptoms of this clinical syndrome are characterized by shortened prodrome, less severe symptoms and prolonged incubation period[2,3]. The presence of Koplik's spot is variable and skin eruption is usually less confluent.

Atypical measles has been reported in recipients of killed measles vaccine, which was used from 1963 to 1968, who later come in contact with wild type measles virus. This is characterized by high fever, myalgia, cough, headache and abdominal pain. Coryza and conjunctivitis are absent. The rash begins more distally, concentrated on ankles, wrist and creases. The morphology of exanthem is variable including vesicular, purpuric, petechial and scarletiniform lesion[4] Sometimes there may be haemorrhagic lesions.

Following measles vaccination a less severe exanthem similar to classical measles exanthem may develop in certain people and known as measles vaccination exanthema. Management is mainly supportive.

Rubella

Rubella also known as German measles, may be asymptomatic in majority. In others, disease presents with a mild prodrome occurring 1-5 days prior to onset of rash. Prodromal symptoms are more common in adolescents and young adults.

The exanthem in rubella is a generalized, erythematous macular and papular eruption with a variable progression[1]. It usually progresses downwards to the trunk and then the extremities. The full expression is usually apparent by 24 hours after its onset and begins to fade in a day or two in the same order of distribution in which it appeared. The eruption is completely absent by third day. Generally the rash consists of discrete pink macules and papules which may become confluent with a morbilliform appearance or it may at times appear scarletiniform. An erythema infectiosum like rash is also described in rubella[5,6]. An exanthem characterized by erythematous and petechial macules on the soft palate (Forscheimer's spots) may also be present[7].

Occipital, posterior auricular and posterior cervical lymphadenopathy is a consistent finding in rubella. It appears during the prodromal period and become prominent during the period of exanthem. The complications are not usual. However, joint involvement as evidenced by arthralgia and arthritis can occur in majority. Other less common complications include encephalitis, myocarditis, pericarditis, hemolytic anaemia, thrombocytopenic purpura and hepatitis.

Treatment is supportive. Prevention is best achieved by vaccination.

Congenital rubella syndrome (CRS): The features in CRS may be grouped into three such as (1) transient, (2) permanent and (3) developmental. The transient abnormalities disappear in a few months from birth, such as thrombocytopenic purpura or hepatitis, the permanent defects persist and include congenital

heart disease, cataract, hearing loss and the developmental group will have defects appearing later in life such as behavioural disorders and endocrine malfunction.

There are a few cutaneous findings as well. These include "Cranberry muffin" lesions characterized by soft 2 to 20 mm raised, erythematous, spongy lesions which later become more classical "Blueberry muffin". In addition petechiae, purpura, morbilliform rash, reticulate erythema of face and acral areas, facial seborrhoea, hyperpigmentation of face and other parts of body, cyanosis, dermatologlyphic changes, leucocytoclastic vasculitis, localized scleroderma are some other not so common manifestations[8].

No specific treatment exists for rubella infection during pregnancy; so also for CRS[1]. Hence it is important to prevent rubella infection by proper immunisation.

Erythema infectiosum

Erythema infectiosum (EI) is otherwise known as "fifth disease", slapped cheek disease. It is caused by human parvovirus B19[1].

The most well known dermatologic manifestation is described as "slapped cheek". This is characterized by bright red macular erythema on either or both cheeks. There is a rim of sparing around mouth. As the disease advances, a generalized eruption occurs. It appears first on proximal extremities and then spreads to the trunk. This is characterized by lacy, reticulate erythema. The palms and soles are spared. Pruritus is also present along with rash. This rash lasts for 3 to 4 weeks with waxing and waning in intensity.

Papular purpuric glove and socks syndrome is another characteristic rash seen in infection with parvovirus B19. The typical features include acral purpuric erythema, occasionally associated with fever and oral lesions. The rash starts as symmetric erythema and edema of the hands, fever with gradual progression to petechiae and purpura. One of the clinical hall marks of the rash is the sharp demarcation on the wrists and ankles. The rash is typically painful. Mucosal involvement such as oral erosions, petechiae and edema of lips, buccal mucosa and palate can also occur.

The treatment of EI is mainly symptomatic. One advance in the treatment of EI in immunocompromised patient is the use of intravenous immunoglobulin (IVIG).

Roseola (Exanthem Subitum)

Roseola is a common exanthematous illness of infancy and young child. It is characterised by high fever of 3-5 days and the appearance of skin rash after defervesence. Roseola is caused by HHV-6, a double stranded DNA Virus.HHV-7 is also implicated in the etiology of this disease[9]. Majority contracts infection during the infancy; between 6 months to 3 years of age.

Hand-foot- and- mouth disease (HFMD)

This is caused mostly by coxasakie A_1b infection. But it may also be due to a variety of other entero viruses such as coxasakie virus A 5,A7, A9, A10, B1, B2, B3, B5 and enterovirus 71[10,11]. The incubation period is 4-6 days and is highly contagious[12]. After a brief period of prodrome, the characteristic enanthem develops which is followed shortly by exanthem.

The enanthem of HFMD consists of vesicles that rapidly rupture to leave behind erosions and ulcers superimposed on an erythematous base. They are usually 4-8 mm in size and occur most commonly on buccal mucosa and tongue, as well as palate, uvula, and anterior tonsillar pillar[12].

The exanthem is vesiculopustule ranging from 3 to 7mm. They are characteristically seen on palms and soles. It is also seen on the buttocks and perineum. This may be associated with submandibular or cervical lymphadenopathy[12]. There is no specific treatment for HFMD.

Herpes simplex virus (HSV) infections

The name herpes is derived from the Greek word meaning 'to creep'[13]. There are two antigenic types of HSV, type 1 and 2. Though HSV1 and 2 can affect any cutaneous site, HSV2 is more frequently associated with genital infection.

The highest rate of HSV infection is in the first 5 years of life. Most children will be asymptomatic or have a trivial illness following exposure to HSV infection. About 50% of children will develop HSV antibody by the age of 5 and 95% will develop antibody by 10 years of age.

Clinical features: The clinical features depend on whether the infection is primary or recurrent. The primary infection includes herpetic gingivostomatitis, herpes genitalis, keratoconjunctivitis and inoculation herpes simplex. Recurrent infection occurs in orolabial and perilabial sites as well as in genitalia.

Primary herpetic gingivostomatitis: This is the commonest clinical manifestation of primary HSV infection in children. The infection starts with fever and malaise which is followed by appearance of vesicles. The fever is high grade. The vesicles occur on the lips, gingivae, palate, buccal mucosa, pharynx, larynx and tonsils. These vesicles later transform into shallow ulcers with yellow exudative base and an erythematous halo. The lesions may coalesce also. Associated tender lymphadenopathy is also present. The gingiva may be swollen and may bleed. Fever may persist for 2-7 days and ulcers recover completely in 2-3 weeks.

Recurrent herpetic gingivostomatitis: The lesions are seen on the lips. The commonest affected site is the mucocutaneous junction of lips. The recurrent lesions are less severe, more localized and heal rapidly.

Herpes genitalis: This is usually caused by type 2 HSV, transmitted through sexual route. Most children with HSV genital infection are adolescents and acquire it after the onset of sexual activity[14]. Younger children may acquire infection through autoinoculation, exogenous inoculation from care given, usually a parent, close non sexual physical contact and sexual abuse[15,16,17].

In HSV seronegative individuals primary HSV infection is severe. Symptoms may be more in females than in males due to the wider area of involvement in the former. Initially one or more prutitic papules develop and then it turns into vesicles which in turn form shallow ulcers which crust. The symptoms include fever, malaise, dysuria, discharge per vaginum, etc. The illness lasts for 2-3 weeks and settles on its own provided there is no secondary bacterial infection.

Recurrent herpes genitalis: This is not very common in children. They are of shorter duration and less severe. The lesion is heralded by prutitus or tingling sensation at the site of involvement, which is soon followed by vesicles. These vesicles rupture easily and crust and then heal in 5 to 7 days.

Keratoconjunctivitis: Primary infection of the eye causes severe and often purulent conjunctivitis with opacity and superficial ulceration of the cornea[18]. The eye lids are edematous and there may be vesicles on the surrounding skin[18]. The preauricular gland enlarges and becomes tender.

Inoculation herpes simplex: Direct inoculation of the virus into an abrasion or into normal skin gives rise to indurated papules, large bullae or irregularly scattered papules and vesicles. The regional nodes are enlarged and tender but fever and constitutional features are usually mild. Inoculation of finger tip usually results in herpetic whitlow.

Complications: A number of complications are seen following HSV infection. These include eczema herpeticum, erythema multiforme, Bell's palsy, recurrent lymphocytic meningitis and encephalitis.

Diagnosis: The history and physical examination is often sufficient for making a diagnosis. However in atypical forms a clinical diagnosis is often difficult. The gold standard of diagnosis is viral culture. Tzanck smear examination is another method for diagnosis in which multi nucleated giant cells are seen in the smear. Detection of viral DNA by PCR is also useful but not commonly used in clinical practice. Serological testing for type specific antibodies is another useful method of diagnosis.

Treatment: Early diagnosis and rapid initiation of antiviral therapy are essential for effective treatment of HSV infection. Mild uncomplicated eruptions need no treatment. In severe primary infection and frequent recurrences antiviral therapy is instituted.

The antiviral drugs used in the treatment of HSV infection are acyclovir, valaciclovir and famciclovir. All these drugs are effective and safe in the treatment of HSV infection. The virus is now showing significant resistance to acyclovir. However, in case of viral resistance foscarnet may be used. Cidofovir is another alternative.

Other than antiviral agents, immune modulators are promising in the treatment of HSV infection. The newer drugs like imiquimod and resiquimod, which cause local release of cytokines and enhances antigen presentation, have shown promise in treatment of herpes genitalis[19]. A 10 minute application of zinc sulphate 0.025 – 0.05% in water to the expected site of the herpes, repeated 2 to 4 times per month, has been reported to prevent recurrent eruption previously associated with erythema multiforme[20].

Eczema herpeticum (EH): EH may be defined as an acute disseminated herpes simplex virus infection in a patient with atopic dermatitis. EH is usually a primary infection in children. It occurs in all age group of children but more common with children of age 2-3 years. There is no seasonal variation in the incidence of EH.

Clinical features: Usually presents as sudden deterioration of child's eczema. Vesicles are the most common lesion; but papules, crusted lesions and punched out ulcers can also occur. Lesions may be either discrete or confluent and tends to occur in crops. Any cutaneous site may be affected; some of the vesicles rupture and ooze. The signs of EH are usually subtle and include fever, vomiting, anorexia, diarrhea, etc. Secondary bacterial infection may occur. Treatment should start early to avoid serious complications. Here again treatment is with anti viral agents – such as acyclovir and valaciclovir. Severe cases are best treated with intravenous acyclovir. The undercurrent bacterial infection must be tackled in its own merit, so also the underlying eczema.

Neonatal HSV infection: Neonatal HSV infection occurs in three clinically recognizable syndromes such as 1. disseminated infection 2. infection localized to skin, eye or mouth and 3. CNS infection. All these will have skin involvement which may be minimal or severe. Neonatal HSV infection tends to manifest within

the first four weeks of life and most commonly within the first week[21]. Upto 30% of infected new borns will have symptoms on the first day of life itself[22].

The infection may manifest with cutaneous or mucosal lesions, with or without signs of sepsis or encephalitis[23]. The skin lesions appear as small, 2 to 4 mm vesicles, with surrounding erythema, often in herpetiform clusters. The skin lesions usually occur on the part of the body in prolonged contact with cervix. These lesions either disseminate or settle by itself. These vesicles may become necrotic and ulcerate. Skin lesions are present in most neonates with disseminated disease (77%) and in 60% of infants who present with CNS disease[23]. The treatment of choice in neonatal herpes infection is acyclovir administered intravenously, regardless of clinical presentation[24] But oral acyclovir will be sufficient for disease limited to skin alone (personal data).

Varicella and zoster infections

Varicella and zoster are caused by the same virus, herpes virus varicella. Varicella occurs throughout the world and transmitted by droplet infection. Patients are infectious from about 2 days before to 5 days after the onset of the rash. Varicella infection confer lasting immunity and second attack is uncommon. Maternal varicella in the first 20 weeks of pregnancy is associated with an approximate 2% risk of fetal damage, including death of the fetus[25]. Maternal zoster during pregnancy is not associated with intrauterine infection[26,27]. Zoster in infancy has followed maternal varicella and the primary infection has occurred in utero[28,29,30]. If mother has varicella within 4 days before to 2 days after term, the neonate would have no maternal antibody and is at a risk of severe varicella, with a mortality rate of upto 30% in the absence of treatment[31,32].

The incubation period of varicella is 14-17 days. The infection starts with fever and malaise. This is followed by the development of papules which rapidly turn into vesicles. The contents become turbid within few hours. Then lesions are surrounded by an erythematous halo. In 2-4 days dry crust forms which separate leaving no scar. The vesicles appear in crops and usually three to five crops are seen. These lesions are mostly seen on the trunk and then on face and scalp and on the limbs. A characteristic feature of varicella is the presence of lesions at different stages of evolution in any given time.

Zoster: The first manifestation of zoster is pain. The pain has varying intensity and sharply localized in the dermatome affected. It may be diffuse and less severe also. The eruption then appears. They start as grouped erythematous papules which rapidly become vesicular and then pustular. New vesicles continue to appear for several days. In children the presence of a prodrome is unusual. The usual site of involvement in children is the thoracic region. Involvement of the nasociliary branch of the trigeminal nerve leads to appearance of the vesicles at the tip of the nose. This is described as Hutchinson's sign. The recognition of this sign is important because it usually indicates involvement of the cornea and conjunctiva. In immunocompromised patients the disease may become disseminated forming disseminated herpes zoster or it may appear at different dermatomes (multidermatomal involvement). The lesions may become necrotic and take more time to heal.

Treatment: Varicella in healthy child requires only symptomatic treatment with analgesics and other supportive measures. Some advocate anti viral treatment. In immuno compromised individuals anti viral drug must be given at the earliest. The drugs used in the treatment are acyclovir or valaciclovir.

Pre-exposure prophylaxis with live attenuated vaccine is effective in preventing varicella in healthy children[33]. It is also effective in children with leukemia wherein it reduces the incidence and severity of varicella[34].

Post exposure prophylaxis is with zoster immunoglobulin (ZIG). It is administered within 10 days of contact. It should be given to neonates whose mothers develop varicella within the period from 7 days before to 7 days after delivery[35]. The other indications for ZIG as post exposure prophylaxis are (1) immunocompromised children (2) those who have not had chickenpox previously, but have taken oral steroid for at least 14 days within the pervious 3 months if exposed to varicella or zoster (3) Exposed non immune pregnant woman[26].

Cytomegalovirus (CMV)

Congenital CMV infection: Severe form presents with hepatosplenomegaly, jaundice and purpura. On the skin it may present as "blueberry muffin" lesions; vesicles rarely occur in congenital CMV infection[36].

CMV mononucleosis: Resembles infectious mononucleosis with fever and lymphocytosis. On the skin there is follicular, maculopapular or rubelliform eruption[37]. Urticaria may also be seen[38] As in Ebstein – Barr virus infection ampicillin can trigger wide spread eruption[38]. Lymphocytic vasculitis is also described as a feature of CMV mononucleosis[39].

CMV infection in immunosuppressed can be severe and even fatal. The dermatological features include a wide spread eruption that may become papular and purpuric with vesiculobullous and pustular lesions. There may be indurated pigmented nodules or plaques[37]. In AIDS, keratotic skin lesions[40] and severe oral[41] and skin ulcerations[42] have been reported.

Cutaneous manifestations of human CMV: Drago et al[43] classified the dermatological manifestation of CMV infection as specific or non specific. Non specific lesions are mostly secondary to post infectious immune derangement or hypersensitivity reactions arising from medical therapy[44,45] and include generalized maculopapular rash and urticarial and scarletinform eruptions. The petechiae, purpura and jaundice are also included among the non-specific manifestations.

Specific lesions depend on the immune status of the patient. The lesions vary from localized genital ulceration or cutaneous ulceration of other sites, verrucous plaques of the heel[46] and crusted papules of the face[47]. Generalized urticaria and a vesiculobullous eruption are also mentioned[48,49].

Patients with intact immune system rarely have cutaneous CMV manifestation[43]. Erythematous, edematous, purpuric papules and plaques over a livido pattern on the lower extremities[39] and an acute papular purpuric dermatosis in the characteristic "glove and socks" distribution is also described[50].

Diagnosis is made based on the typical intra nuclear inclusions surrounded by a clear halo in enlarged cells. Virus isolation and immunohistochemistry are also useful. Detection of CMV antigenemia and PCR are rapid and sensitive methods of diagnosis of CMV. CMV antibody detection will also help in the diagnosis.

Treatment: Most CMV infections do not require treatment but in life threatening or vision threatening as on CMV retinitis, ganciclovir and foscarnet have been used.

Human Papilloma virus

Papilloma viruses are small DNA viruses that infect squamous epithelia, causing cell

proliferation. The commonest effect of this infection is the development of warts (verrucae).

Warts: Human papillomavirus (HPV) can infect any site with stratified squamous epithelium. The usual clinical presentation can be divided into cutaneous warts, genital warts, oral warts and laryngeal warts. The tissue specificity is mostly governed by the type of HPV eg. Nongenital plantar wart is caused by HPV 1; oral lesions are caused by HPV 13,32,57[51].

Warts occur at any age but are unusual in infancy and early childhood. The incidence increases during the school years and peaks in adolescences and early adulthood[52,53,54].

Modes of transmission: Warts spread by direct or indirect contact. Trauma and maceration predisposes the entry of virus into the skin.

Anogenital warts are uncommon among children. In them, infection from mother's genital tract at delivery is considered as a frequent source of infection at this site. However sexual abuse may also be considered if anogenital infection is seen in children. Postnatally, transmission from adults with genital warts may occur non-sexually such as sharing a bath with an infected adult[55].

Common warts: These are found on all body surfaces and are commonly associated with HPV 2; it is also associated with HPV-57, 1 and HPV-4. Clinically characterized by firm papules with verrucous surface of size 1mm to 1cm. Sometimes it may reach larger sizes. Usually these are located over extremities. In children the other favoured site is around knees. In habitual nail biters warts may be located periungually Common warts are sessile in most of the times; however small pedunculated warts may also seen (filiform warts). Common warts can also occur on genitalia.

Plantar warts: Plantar warts are caused by HPV-1, -2, -4 or –57. The deep myrmecia form is due to HPV-1, while the mosaic warts are caused by HPV-2. At first it appears as a small, shiny deep seated papule and later assumes the well defined rounded shape. Surrounding the papule is a collar of hyperkeratotic epithelium. Most plantar warts are seen over pressure areas such as over the heads of metatarsals, heel and lateral aspect of foot.

In most cases pain is a common symptom; however, sometimes it may be absent. Plantar warts are commonly confused with callosities. The differentiation can be made by noting the interface between the epidermis and wart as well as by noting bleeding points on paring. Another useful sign may be application of pressure from sides which causes pain in plantar warts.

Plane warts: Plane warts are mainly due to HPV-3 and HPV-10. They are smooth, minimally elevated, brownish or hyperpigmented papules. It may be rounded or polygonal and there will not be any scaling on the surface. The usual sites of involvement are face and dorsum of hands. The number may range from a few to many. These warts are relatively less common in children.

Filiform warts: These are usually seen in face and neck. It can also occur in hairy regions. They appear as slender verrucous papules and the number may range from a few to many.

Anogenital warts: These are variously termed as condyloma acuminatum, genital warts or venereal warts. Anogenital warts are caused mainly by HPV-6, -11, -16 and –18[55,56]. In children HPV-2 and -4 are also isolated[57]. Oncogenic progression occurs with infection due to HPV-16 and –18.

The typical anogenital warts are soft, hyperpigmented elongated and sometimes pedunculated. The lesions are usually multiple. They are classically distributed around anal

orifice and may extend to the contiguous anal mucosa. The other areas could be frenulum, corona and glans penis as well as posterior fourchette. These warts may persist for a variable period from a few weeks to many years[58]. In some situations, anogenital warts are associated with other sexually transmitted infections. When these lesions are present, a careful history must be obtained from child and parents for possible sexual transmission and the child must be evaluated for any other signs of abuse. The usual differential diagnosis includes condylomata lata, anogenital mollusca, skin tags and rarely skin lesion of Crohn's disease.

Treatment: Being self limited disease, warts require a balanced approach for treatment. The agents used for topical application are salicylic acid, gluteraldehyde, podophyllin and podophyllotoxine, formalin, 5-flurouracil and retinoic acid. Surgical methods include excision, curettage and cautery, cryotherapy and laser ablation. Intra lesional injections with interferon and bleomycin are also advocated as treatment for warts. Anti viral drug cidofovir applied topically as 1% gel or by intra lesional injection is effective. Plantar, anogenital and laryngeal warts resolve completely[59]. Cimetidine given in a dose of 30-40mg/Kg daily for a prolonged period may be effective. In a placebo controlled study there is not much of difference in the outcome[60]. Topical immunomodulation is a promising new treatment for warts. Imiquimod 5% cream is currently used as a topical therapy for warts.

Epidermodysplasia verruciformis (EV): EV is a genetic disease characterized by HPV infection giving rise to characteristic combination of plane warts, pityriasis versicolor like lesions and reddish plaques. Malignant change is common. Susceptibility to virus is inherited. The common mode of inheritance is autosomal recessive; however X-linked or autosomal dominent patterns are also observed[61]. The lesions are seen on face, neck, trunk and limbs. The lesions may be macular or plaque like. In children, the lesions spread fast. The colour of the lesion may be hypopigmented or brownish. Dysplasia and malignant changes occur in sun exposed skin. The effective treatment for EV is still to be found out. However, etritinate in the dose of 1mg/Kg is found to be useful. The effect is dose dependent and relapse occurs if the drug is stopped.

Poxvirus infections

The poxvirus family consists of DNA viruses that can infect animals and human beings. They are brick - or oval shaped and are generally large enough to be seen by light microscopy. There are four genera of pox viruses and molluscum contageosum virus is the most commonly encountered one.

Molluscum contagiosum: Molluscum contageosum (MC) is a benign self limiting infection of skin caused by Molluscum contageosum virus (MCV)

The individual lesion is a shiny, pearly white, hemispherical, umbilicated papule. The size may vary from 1 mm to 1cm. In certain situations it may become more than one cm and is known as giant molluscum. These are usually seen in immuno compromised individuals. The number of lesions is also variable; usually in the range of 10-20. But innumerable lesions are seen in immunosuppressed individuals. Even though it can occur at any site, the usual sites of involvement are trunk and limbs. The genitals are also affected. The lesions resolve spontaneously with or without inflammation. Occasionally, an eczematous reaction around a molluscum papule occurs, termed as molluscum dermatitis. This reaction usually resolves on its own[62] when molluscum is treated or regresses. Periocular molluscum may be associated with

conjunctival molluscum and with "toxic" conjunctivitis. Molluscum folliculitis is also reported in which the lesions are confined to hair follicles[63].

Diagnosis: The typical morphology gives an important clue to diagnosis. However differential diagnosis such as milia, juvenile xanthogranuloma, cryptococcal skin infection, warts, papillomas and basal cell carcinoma need be considered in not so typical cases. In difficult cases biopsy of the lesion will give the diagnosis.

Treatment: In many instances therapy is not needed. However, treatment may be contemplated when the resolution is slow, lesions are symptomatic and the child is immunosuppressed. The destruction of the lesion or production of inflammation in the lesion is the basis of treatment. Destruction may be done with cryotherapy, curettage and diathermy, expression of contents by squeezing and pricking the lesion with a sharp needle. Topical preparation can be used to produce an inflammatory response. The usual agents used are liquefied phenol, 10% potassium hydroxide, cantheridine, salicylic acid, podophyllotoxin, nitric oxide cream and silver nitrate paste.

The anti viral agent, cidofovir has been shown to be effective[64] It is used either as topical ointment or cream or intravenously. Intravenous cidofovir is indicated when there is failure of other modalities in immunocompetent individuals and in extensive disease in immuno suppressed.

Local immune stimulation with imiquimod cream is also effective. The treatment has various application protocols from one to three applications daily for 3 to 7 days per week for 4-16 weeks[65,66]. The immunomodulatory effect of cimetidine may also be used for treatment of molluscum contageosum[67].

Points to remember

1. ***Proper diagnosis of cutaneous viral infections will prevent morbidity and mortality and can avoid unnecessary investigations and treatments.***
2. ***It can help preventing spread of the infection in the community.***
3. ***Skin lesions that are formed during the course of illness or in the beginning of infection may be specific at certain situations so that a proper diagnosis may be made by the examination of skin lesions alone.***
4. ***Anti-virals have limited use.***

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NEWS AND NOTES

UP NEOCON 2005

Date : October 15, 2005

Venue : Lucknow

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LUDHICON 2005

Date : September 18, 2005.

Host : IAP-Ludhiana district Branch, In association with NNF Punjab state and IAP-Intensive care chapter, Punjab state branch

Contact : Dr Harinder Singh, Organizing secretary, 8-A, Model town extension, Ludhiana. Email:harinder_dr@rediffmail.com, Ph: 0161-2450074, 9814117501. Website: www.geocities.com/iapludhiana

2nd National CME

on

CHILDHOOD ALLERGIES – AN UPDATE

Organized by

IAP-TNSC & IAP KANCHEEPURAM BRANCH

Date : 13th November 2005 (Sunday) at Chennai.

Delegate fee : Rs.300/-

For details: **Dr.(Major) K.Nagaraju**, Organizing Secretary, IAP House, IAP-TNSC Flat, 56(33), F Block, Ground Floor, Halls Towers, Halls Road, Egmore, Chennai – 600 008. Tamilnadu. Mobile: 98402 30199, Email: majorknr@yahoo.co.in

NUTRITION

PREVENTION OF ADULT DISEASES IN CHILDREN: NUTRITIONAL PERSPECTIVES

**** Panna Choudhury***

***** Jitender Nagpal***

Abstract: *Adult metabolic diseases (like insulin resistance, type 2 diabetes, hypertension, coronary artery disease, hyperlipidemia) are increasing rapidly and often have their origin in childhood. Central to this disease is abdominal obesity and excess weight gain relative to the individual growth trajectory. For prevention of these diseases, pediatricians need to play a crucial role in identifying children at risk of obesity. Serial measurement of body mass index, emphasis on physical activity and 'healthy' balanced diet needs to be in built in pediatricians' routine practice.*

Key Words: *Activity, Children, Metabolic, Nutrition.*

In the recent times there has been a significant rise in many adult diseases linked with obesity like insulin resistance type 2 diabetes, hypertension, coronary artery disease, hyperlipidemia, stroke and certain cancers. The prevalence of coronary heart disease has increased by a factor of six to eight, over the past four decades[1] with estimates suggesting that by 2025, India will have more people with diabetics (57 million) than any other country[2]. Rise in obesity is a consequence of rapid nutrition transition and urbanization. Also, for a comparable Body Mass Index (BMI), Indians have more body fat and lower muscle volumes than other ethnic groups (thin fat Indian phenotype). This means that many Indians have high body fat, at BMI values that are in nonobese range[3].

The pediatrician cannot afford to ignore this situation, particularly with the rapidly accumulating evidence that adult metabolic diseases have their origin in adolescence (or earlier in childhood and even in fetal life), and manifest due to interactions and accumulation of various risk factors, throughout life. Longitudinal data indicate that sustained and accelerated childhood weight and BMI gain(crossing into higher categories) is associated with adult morbidity including diabetes, hypertension and coronary artery disease[4]. Estimates of childhood obesity are even more disheartening. The calculated global prevalence of overweight (including obesity) in children aged 5-17 years is estimated to be 10%. A prevalence of overweight of 31% and obesity of 7.5% has been documented in 13-18 year old adolescents from a Delhi School (tuition fee >Rs. 2500/month)[5]. Interestingly many children and adolescents with insulin resistance are not overweight by International standards though getting bulkier relative to themselves. Thus it is important that an individual child is monitored with regular weight and or serial BMI measurements. It is ironic that a problem of "plenty" namely childhood obesity has arisen while we are still

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fighting undernutrition and infectious diseases. Adverse health consequences of positive nutrition transition in children were undermined as these were seemingly "remote" and therefore "relatively invisible". However these are now gaining prominence with early markers of atherosclerosis like endothelial dysfunction becoming evident in early adolescence. Further late childhood and early adolescence remains the ideal age group for establishment of healthy lifestyle and dietary patterns (and modifications where necessary). Thus, if the epidemic of adult metabolic diseases is to be controlled, it is actually the pediatricians who will now have to perform a crucial role by looking after children and adolescents more meaningfully, as intervention must commence early in life.

The beneficial effects of exercise and lifestyle modification in decreasing the risk for developing coronary artery disease and diabetes is well established in adults. Data also suggests that exercise[6] and dietary modifications[7] improve the fore-bringers of atherosclerosis like endothelial dysfunction. A Western diet high in saturated fat, simple sugars and salt and low in fiber, fish oils and antioxidants has been associated with an increased risk of atherosclerosis, an effect which is likely to be mediated through elevations in orthodox risk factors and possibly also through pro-inflammatory, pro-oxidant and prothrombotic mechanisms. Populations from Southern Europe, who consume a Mediterranean-style diet low in saturated fat, rich in oleic acid and antioxidants, have a lower incidence of cardiovascular disease as do populations, such as the Greenland Inuit, who consume diets rich in omega-3 polyunsaturated fatty acids derived from oily fish[8].

These observations have led to prospective randomized control trials based on a variety of dietary combinations in at risk adult populations. Ambring et al[9] has recently documented in a randomized trial that a Mediterranean diet (twice the amount of fiber, 4–9 times more antioxidants, three times the amount of polyunsaturated and omega-3 fatty acids) when given for four weeks in a cross over design with the normal Swedish diet caused approximately 20 % reduction in total and LDL (low-density lipoprotein)-cholesterol, triacylglycerols (triglycerides) and apo B (apolipoprotein B). The absence of a carry-over effect on plasma lipids between the arms of the study suggests such dietary interventions need to be maintained to sustain the changes in lipid profile. Similarly in children (9-12 years) improvement in cholesterol levels and endothelial function was documented after six weeks of a diet providing 900-1200 kcal/day (Low in fat (20-25%); high in complex carbohydrate (50-60%); and sufficient in protein (25-30%) over 6 weeks[10].

Data is also available of single step dietary interventions such as the introduction of soy protein and/or flavonoids in adults . Soy is a rich source of polyphenolic isoflavones –genistein and diadzein. These are structurally similar to estradiol and genistein in particular has several cellular activities (inhibition of tyrosine kinase activity, decreased smooth muscle cell proliferation and nitric oxide dependent relaxation) which may influence vascular tissue metabolism. Steinberg et al[11] in a randomized, double blind cross over study enrolled 28 healthy post menopausal women and they consumed 25 grams/day of the 3 products for 6 weeks each with intervening washout periods. The products were isolated soy protein with isoflavones, ethanol washed soy protein with trace isoflavones and total milk protein which supplied 107, 2 and 0 isoflavone units per day. Improvement was documented in endothelial function independent of the anti-oxidant and lipid effects. Similar data is however not available in children.

Many epidemiological studies have investigated the relationship between flavonoid and cardiovascular disease risk. The subject has

been reviewed; overall the evidence suggests that individuals with highest flavonoid intake have moderately reduced risks for cardiovascular disease. Tea, apples, onions and red wine are particularly rich in flavonoids with particularly strong evidence in favor of tea with a meta-analysis by Peters et al[12] suggesting an overall reduction in cardiovascular disease ~11% with consumption of 3 cups per day.

Further, in a recent study from low socioeconomic stratum residing in urban slums of New Delhi, cardiovascular risks like hypertension and hypertriglyceridemia were noted in a significant number of cases even with BMI and waist circumference (WC) values considered "normal." The data suggested that definitions of "normal" ranges of BMI and WC need to be revised for Asian Indians[13]. The International Obesity Task Force (IOTF) has proposed the standards for adult obesity in Asia and India as BMI >23 as overweight and BMI >25 as obesity[14].

To create awareness among pediatricians of their role in the prevention of these metabolic conditions, and to provide clear guidelines for actions to be taken by them, the Indian Academy of Pediatrics established a National Task Force on Childhood Prevention of Adult Diseases. The Task Force had recently published its recommendations in a series of articles[15-17]. It is important that the pediatricians integrate these recommendations in their routine daily clinic practices. The salient features of these recommendations are summarized here.

Important Features of Recommendations

1. Identifying Cases 'at risk'by Orienting Routine Clinical Practices

i) History:

a) Personal history of fattening diet, physical inactivity, sedentary behaviour (like >2 hrs TV viewing);

b) Family history of early hypertension, coronary artery disease and diabetes.

ii) Physical examination:

a) Linear growth should be assessed by yearly growth (height, weight and weight for height / BMI) charting 3 to 6 monthly from birth to 5 years of age and 6 to 12 monthly thereafter. Any accelerated weight gain should be considered as risk factor. If feasible, multiple skin fold thickness (biceps, triceps, subscapular, suprailiac), waist circumference should be measured.

b) All Indian children >10 years in age who are overweight (BMI >85th centile for age or weight >120% of the 50th centile weight for height by national standards), and have any one of the following risk factors: family history of type 2 diabetes in first or second degree relative, polycystic ovaries, acanthosis nigricans, dyslipidemia or hypertension. Pending the availability of good Indian National representative standards for BMI in childhood, the NCHS/ CDC BMI chart may be followed at present.

c) To regularly monitor blood pressure in all children from age 3 years and to look for acanthosis nigricans and polycystic ovaries from 10 years of age.

iii) Investigations:

a) Blood glucose screening should be done once in 2 year for children at risk after 10 years of age. Diabetes is diagnosed if fasting plasma glucose is >126 mg/dL and or 2 hour post prandial plasma glucose value is >200 mg/dL.

b) Lipid profile should be done in children age > 2 years with family history of dyslipidemia or premature cardio-vascular

disease; or anytime in children with no definite family history but with any risk factor for insulin resistance.

2. Interventions

a) Dietary modifications

Emphasis should be on nutrition rather than 'dieting'. It is important to maintain healthy components of traditional diets (i.e., micronutrient rich food such as fruits, vegetables and whole grain cereals) and guard against heavily marketed energy dense fatty and salty foods (e.g., pre-packaged snacks, ice-creams and chocolates) and the sugary cold drinks. The strategy should be to recognise and eliminate risk factors of high calorie intake such as frequent snacking (samosas, potato chips, chidwas), eating out frequently (burgers, dosas), celebrating with food (cake, chocolates) and drinks (colas, beers). Healthier alternatives can be suggested. Habits attained early have more chance of remaining throughout life.It is prudent to prevent feeding excess calories to children with low weight for age but normal weight for height i.e., 'stunted children'.

b) Increase physical activity level

The WHO recommends atleast 30 minutes of cumulative moderate exercise (equivalent to walking briskly) for all ages; plus for children, an additional 20 minutes of vigorous exercise (equivalent to running), three times a week. In general, moderate to vigorous activities for a period of atleast one hour a day may be a more practical recommendation for all school going children. Perhaps even more important is decreasing sedentary behavior like viewing television (should be restricted to no more than 2 hours a day), computers, telephone conversations.

c) Modulating risk factors: Parental smoking, passive smoking, non smoking tobacco use, alcholism and drug abuse shoud be discouraged.

d) Creating various channels of intervention/ health education

School based programs to enhance physical activity are already in place in many developed countries. 'Child Friendly School Initiative" with reservation of certain hours for exercise in school setting has been proposed[18]. Campaign against substance abuse like smoking, non smoking tobacco use, alcoholism need intensification. Advocacy at all levels notably teachers, government functionaries,professionals, media, academic bodies, food regulatory authorities and so on are urgently needed to stall the ensuing epidemic of metabolic syndrome.

Key messages

1. ***Adult metabolic diseases are increasing rapidly.***
2. ***Origin of these diseases are in childhood.***
3. ***Pediatricians as "Saviours" need to identify those "at Risk".***
4. ***Intervention lies mainly on increasing physical activity, emphasizing "healthy" balanced diet and modulating other risk factors like smoking.***

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Lebovitz HE. Body composition, visceral fat, leptin and insulin resistance in Asian Indian men. J Clin Endocrinol Metab 1999; 84: 137-144.

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NEWS AND NOTES

PALS COURSE

Date: October, 1-2, 2005 **Venue:** Delhi

Contact: Dr.K.K.Jani, Cell: 98103 40599, Email: jkk00001@yahoo.co.in
Dr.Alok Kumar Agarwal, Cell: 98181 09691, Email: alokkragarwal@hotmail.com

RADIOLOGIST TALKS TO YOU

RENAL CYSTIC DISEASE

**** Vijayalakshmi G***
***** Natarajan B***
****** Ramalingam A***

One of the common finding in any ultrasound report of adults is the simple renal cyst. This is a normal consequence of aging. More than fifty percent of people over the age of fifty years have renal cysts. This is rare in a child. The pathogenesis is uncertain. Focal tubular obstruction, past trauma or ischemia followed by necrosis have been proposed.

The ultrasound criteria for a simple cyst are that it should be unilocular, have a smooth wall and have no communication with the collecting system. It may involve the right or left kidney but the upper pole is frequently involved.(Fig.1a). When you see an upper pole cyst make sure you are not dealing with an adrenal cyst (Fig. 1b) or the upper moiety of duplication. Once diagnosed as a simple renal cyst no further investigation is necessary.

Congenital polycystic disease is an inherited disorder. There are two types, the dominant (ADPKD) and the recessive(ARPKD). The dominant type or the adult type is rarely recognized in the child. This is because they are not symptomatic till adulthood and that cysts take a long time to develop. Ultrasound may be used to screen these children though they can be declared free of disease only if they have not developed any cysts by thirty years of age. CT and MRI can also detect these cysts, but are not required as ultrasound provides adequate information.

In the adult type of polycystic disease both kidneys are symmetrically involved and are enlarged to the same degree with cysts of varying sizes. In the initial stage two or more cysts in any kidney should raise the suspicion of the disease. In the fully developed stage ultrasound shows multiple cysts filling the entire kidney (Fig 2). In contrast to polycystic disease the involvement is usually unilateral in multicystic kidney disease. Exceptionally it may be bilateral but the kidneys are asymmetrically involved. A multicystic kidney disease is not inherited and has a sporadic occurrence. Patients with the adult type of polycystic disease also develop cysts in other organs like liver and pancreas.

The recessive type of congenital polycystic disease is a more serious entity associated with poor renal function. It manifests in the intrauterine period itself as oligohydramnios. In this, both the kidneys are involved symmetrically. The cysts are too tiny to be resolved by ultrasound. But the innumerable cyst walls reflect almost all the ultrasonic waves so that the kidneys appear bright. Bilateral, symmetrically large, bright white kidneys seen in the neonate or the fetus points to a diagnosis of autosomal recessive polycystic disease (ARPKD) (Fig 3).

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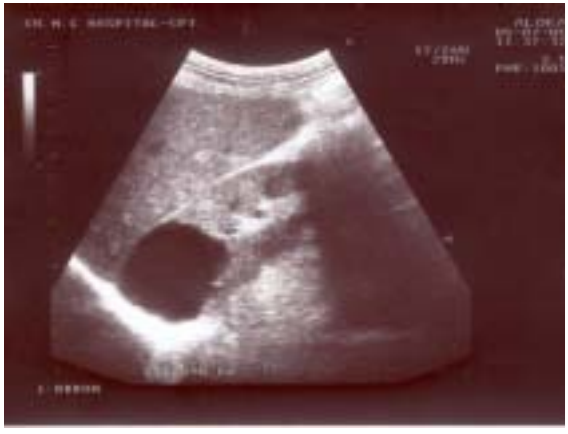

Fig 1a. Simple cyst in the upper pole of the kidney

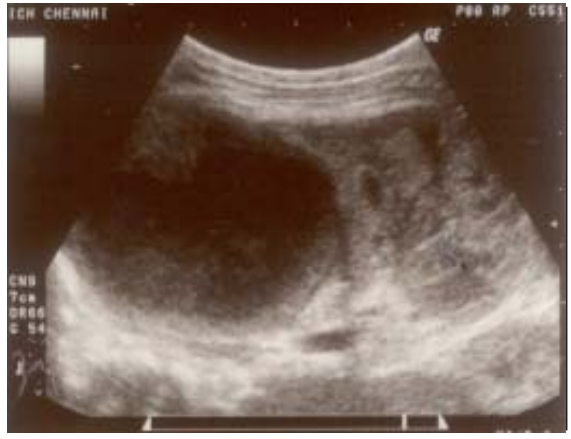

Fig 1b. Adrenal hemorrhage in a newborn

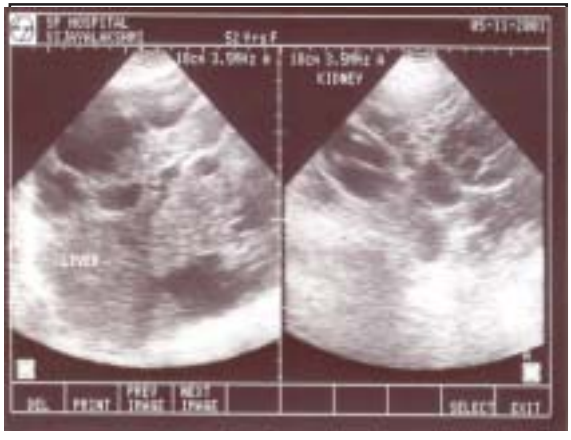

Fig 2. Autosomal dominant polycystic kidneys - Liver & kidney cysts

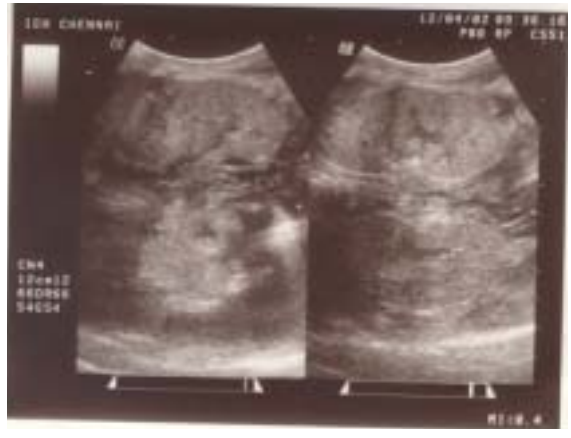

Fig 3. Autosomal recessive polycystic kidneys

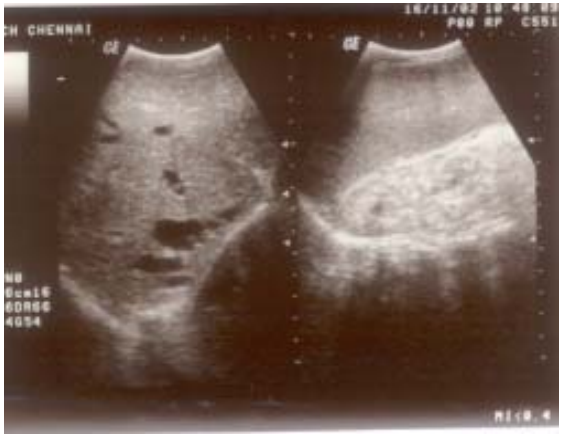

Fig 4. Autosomal recessive polycystic kidneys - Juvenile type

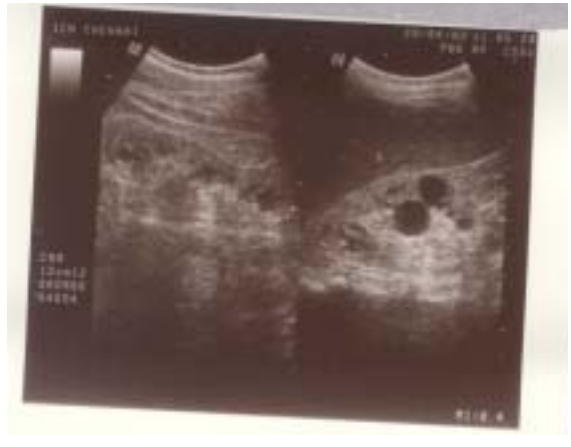

Fig 5. Nephronophthisis

Sometimes these children have enough renal function to survive a few years. Renal failure may manifest only at the end of the first decade or in the second decade. In such cases also the kidneys are large and bright. The liver also shows multiple cysts (Fig. 4). These are due to cystic dilation of malformed biliary ducts. In the initial stage the liver is normal in size or enlarged with a normal echotexture and a few cysts. Later fibrosis sets in and the echotexture becomes patchy. Liver shrinkage continues with deteriorating liver function and the child succumbs to hepatic failure rather than renal failure.

Medullary cystic disease is another spectrum of inherited renal cystic disease where there is a reduction of renal parenchyma due to fibrosis. In ultrasound, the kidneys are either normal sized or moderately reduced in size. Corticomedullary differentiation is lost. Parenchymal echotexture is increased. Cysts are present in the medullary region or in the corticomedullary area (Fig 5). These cysts are not large. Some may be too tiny to be seen in ultrasound. Hepatic fibrosis may also be present. A similar picture is also seen in Jeunes syndrome, Ellis Van Creveld and Laurence Moon Biedle syndromes.

Finally a word about medullary sponge kidney. The condition is characterized by cystic dilations of the collecting tubules in the medullary pyramids. Stasis calculi form in these and may cause hematuria. The calculi may be picked up by ultrasound as nephrocalcinosis. The IVU is specific and shows an enlarged papilla with tiny calculi resembling a bunch of grapes.

To sum up, ultrasound is the only investigation necessary to diagnose polycystic disease. Early dominant polycystic disease can be followed up with serial scans. In medullary cystic disease also, ultrasound will be confirmative except when cysts may be too tiny to be visualized. The kidneys are then contracted as in any end stage renal disease.

CONGRATULATION

Dr.Bharat R Agarwal, Mumbai has been elected as the Honorary Secretary General of SIOP for a period of 3 years (2006-2008). SIOP did not have a general secretary from any continent other than Europe or North America in the past. This election of an Indian for the first time in the history of SIOP promises to bring hope to a large pool of children with cancer from our region.

SIOP is the major global organization concerned with the issues of children and young people who have cancer. The official name of this society is the "Societe Internationale d'Oncologie Pediatrrique" with the acronym SIOP. It is also known by the English translation; namely, the International Society of Paediatric Oncology (Website: www.siop.nl).

Beginning with a few members in the late 1960s, the Society has now grown to + 1,150 members living and working all over the world. For the past 40 years it has brought together doctors of many different disciplines to develop better care for this disease. SIOPs mission is to bring the best possible care for children with cancer to the farthest corners of the globe. SIOP aims to bring together all of those concerned with the care of children with cancer.

PRACTITIONER'S COLUMN

PERSISTENT COUGH IN CHILDREN

**** Paramesh H***

Abstract: *Persistent cough constitutes 8 percent of general pediatric out patient visits. A systematic clinical evaluation, including hearing the type of cough for the location of the pathology, auscultating at the open mouth for the fine wheeze of peripheral airway obstruction and auscultating on trachea for sub glottic foreign body contributes significantly for establishing the diagnosis. Specific investigations are needed in a small group of children who are poor responders to therapeutic trial of bronchodilators and children suspected of having some complications .The most common cause for persistent cough in children are cough variant asthma and post nasal drip. However it is essential to have a high index of suspicion for foreign body aspiration in children under five years of age since many times there is no history of aspiration .*

Key words*: Persistent cough, chronic cough, cough variant asthma, evaluation of cough*

Cough is a reflex response to mechanical, inflammatory or chemical irritation of respiratory tract, meant to clear secretions, when other defence mechanisms of lung like mucociliary elevator, airway and alveolar macrophages fail.

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The word persistent (Chronic) has an arbitrary time duration. According to Professor William Wering in the 1970's any symptom lasting for more than 3 months is considered persistent (chronic)[1]. In 1980's more than 3 weeks (Chronic)[2]. In 1990' persisting cough was considered persistent (chronic) if it persisted for more than 10 days cough after a bout of upper respiratory tract infections should be considered as asthma and needed therapeutic trial of bronchodilators[3]. The change in time frame is the reflection of better understanding of pathophysiology and availability of newer diagnostic modalities.

The prevalence of persistent cough is 8% among general pediatric out patient[4]. Ninety percent of asthmatic children present with cough only[5]. In adult studies 27 percent of traffic police officers have persistent cough in comparison to 14.04 percent of non traffic police officers[6,7]. A systematic clinical approach is needed to determine the most likely underlying pathogenic mechanism and investigations in selected cases as well as selecting the simplest effective therapy for the underlying process.

Pathophysiology of cough mechanism

Mechanics of cough: Cough is a very co-ordinated act, where there is a brief inspiration longer than normal resting tidal volume. The glottis closes briefly allowing the increase in abdominal thoracic pressure from 50 to100 mm of Hg. By fixing the abdominal wall and expiratory muscles respectively, the pelvic floor elevates, further increasing intra-abdominal pressure which is transmitted through the chest

.Then there is a sudden opening of glottis and air rushes out rapidly at a velocity of 500 to 750 km per hour .There is 80% dynamic compression of intrathoracic airways where the secretions from small airways are milked out to central airways in which the air flow is higher for effective clearance.

The cough center is situated in the brain stem and pons, the afferent is from vagus nerve while the efferent is also from vagus nerve and spinal nerves of C3 to S2. The stretch receptors of the small airway respond where airway caliber alters abnormally, for example in ventilated patient with high pressure set up. The receptors are highly concentrated at the larynx, carina, and bronchi. Any pathology in these areas can cause distressing cough. However a patient with epiglottitis does not cough since the cough receptors are absent[7,8].

Evaluation of persistent cough

There are a number of causes responsible for persistent cough is given in Table 1. When a clinician is posed with a child having persistent cough, a systematic history and clinical examination is a must. The points to be focused during evaluation are: duration and type of cough, timing of cough, onset and progression of cough, response to previous medications, associated clinical features, seriousness of the problem, possible clinical diagnosis, need for any investigation and specific therapy.

The dry type of cough is usually from upper airway passages. A dry hacky, throaty type is usually due to postnasal drip, habit tick, anxiety and decreased humidity at night. Seal barking dry type of cough is from laryngeal level and brassy type from tracheal area. The lower airway cough is usually wet type .A paroxysmal cough is usually due to foreign body aspiration, pertusis syndrome, bronchiolitis, asthma or cystic fibrosis. Bronchial cough has a wet prolonged phase,

Table 1. Causes

Central origin
· Psychogenic
· Anxiety
· Habit tic
Peripheral origin
· Pulmonary causes
- Nasopharyngeal, laryngeal, tracheal, bronchial, pleural
· Non pulmonary causes
- CVS
- Pericardial
- Diaphramatic
- Gasgtroesophageal reflux
- Distension of esophagus / abdominal disease

which may be dry initially. Parenchymal cough is wet, short and shallow due to restrictive phenomenon. It is always better that the clinician will hear the cough to identify the location of pathology and later look into the sputum. A white sticky sputum is always from asthma. Purulent sputum is due to suppurative lung disease, cystic fibrosis with infection. Bloody sputum should give rise to the suspicion of foreign body, endobronchial tuberculosis, bronchiectesis and hemosiderosis as the possible causes.

The time of cough caused to give clue us for the possible causes as in Table 2.

The onset of cough and its progression can also give clues in establishing the diagnosis as in Table 3.

The cough which responds to antihistamine is usually due to allergic rhinitis with post nasal drip, when responds to bronchodilators it is due to asthma or cough variant asthma and to antibiotic one has to think of infections cause .In the other hand steroids helps in suppressing the cough it could be asthma or other inflammatory

Table 2. Timing of cough and its etiology

· Nocturnal : Soon after going to bed 1AM to 3 AM 3AM to 5AM	· Post nasal drip , sinusitis · Gastroesophageal reflux disease · Asthma
· While arising in moring	· Bronchietesis, cystic fibrosis
· Related to feeding	· Pharyngeal incoordination, tracheoesophageal fistula, mass in hypopharynx
· Winter / Rainy Season	· Allergic cough, reactive airway disease
· Absent at night	· Psychogenic , habit tic
· During exercise , crying , laughing	· Exercise induced, emotional stress induced asthma

Table 3. Onset and progression of cough

· Sudden onset with gagging while eating or playing	· Foreign body aspiration
· Fever with cold followed by persistent cough and wheeze	· Post viral reactive airway disease, wheeze associated lower respiratory infections.
· Itching of nose , rhinorrhea and persistent cough	· Cough variant asthma, post nasal drip, sinusitis

respiratory disorders. ACE inhibitors used in treating hypertension causes exaggeration of cough which is dry, throaty, nocturnal in supine position, often leads to change in tone of voice . The reflex is mediated via alteration of neurohumoral regulatory chains[8]. While evaluating the child with persistent cough any child shows any of the serious clinical finding as mentioned in Table 4 needs admission for proper management[9].

The possible causes for persistent cough fall into five categories: Anamolies, aspiration, infection, tumors or allergic causes either in upper airway, lower airway or parenchyma as in Table 5.

Symptoms in congenital anamolies usually start in early life, intensifies with age and worsens with any respiratory infections and activity but disappears during quite breathing .

Foreign body aspiration is common in the age group of 1-5 years of age. One has to have high index of suspicion since nearly 40 percent of the time there is no history of foreign body aspiration. Majority are vegetable foreign bodies like ground nut, arecanut, seeds, dal and melon seeds and often they are treated as asthma .

Small infants who suck vigorously have small aspiration and cough without producing any pneumonia and they do thrive very well without any problem . They are grouped as fatigue aspiration[10].

Psychogenic cough usually occurs in older children and adolescents, characteristically has

Table 4. Life threatening / serious persistent cough

· Dyspnea, dysphagia, dysphonea, drooling , odynophagia	· Upper airway problems
· Increased working of abdominal muscles, subcostal, intercostal, suprasternal retractions , nasal flaring	· Lower airway problems
· Trachypnea , flaring of nostils, grunting, signs of hypoxia, hypercarbia	· Parenchymal problems

Table 5. Possible causes for persistent cough

Categories	Upper airway	Lower airway	Parenchyma
Anomalies	Pharyngeal incoordination, tracheal stenosis, elongated uvula	Tracheoeosphageal fistula, vascular ring	Lobar emphysema, congenital - bronchiectasis
Aspiration	Post nasal drip from allergic rhinitis, sinusitis, Fatigue aspiration in infants	Foreign body	Chemical pneumonia
Infection	Sinusitis, upper respiratory infections	Pertussis syndrome, bronchiolitis	Chlamydia, mycoplasma
Tumors	Papilloma, hemangioma, lymphangioma	Bronchial cysts , bronchial carcinama	-
Allergic	Allergic rhinitis,	Asthma	-

barking or honking nature, dry variety, isolated and explosive, significantly absent during sleep and most noticeable when the child is under stress or when the attention is drawn to the cough.

The following are few findings of psychoganic cough. Over protective parents, stress at school, not able to cope with school work, sibling rivalry and parental comparison with other sibling.

Further personality analysis revealed that attention seeking, psychological insecurity, unable to face competition, hypersensitivity to criticism were some other causes.

Sometimes laryngeal dyskinesia can mimic asthma or labelled as psychogenic cough . In this situation there is paradoxic movement of the vocal cords during inspiration resisting in cough. These children have a negative result in methacholine challenge study and normal pulmonary function testing. Bronchoscopy including upper airway examination for dynamic vocal cord movement can diagnose the laryngeal dyskinesia.

The physician should investigate in an organized manner to arrive at or ruling out the diagnosis.

The routine investigations are complete blood count, an erythrocyte sedimentation rate absolute eosinophil count, IgE level .

Eosinophils in the nasal smear and sputum is a simple test indicative of allergic rhinitis and asthma respectively .

Table 6. Specific Treatment For Persistent Cough

Indications	Medicines
• Dry non productive cough which disturbs sleep and wet cough only when there is hemoptysis .	• Central cough suppressants - Codeine - Dextromethorphan
• Asthma / Reactive airway disease	• Bronchodilators / Anti-inflammatory drugs (oral, inhalers)
• Allergic rhinitis, sinusitis	• Antihistamine / Nasal spray (steroids)
• Mouth breathers with dry cough , sore throat	• lozenges, candies / humidifier / mist
• Psychogenic cough (Honkers cough)	• Psychotherapy
• Bronchitis from mycoplasma	• Antibiotics

Peak flow values before and after bronchodilators in older children compared with local standards will give additional information[11].

Inspiratory and expiratory chest films are needed to delineate foreign body in the lower airway . Chest X-ray can be normal in 15-20% of children with bronchial foreign body and is 61% of laryngeal and tracheal foreign body.

C.T.Scan is great help in identifying the mediastinal and carinal lymph models .

In general, the investigations contribute only 8 percent in establishing the diagnosis.

Serological test does help in specific diagnosis. We need acute and convalescent phase serum to see the rising titre ;however in infectious mononucleosis single titre is sufficient.

PCR is the most sensitive test where specific nucleic acid probes are used .

When indicated, bronchial provocative challenge tests can be done in a special research laboratory using histamine, methacholine, exercise, hypertonic saline, cold air, distilled water and observing the drop in forced vital capacity by 20 percent can be diagnostic of cough variant asthma.Chang AB has observed that children with cough alone are usually less atopic less responsive to usual challenge tests but more responsive to cough receptor challenge test with capsaicin. There is a small group of children with persistent cough who are non responsive to usual bronchodilator therapy, grouped under "Hypersensitive cough receptor syndrome"[12,13].

Treatment

In general, regardless of duration, a productive cough should not be suppressed. However a productive cough with hemoptysis or dry cough in influenza and convalescent phase of pertussis can be suppressed by central antitussive agents . Treatment of persistent cough is summarized in Table 6.

The two most commonly used central antitussive agents are codeine and dextromethorphan. Dextromethorphan will be a substitute for opiates dependent individuals. Dosage is similar to codeine, the safe close range appears to be considerably higher than codeine. Diphenhydramine hydrochloride was considered to be effective to some extent.

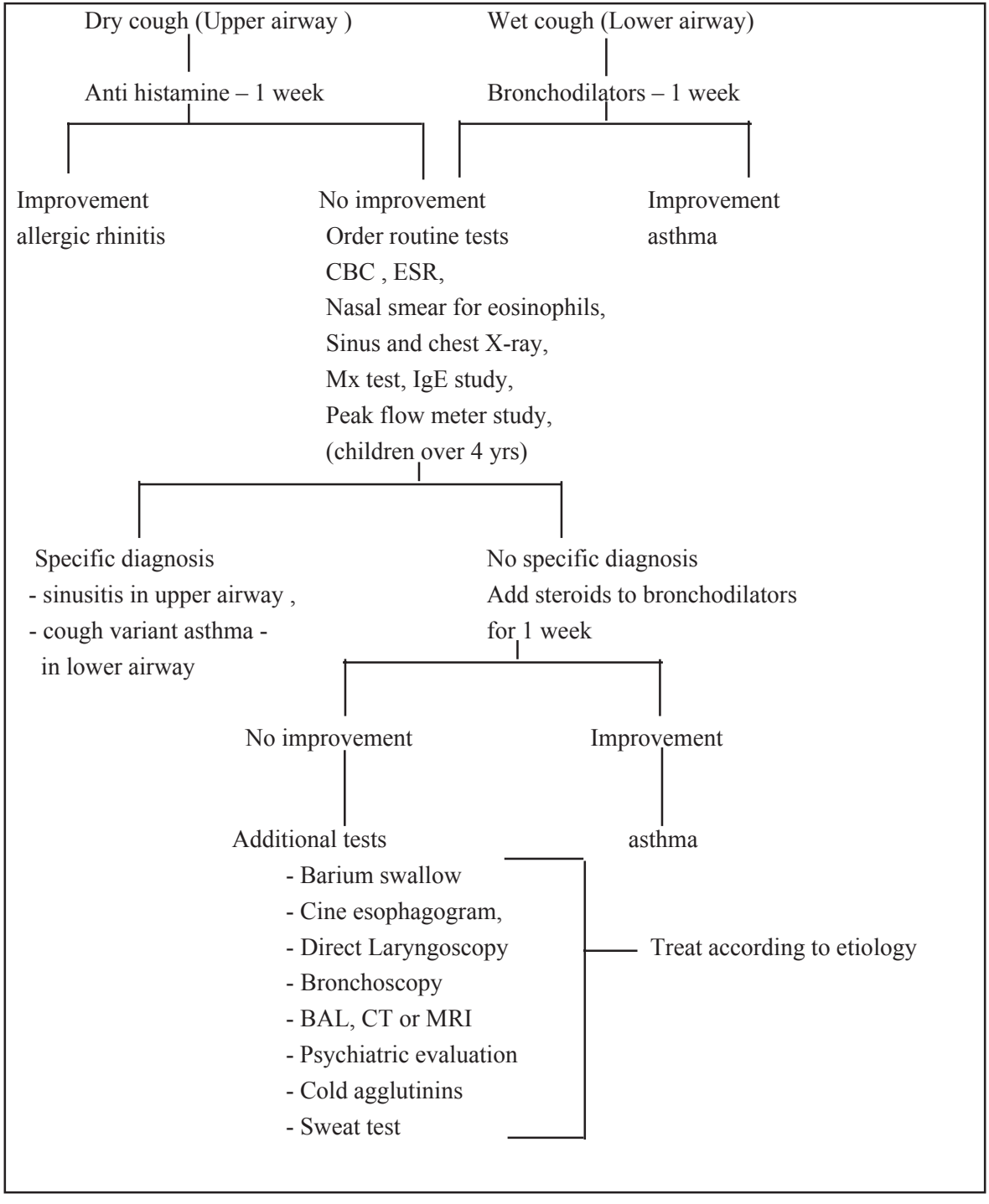

Fig.1 Approach to persistent cough in children

Conclusion

Persistent cough is a common problem in children for which parents consult the pediatricians.

A systematic symptoms analysis detail physical examination are sufficient in diagnosing the possible cause and special investigations are needed only in few cases.

The algorithm (Fig. 1) would aid in approaching the problem in an orderly manner to establish the diagnosis in almost all cases.

Points to remember

1. ***Commonest cause for persistent cough in children are cough variant asthma and post nasal drip secondary to allergic rhinitis and sinusitis***
2. ***Detailed history and thorough physical examination is enough to diagnose the cause for persistent cough in majority of cases .***
3. ***Special laboratory tests are needed in small percentage of cases proportion.***
4. ***Therapeutic trial of bronchodialtors is in vogue before any investigation.***

NEWS AND NOTES

CME PROGRAMME
ON
PEDIATRIC DERMATOLOGY
AT
CHENNAI
ORGANIZED BY IAP - DERMATOLOGY GROUP

Date	:	6th November, 2005
Venue	:	Savera Hotel, Chennai
Time	:	9.00 am to 4.30 pm
Tentative Programme	:	Eczema Infections Drug reaction Urticaria in children Cutaneous markers of Genetic disorders Fever with rash Panel discussion - Life threatening dermatoses
Registration	:	Delegates - Rs. 300/-, PG students - Rs. 250/- (Certificate from HOD). Send DD in the name of 'IAP Dermatology Group' payable at Chennai. Last date for registration on or before 15th October 2005. No spot registration
Correspondence	:	Dr. C. Vijayabhaskar, Door # 4, Gandhi Street, SS Nagar Extension, Thirumullivoyal, Chennai 600 062, Tamilnadu. Ph:044-28190032 Email:iapdermatology@yahoo.co.in

CASE STUDY

CAMPTODACTYLY – A CASE REPORT

*** Mahesh A**
**** Panchapakesa Rajendran C**
***** Porkodi R**
******Vasanthy S**
*** Bala Meena S**

***Abstract**: Camptodactyly is a noninflammatory condition characterized by soft tissue tightening without limitation of flexion. This rare condition can be mistaken for juvenile idiopathic arthritis. Non tender swelling and minimal flexion contracture of proximal inter phalangial joint of fingers, commonly involving fifth digit but also other fingers except thumb. It may be associated with familial arthritis and other disease states.*

***Key words**: Camptodactyly, Differential diagnosis.*

Camptodactyly is the term used to describe the presence of congenital or acquired flexion contractures of the proximal interphalangeal joints, due to soft tissue tightening and without limitation of flexion[1]. We report a case presenting with camptodactyly. This is a rare condition and it may be mistaken for juvenile idiopathic arthritis (J.I.A.) in its gross appearance as it has happened in this case.

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*** Assistant Professor
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Case report

An eight year old school going boy presented with swelling involving the proximal inter phalangeal joints of the fingers and toes sparing his thumbs and great toes. His mother had noticed this swelling since the child was three years old. He had normal milestones and was doing well in studies. He was asymptomatic but for the difficulty in fully extending his fingers. He was diagnosed to have J.I.A. and was treated with drugs for the same. His aunt who had a similar manifestation, was evaluated for the presence of any connective tissue disease and was found negative.

Examination of the joints revealed non-tender firm swelling and minimal flexion contracture involving the proximal inter phalangeal joints of his fingers and toes, sparing his thumbs and great toes (Fig.1). He was otherwise normal.

Investigations showed normal hematological, biochemical and immunological profile. X-ray hands showed soft tissue swelling over the proximal interphalangeal joints (Fig.2). No bony changes were made out.

Discussion

Camptodactyly is a non-inflammatory condition characterized by soft tissue tightening. It commonly involves the fifth digit but can occur in other fingers except the thumb. The cause is unknown. Fibrotic changes are observed in the subcutaneous tissue of the palmar aspect of the hand. Radiographs do not show bony or articular abnormalities.

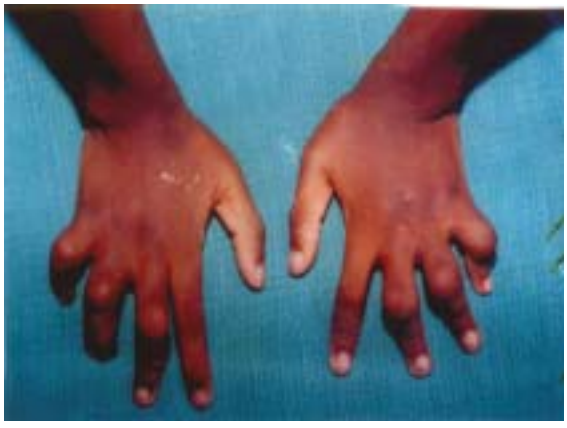

Fig 1. Contracture involving PIP joints of hand sparing thumb

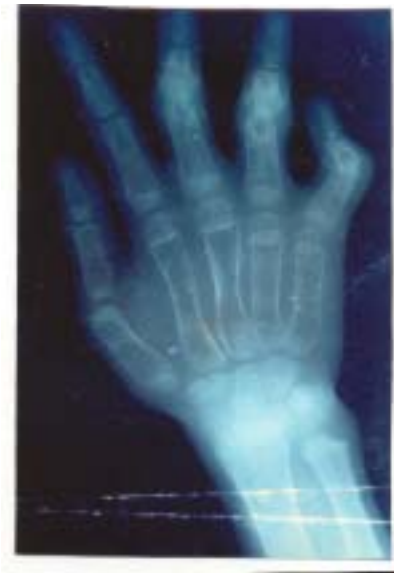

Fig 2. X-ray hand showing soft tissue swelling around PIP joints

Contractures can also result from failure of differentiation, including congenital clasp thumb, arthrogryposis multiplex congenita and clinodactyly. Congenital clasp thumb is twice common in males and usually bilateral. It shows extreme flexion of metacarpo phalangeal joints and adduction of thumb into the palm. It is caused by hypoplasia or absence of extensor pollicis brevis and occasionally extensor pollicis longus.

In arthrogryposis multiplex, stiffness of multiple joints, with under developed muscles which have been replaced by fibrous tissue is seen. Clinodactyly is a congenital radial or ulnar deviation of the digit due to abnormal development of the middle phalanx leading to maldevelopment of interphalangeal joint surface. It is commonly seen in trisomy21. Kniest syndrome consists of disproportionate dwarfism, kyphoscoliosis, hearing loss, flat and rounded facies and enlarged articular structure with fixed flexion contracture of upper or lower limbs.

Progressive pseudo rheumatoid arthropathy is seen in young children as autosomal recessive inheritance and affects small and large joints. Swollen joints with early morning stiffness may be present along with kyphoscoliosis and platyspondyly. There will not be any increase of acute phase reactants and does not need immunosuppressive therapy but only physical therapy.

Congenital form of camptodactyly is familial, associated with hypertrophic synovitis and is seen without signs of inflammation. Tenosynovitis may be seen occasionally. It is treated surgically if it progresses rapidly in adolescence.

Camptodactyly may be familial, associated with familial arthritis and with Marfan syndrome. Malleson[2] reported three children in one family with camptodactyly, iridocyclitis and familial arthritis. One amongst them died suddenly and postmortem examination revealed chronic synovitis and granulomatous arteritis involving the aorta, coronary arteries, myocardium and pericardium. Bahabri[3] reported the camptodactyly, arthritis, coxa vara and percicorditis syndrome. Our patient had only

camptodactyly without any other associated manifestations.

Conclusion

Camptodactyly is an easily idenfifiable clinical manifestation and is a non-inflammatory condition by itself. It is associated with a plethora of syndrome complexes, disease states and familial arthritis. Awareness of this entity would help in the early detection of co-existing morbid conditions.

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OBITUARY

Dr.N.Sundaravalli is one of the very few pediatricians with AB pediatrics to come back to serve our nation in those days. She had contributed her service to the development of pediatrics, Madras Medical College, ever since it was functioning at the Government General Hospital, Chennai, as well as after moving in to the campus as separate institution, the Institute of Child Health and Hospital for children. Dr.N.Sundaravalli, as an individual was a soft spoken, simple to move with and kind hearted doctor. She had done yeomen service to the downtrodden by virtue of her various positions in lioness club. She had been a key person in organizing health check up and immunization camps in Tamilnadu and neighbouring states. She was promoting research in Protein Energy Malnutrition, "Infectious Diseases" and "Liver Disorders" especially "Indian Childhood Cirrhosis". Her contribution along with Dr.V.Balagobalraju in the field of Indian Childhood Cirrhosis in yester years is commendable. She was an active member of Indian Academy of Pediatrics and was known all over India. She was the Executive Board Member of IAP for the year 1976, 1980 and 1981. She was the President of IAP for the year 1986 and Ex-officio Member for the year 1987. She was one the popular presidents of IAP elected from Tamilnadu. She was also conferred with FIAP. We pray the almighty to rest her sole in peace.

CASE STUDY

HYPOTHYROIDISM CAUSING BILATERAL OVARIAN CYSTS IN A 4-YEAR-OLD GIRL - A CASE REPORT

**** Khadilkar V***
***** Khadilkar AV***

Abstract: *Most ovarian cysts in the pediatric population develop as a result of perturbed hormonal stimulation of the ovary and are likely to occur in the first year of life or around menarche. When ovarian cysts are found in prepubescent girls, the possibility of associated hypothyroidism should be considered.*

Key words: *Ovarian cyst, child, hypothyroidism*

Introduction

When an ovarian cyst is found in a girl who is prepubescent, the possibility of associated hypothyroidism should be considered. We present a case of a four-year-old child with hypothyroidism and ovarian cysts.

Case report

A 3 and ¾ years old girl presented with bleeding per vaginum. On examination there was no breast development and no axillary and pubic hair. An abdominal and pelvic ultrasound showed a large thin walled right ovarian cyst measuring 5.1 by 5 cm. The cyst showed thick internal septae. The uterus was bulky for age and measured 4 by 1.5 cm and the endometrial echo was 5 mm. A pediatric surgical opinion was sought and an ovarian malignancy was suspected. Investigations showed the alfa feto protein to be 25.96 ng/ml (range up to 40 ng/ml), CA-125 (Carcinoembryonic antigen) was 20.84 U/ml (normal range <35U/ml), serum creatinine was 0.70 mg/dl (normal range up to 1.5mg/dl). The hemogram showed haemoglobin of 10.3gm%, normal WBC and platelet count and mild anisocytosis. The routine urine examination was normal.

A salpingoopherectomy was performed under GA. At surgery the right ovary was 7 by 7 cm with a smooth surface, the left ovary also appeared slightly enlarged and the uterus was bulky for the age. The histopathological findings were consistent with a benign ovarian cyst.

Two months later there was a second episode of vaginal bleeding similar to the first one. At this stage the patient was referred to the authors. A repeat ultrasound examination showed the left ovary to have a well-defined septate cyst measuring 3.4 by 2.8 cm (fig.1). The uterus was enlarged and measured 4.4 by 2.0 cm and had a pear shaped-adult configuration.

The endometrial echo was 3 mm thick. At this time a pediatric endocrine opinion was sought. On detailed questioning there was history of chronic constipation. On examination her height was 82 cm (Below 3rd centile on NCHS charts) and her weight was 8.1Kg (Below 3rd centile on NCHS charts), the rest of the physical examination including perineum was normal. Primary hypothyroidism was suspected and

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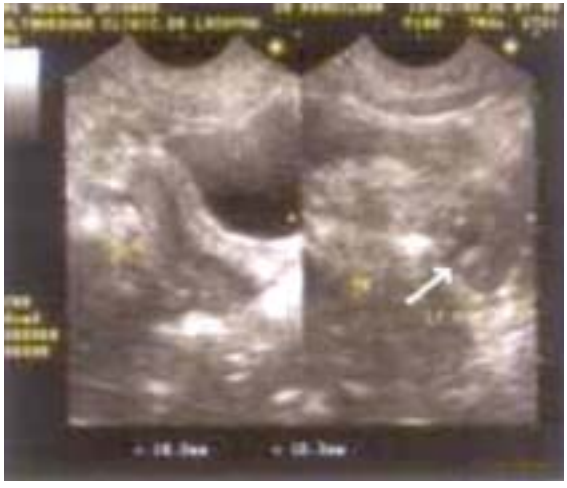

Fig.1-Well defined septated, left ovarian cyst measuring 3.4 by 2.8 cm is seen. Please note an additional small cyst within the cyst.

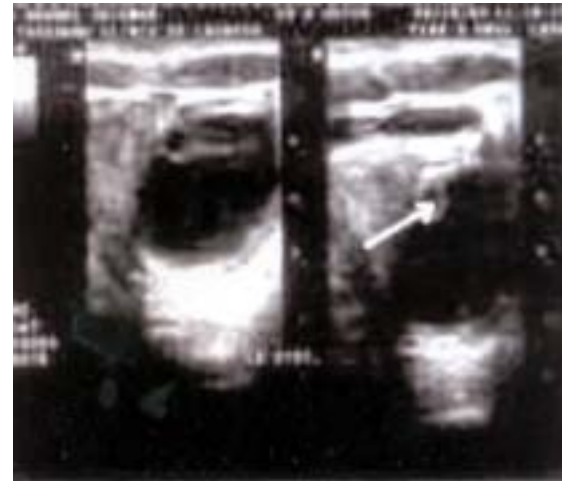

Fig.2- Left ovary is normal. Previous cyst has completely regressed.

hormonal tests were requested. The serum T4 was 0.80 µg/dL (range-7.3 to 15.0), thyroid stimulating hormone (TSH) was 41mIU/ml (range-0.60-6.30), the serum follicle stimulating hormone was 11.6 mIU/ml (range-<1 mIU/ml), the leutinising hormone was 0.55mIU/ml (range -<1 mIU/ml), the serum prolactin was 138 ngm/ml (range-<20 ngm/ml) and serum estradiol (E2) was 57.50 pgm/ml (range-<20 pgm/ml). Thyroid antibodies were tested and found to be strongly positive.

The patient was started on 50 micrograms of thyroxine per day. A repeat thyroid function test and ultrasound examination was performed after 6 weeks. The T4 was 12mcg/dl and the TSH was 0.629mIU/ml (both normal). The abdominal and pelvic ultrasound showed the size of the uterus to be 4 by 1.8 cms, and the endometrium was 1mm thick.

The left ovary was normal and the cyst had completely regressed (fig.2). One year follow up showed that she had "caught up growth" in terms of her height, she has had no further episodes of vaginal bleeding, her TSH was 3.2 mIu/ml and T4 was 12 µg/dL (both normal).

Discussion

Majority of ovarian cysts in the pediatric population develop as a result of perturbed hormonal stimulation of the ovary and are likely to occur in the first year of life or around menarche. The development of an ovarian cyst at other times should raise suspicion of aberrant hormonal release as is seen in severe hypothyroidism[1]. In severe juvenile hypothyroidism large multicystic ovaries may develop in response to hormonal overlap from TSH or prolactin[2].

It is suggested that the pseudoprecocious puberty seen in girls with hypothyroidism occurs because TSH shares a common alpha-subunit with the gonadotrophins, and this results in hyperstimulation of the ovaries and cyst formation. The second mechanism suggested for pseudoprecocious puberty is that the elevated TRH (Thyrotropin releasing hormone) drive

leads to increased production of prolactin. This sensitizes the ovaries for positive feedback to FSH leading to activation of FSH ovarian axis[1]. Another explanation given is that the TRH stimulates the FSH leading to ovarian cysts and this is particularly true in hypothyroidism[3].

Our patient had short stature, a high FSH and estradiol, low LH and the LH/FSH ratio was less than 1. So these findings ruled out true (central) precocious puberty. True precocious puberty results from premature activation of the hypothalamo- pituitary – gonadal (HPG) axis and together with a growth spurt the LH/FSH ratio is usually above 1.

It has been noted that when ovarian cysts are found in prepubescent girls, the possibility of associated hypothyroidism should be considered[4,5,6,7,8].

Clinical experience in children shows that ovarian cysts usually regress without treatment and are seldom associated with malignancy[9]. This case demonstrates the importance of assessing thyroid function in girls with cystic ovaries, and awareness of this association can avoid unnecessary surgery and improve ovarian preservation rates.

Acknowledgment: We are grateful for the valuable guidance by Dr.A.S. Kinnare for helping with the ultrasonographic pictures.

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