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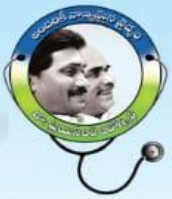

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DEPARTMENT OF PAEDIATRICS, ANDHRA HOSPITALS, VIJAYAWADA
E-JOURNAL

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Foreword

Greetings from the Andhra Hospitals!

For the past two decades, we are delivering excellence in terms of quality health care in the field of Paediatrics including Paediatric and Neonatal intensive care, Paediatric cardiac intensive care and other allied Paediatric sub-specialities.We take pride in introducing ECMO in pediatric specialty for the first time in the state of Andhra Pradesh. In this context, we convey our heartfelt thanks to you for your continued support and encouragement which played a pivotal role in our success.

As a token of our commitment to contribute to continuous medical education, we are introducing this monthly E-journal to showcase important clinical guidelines, recent advances in paediatric sub-specialties, interesting case reports, image quiz, OSCE scenarios etc, gathered from our patient database.

We hope this endeavor would prove to be useful to practicing paediatricians, intensivists, neonatologists and post-graduate students.

Please send your valuable feedback and suggestions to **maramkp@gmail.com**.

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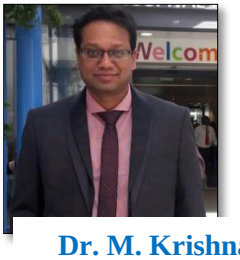

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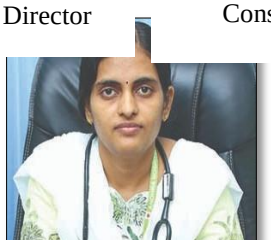

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The goals of metabolic and nutritional support in children are:

a) To minimize the deleterious effects of the hyper-metabolism and catabolism that areinduced by sepsis or acute injury.
b) To promote a positive nitrogen balance

Surveys of hospitalized paediatric patients reveal a high incidence of both acute and chronic malnutrition In critically ill children.Although few studies have been conducted specifically in critically ill children, there is evidence that children in the paediatric intensive care unit (PICU), especially those less than 2 years of age, are especially at risk for developing Protein Energy Malnutrition.

Malnutrition should be regarded as a severe multi-system disorder (Table 1), and is clearly linked to adverse outcomes such as increased morbidity, mortality and length of hospital stay. Even mild or moderate malnutrition may increase mortality, as shown in a meta-analysisof 28 studies.

Table 1

The Secondary Effects of Malnutrition

Myocardial dysfunction
Respiratory dysfunction
Immunodeficiency
Impaired wound healing
Impaired brain development
Impaired gastrointestinal function

The benefits of nutritional support have been demonstrated in chronically malnourished children with other co-morbid conditions.Studies of outcomes with and without nutritional support are clearly unethical. However, much circumstantial evidence points to decreased morbidity and improved survival when effective nutritional support is given during periods of acute illness.

It is also important to note that the neonatal brain accounts for around 2/3 of basal energy requirements. Caloric deprivation in the newborn period is an important factor in brain development. but not final growth.

Summary of requirements for nutritional management

- Early nutritional assessment of the critically ill child
- Calculation of caloric needs
- Enteral or Parenteral feeds to meet calculated requirements
- Regular monitoring and reassessment

The physiological response to acute injury

The so-called 'stress response' is the hormonal and metabolic response to injury, originally characterised by Cuthbertson, 1969. It has been described as consisting of 3 phases:

- An early hyper-metabolic phase (minutes/hours)
- A second Ebb phase during which metabolic rate decreases (typically lasting 12–72hours). Longer in severe injury/stress. Shortened by effective resuscitation.
- A final Flow phase (typically 3–10 days) characterised by hyper-catabolism with net protein loss, again longer in severe injury/stress.

Table 2 The Metabolic response to injury

EBB phase	Increased sympathetic activity leads to increases in: Cortisol ACTH ADH GH Lactate Ketogenesis Acute phase protein synthesis
FLOW phase	Increases in: Hepatic gluconeogenesis Lipolysis Cytokine release Urinary nitrogen excretion Protein breakdown (reduced lean body mass)

Infants and children are especially susceptible to iatrogenic malnutrition because of their relatively high metabolic requirements and relatively low metabolic reserves. A healthy infant has protein reserves for 6 days, and a child of 8-10 years has reserves for 10-15 daysThis compares to 70 days in the average adult.

Nutritional support for infants and children must therefore be designed to meet protein andenergy requirements during the flow phase, and supply sufficient requirements for normal activity and growth as recovery ensues (the fourth anabolic or recovery phase).

Nutritional Assessment

Assessment should take account of existing nutritional deficits as seen for instance in an infant 'failing to thrive'. The current metabolic and nutritional needs must be established.

- Some anthropomorphic measurements such as skin fold thickness, limb circumference measurements are extremely useful in the nutritional assessment of well children but most are difficult to perform in the PICU environment and are of questionable value in that situation.

- Simple measures such as admission weight and pre-morbid weight, height and growth history (charts/ child health records) are however useful in detecting chronic malnutrition.

When correlated with clinical examination and clinical status these measures usually permit a nutritional benchmark to be established.

- Several serum proteins may be used as surrogate markers of nutritional well being in stable nutritionally impaired children. Proteins with short half -lives such as pre-albumin ($t_{1/2}$ 2 days) or retinal binding protein ($t_{1/2}$ 0.5 days) correlate with acute changes in nutritional status. Albumin ($t_{1/2}$ 20 days) tends to be decreased in chronically malnourished children. Unfortunately in critically ill patients there are many other causes for changes in serum protein concentrations such as losses, dilution due to fluid administration and acute phase protein synthesis and absolute values should therefore be viewed with caution.

Determining caloric requirements

Energy expenditure (EE) can be estimated in critically ill children by measuring oxygen consumption. In a typical PICU however, clinicians must rely on estimates based on age weight and height modified by factors related to the child's clinical status.

Caloric requirements of children are made up of basal requirements (basal metabolic rate, BMR) and energy that must be supplied in addition for activities above basal level, and requirements for growth. As an example of pathologically increased activity, infants with severe chronic conditions such as bronchopulmonary dysplasia or chronic heart failure may require caloric intakes of 140-160 Cal/kg/day to achieve growth because of the increased 'work' imposed by their disease process.

Factors increasing energy expenditure (EE)

- Fever 12% increase per $^{\circ}C$
- Cardiac failure 15 – 25%
- Major surgery 30 - 30%
- Burns up to 100% in severe burns (>40% BSA)
- Severe sepsis 40-50%
- Catecholamines – dose dependent increase in metabolic rateSystemic steroids – induce hyper-metabolic response

Recommended daily intake of Calories (RDI)

Preterm	Weight	130-150 kcal/kg
< 1 year	3 - 10 kg	100 kcal/kg
>1 – 6 years	11- 20 kg	90 - 75 kcal/kg (1000 Cals + 50 Cals for each kg over 10kg]
7-16 years	21 – 70kg	75 – 45 kcal/kg [1500 Cals + 20 Cals for each Kg over 30 Kg]

The following table gives examples of the increases above basal requirements imposed by critical illness in children:

Age	% of (RDI) Recommended Daily Intake	
RDI	100	Recommended intakes for growth in healthy children undertaking normallife activities
Basal	55	Basal = deep sedation, ebb phase injury, mechanical ventilation
Maintenance	66	Maintenance = mechanical ventilation, enteral feeds, lying quietly
Minor stress	76	Minor stress = skeletal trauma, minor surgery, peritonitis, fever <39C
Major stress	98	Major stress = Multitrauma, large open wound, sepsis, major cardiac Surgery
Burns		
<20% BSA	100	
20-40% BSA	120	
>40% BSA	130	

It is important to note that overfeeding i.e. giving calories in excess of requirements

- Cannot reverse catabolism during hyper-metabolic states
- Excess carbohydrate can increase CO2 production and RQ
- Excess carbohydrate administration results in fatty deposits in the liver

Nutritional and metabolic support during critical illness

The purpose of metabolic support of the acutely ill patient is to minimise catabolism and prevent metabolic failure. This contrasts to the situation in chronic nutritional failure e.g. failure to thrive, where the purpose of nutritional support is to promote growth and anabolism.

Enteral feeding(EF) versus parenteral feeding(PF)

Unless an absolute contraindication exists enteral, rather than parenteral, feeding should be instituted.

Enteral feeding (EF) is contraindicated in the following circumstances :

- Necrotising enterocolitis (feeds usually withheld for 7-10 days)
- Recent gastrointestinal surgery (within last 24-36 hours)

Starting enteral feeding Unless a contraindication exists, enteral feeds should start within 12 hours of PICU admission

Advantages of enteral feeding

- Stimulates GI hormone production
- Stimulates normal GI secretions
- Stimulates GI mucosal blood flow
- Optimises GI mucosal nutrition
- Prevents bacterial translocation

Even small volume 'trophic' feeds are believed to have beneficial effects in promoting GI integrity.

Techniques of enteral feeding

Nutritional support should be provided by the least invasive route.

Supplemented oral intake
Most critically ill children cannot ingest sufficient food and fluid by mouth and therefore must receive some or all feeds by alternative routes.

Nasogastric feeding

- Tubes easily placed
- Success depends on normal gastric motility and absence of clinically important gastro-oesophageal reflux.
- Often fails initially if gastric motility is impaired (e.g. by many factors including analgesic and sedative drugs, the critical illness itself, and feed composition)
- Gastric promotilants can be effective in overcoming gastro-duodenal paresis.
- Gastro-oesophageal reflux should be diagnosed and managed appropriately.
- Risk of feed regurgitation / aspiration if gastric stasis occurs

Transpyloric feeding is achieved by advancing a feeding tube through the pylorus into the jejeunum eliminates problems related to delayed gastric emptying. The risk of gastric distension and aspiration and gastro-oesophageal reflux is reduced compared to gastricfeeding.Jejeunal tubes are more difficult to place than gastric tubes. Blind placement can be done with subsequent pH and radiographic confirmation. Endoscopic and fluoroscopic placement are alternative techniques.Jejeunal feeding sometimes results in abdominal discomfort and diarrhoea.Surgical or percutaneous gastrostomy or jejeunostomy may be indicated for long term nutritional support

Continuous versus bolus enteral feeds

Where gastric emptying is impaired continuous gastric feeds are usually better tolerated thanbolus feeds

Feed composition

The type of enteral feed should be chosen on the basis of the patients age to achieve therequired caloric and other metabolic requirements.

Click on the links to view the composition of standard baby milks, modified baby feeds andfeeds suitable for older children.

A few observations are pertinent:

- Breast milk is should be used whenever possible when feeding neonates even if additional formula is required to maintain nutritional requirements.

- Carbohydrates
  The mucosal brush border di-saccharidases may be compromised in acute illness limiting the ability of the gut to digest complex carbohydrates. Glucose polymers may be better digested and absorbed. Carbohydrate absorption can be assessed by testing liquid stool for reducing sugars.

- Proteins
  Protein absorption may also be compromised during critical illness by cardiopulmonary bypass and the long-term effects of cardiac failure and systemic venous hypertension. If whole protein feeds are not tolerated, pre-digested feeds (protein hydrolysates) may be used.

Elemental feeds contain free amino acids which require no digestion, but which deliver a high osmotic load to the gut. They are only used in very severe enteropathy, usually after expert consultation.

- Fats
  Long chain triglycerides (LCT) require bile salt and lipase activity to be intact before successful absorption into the lymphatic system can occur. Medium chain triglycerides (MCT) are absorbed directly into the portal circulation; are absorbed more rapidly than LCTs and have less inhibitory effect on gastric emptying.

  Children who develop problems with chylothorax or lymphatic pleural effusions are often managed on low LCT, high MCT diets in an effort to minimise lymphatic drainage.

- Special formulae
  A number of studies, principally conducted in adults, suggest that ICU outcome may be improved by dietary modulation of the immune system. Convincing studies in children are awaited.

Common problems during enteral feeding

Gastric stasis

Gastric promotilants such as metaclopramide, domperidone or erythromycin are used to overcome gastroduodenal paresis. Cisapride[1] should not usually be used in children because of a possible link to prolonged QT. The risk of arrhythmia is believed to be increased if cisapride is administered with other drugs which inhibit the cytochrome P450 enzyme system such as fluconazole (and other –onazole antifungals), erythromycin and some antihistamines.

Gastro-oesophageal reflux (GOR)

Common in neonates leading to poor weight gain, reflux oesophagitis or aspiration. Episodes may also present with bradycardia, laryngospasm, bronchospasm or recurrent stridor. The clinical effects of GOR decline markedly after 1 year of age because of the beneficial effects of gravity once a child assumes an upright posture.

Diagnosis

PH probe – on or off anti-reflux Rx, but always off H2 receptor blockers (e.g. ranitidine) and proton pump inhibitors (Pantoprazole).

Treatment

- Posture
- Thickening of feeds
- Promotilants e.g. domperidone, low-dose erythromycin
- Agents increasing gastric pH e.g. ranitidine or Pantoprazole

Diarrhoea

Diarrhoea occurs frequently in critically ill children.
Common causes include:

- Feed intolerance
- VGI viral, bacterial or toxin induced enterocolitis
- 'Overflow' from constipation mimicking diarrhoea should be excluded

It is essential that enteral infectious precautions are instituted if in any child with diarrhoea. Do not wait for positive microbiology since other children could be at risk

Investigation and Management of Diarrhoea

Definition: > 6 watery stools per day

>2 watery stools + 1/2 % reducing substances

Investigations:

- Full blood count
- Plasma urea and electrolytes
- Stool for Microscopy, culture and sensitivity
- Virology x specimens for electron microscopyReducing substances
- Clostridium Difficile toxin

Management :

Clear fluids for 24 hours

Treat constipation / overflow if present.

Increase feed strength every 12-24 hours

If diarrhoea persists, with reducing substances

-Clear fluids 24 hours
-Dioralyte (oral rehydration solution)
- Then slow regrade with lactose free pre-digested milk

If diarrhoea occurs when on fortified feeds, this is usually due to the high osmoticload.
Check osmolality of feed with dietician
Try continuous feeds until GI tract adapts

If gentle regrading is unsuccessful consider referral to a paediatric gastroenterologist for advice

Oral vancomycin or metronidazole treatment may be started if there is a strong clinical suspicion of Clostridium Difficile induced colitis. In many laboratories the toxin assay may take several days to process and may be falsely negative. Treatment should therefore be started on clinical grounds.

Parenteral nutrition

Parenteral nutrition (PN) was adopted as almost a badge of office by intensivists in the 1970s and 80s. The potential for the gut to absorb some or all of the patient's required metabolic and nutritional intake was often ignored. The pendulum has swung back in favour of enteral nutrition in many circumstances where previously PN would have been used.

Compared to enteral nutrition, parenteral nutrition:

- Is more expensive
- May cause cholestasis
- May impair reticuloendothelial function in vitro; clinical relevance uncertain.
- Is associated with gut mucosal atrophy and bacterial translocation (lack of luminal nutrients)
- Requires central venous access which is associated with technical, infective and thrombotic complications.

A recently conducted a meta-analysis of 26 studies (Heyland et al) which compared parenteral and

oral/gastric nutrition in adults found that Total Parenteral Nutrition did not influence overall mortality in surgical and critically ill patients.

Some children with severe GI dysfunction during critical illness cannot be adequately fed via their gut and partial or total parenteral nutrition is required. Key metabolic components (carbohydrates, protein and lipid), electrolytes, and other nutritional additives (vitamins, trace elements) must be delivered and their effects closely monitored.

Glucose – Lipid mixtures have been shown to confer significant advantages over glucose alone. Amino acid oxidation, glucose oxidation and reduced protein turnover (Bresson 1991) and respiratory quotient (R/Q) are reduced . Since the body's glucose oxidation capacity is limited, any excess glucose is converted to fat . Fatty deposits in the liver lead to jaundice and hepatic dysfunction (Bresson 1989, Burke 1979) which were particularly common when high glucose low-lipid TPN regimes were used.

- Aim to provide 40-50% of non-protein energy as lipid with the balance as glucose.

Glucose delivers approximately 3.4 kcal / g. A 10% glucose infusion provides 200kcal / litre.
Term neonates typically require 4 mg/kg/min (6g/kg/day) on Day 1, increasing to 8mg/kg/min (12g/kg/day on Day 2 of life. Higher glucose intakes may be required in hypoglycaemia or critical illness, typically up to but not exceeding 12 mg/kg/min (18g/kg/day). Beyond this, higher energy intakes are best supplied by adding fat to TPN regime whilst maintaining fat : glucose ratio. A typical neonatal TPN regime will commence with 10g glucose /kg/day on TPN Day 1.

In adult patients, a glucose infusion rate of 4 – 5 mg/kg/min (approximately 6g/kg/day) is optimal.

- Presence of glycosuria and plasma glucose concentration should be monitored closely for signs of glucose intolerance as glucose load is increased.
- Always increase glucose infusion rates gradually (over 3-4 days) to ensure appropriate insulin response, thereby avoiding hyperglycaemia and glycosuria.

Lipid

Lipid emulsions are rich in essential fatty acids, isotonic and calorie dense.

10% Lipid solution	300 mosmol/kg	1 kcal / ml
20% Lipid solution	350 mosmol/kg	2 kcal / ml

Clearance from plasma is dependent on activity of endothelial cell lipoprotein lipase. As with glucose, lipid has a protein–sparing effect and is a useful source of non-protein calories for parenteral nutrition. There is a higher phospholipid – triglyceride ratio in 10 emulsions which results in slower peripheral lipid hydrolysis to a clinically relevant extend, thus 20% lipid solutions are generally preferred as risk of hyper-triglyceridaemia is reduced.

Lipid clearance and therefore tolerance is reduced in sepsis and in the newborn, especially preterms.

- Introduce parenteral lipid slowly starting at 0.5 – 1g/kg/day, increasing by 0.5 g/kg/day to a maximum of 4g/kg/day depending on plasma clearance for term babies and older children.
- Monitor tolerance daily in critical illness by measuring plasma triglyceride levels 4 hours after ceasing lipid infusion since lipid clearance is often impaired. Aim to keep triglycerides < 2mmol/l.
- A minimum of 0.5 – 1.0 g/kg/day lipid is sufficient to prevent deficiency of essential fatty acids.

Two recent studies have confirmed that a balanced carbohydrate + lipid PN regimen is required for optimal nutrition. Bresson et al. found that optimal metabolism existed when 50% of non- protein calories were derived from lipid. Salas-Salvado presented the optimal figure as 40%.

Problems with lipid infusions

- Rapid infusion of high doses of lipid have been shown to enhance pro-inflammatory and vasoconstricting cytokines in some studies.

- Rapid infusions of lipid have also been shown to adversely affect alveolar-arterial oxygen gradient in both pre-term and adult patients with ARDS. However, slow continuous lipid infusions at doses recommended have not been shown to have adverse respiratory effects.

Recommendations

- Use only 20% lipid solution
- Start lipids at at 0.5 – 1g/kg/day
- Increase by 0.5 – 1 g/kg/day until 40-50% of required non-protein calories are from fat. Maximum recommended lipid infusion rate 1 ml/kg/hour 20% lipid solution.
- Always administer lipids over 18-20 hours
- Check triglyceride levels daily during build up. Then twice weekly. Maintain serum TG < 2mmol/l.

Amino acids

Crystalline amino acids solutions are used a nitrogen source in PN. Recommended protein requirements are set out below.

Table **Daily protein requirements**

Age	Recommended intake (WHO) (g/kg/day)	Critical illness (g/kg/day)	Burns (g/kg/day)
0-6 months	2.0	2.0 - 4.0	3
6-12 months	1.6	2.0 – 4.0	3
1-3 years	1.2	1.5 – 2.0	3
3-10 years	1.0	1.5 – 2.0	2.5
10-18 years	1.0	1.5 – 2.0	2.5
Optimal NPE:N ratio	630 – 840 :1	630 :1 minor stress	630:1
		420 :1 major stress	420:1

Clearly protein requirements vary depending on the need for growth, replacement of losses and increased metabolic demands of critical illness. As general rule of thumb, 10 – 20 % calories should be from protein, more precisely expressed in terms of non-protein-energy : nitrogen ratio. There is no consensus on whether or not protein intake should be counted as part of the calorie calculations. The precise proportion of protein which is used as energy substrate rather than contributes to protein synthesis is probably unimportant, provided the concept of balance between non-protein and protein calories is understood, and metabolic goals are achieved.

Electrolytes

The essential electrolytes that we deliver and monitor on an individual basis are:
Sodium The normal sodium requirement is approximately 1.5 - 3 mmol/kg/day. Sodium requirements are increased in very small infants (immature renal tubular function), congestive heart failure (diuretic therapy) and other situations where losses are increased. Sodium can be administered as sodium chloride or as sodium bicarbonate or acetate if buffering is required.

Potassium Requirements are uninfluenced by PN. The normal requirement for potassium is approximately 2 – 3.0 mmol/kg/day in infants, and 1.0-2.0 mmol/kg/day in children. This may require adjustment if the infant is on diuretics (increased losses) or has poor urine output (decreased losses). Potassium may be incorporated in PN as potassium acid phosphate or aspotassium chloride.

Calcium Typical requirement are 1mmol/kg /day. The calcium dose may need adjustment if the infant is on diuretics or is osteopenic. Infants who have been severely asphyxiated or have diabetic mothers may also have unusually high calcium requirements, as do those with Di George anomaly.

Phosphorus The usual dose is 0.2 - 1 mmol /kg /day delivered as sodium glycerophosphate. Larger amounts of phosphorus may be needed by infants on prolonged parenteral nutrition who develop osteopenia . Phosphate supplementation is required during haemofiltration.

Calcium-Phosphorus Ratio A normal calcium-phosphorus ratio promotes optimal bone mineralization. A ratio of 1.7 :1, the retention ratio in the foetus, has been recommended as optimal. A reversed calcium-phosphorus ratio can cause hypocalcaemia, an increase in PTHsecretion (which leads to increased phosphate loss in the urine), and osteopenia.

Causes of hyperphosphataemia include: hypoparathyroidism, excessive intake, vitamin D intoxication.

Causes of hypohosphataemia include: vitamin D deficiency, primary hypoparathyroidism, inadequate intake, diabetic ketoacidosis, hypophosphataemic rickets, phosphate binding agents (magnesium and aluminium salts)

Magnesium: Approximately 60% of the magnesium in the body is firmly fixed to bone, and the remainder is largely intracellular. Because of the slow rate of magnesium exchange between bone and blood, serum magnesium levels do not accurately reflect total body magnesium content. Nevertheless, because total body magnesium is difficult to measure clinically, intravenous magnesium supplementation is directed toward establishing and maintaining normal serum concentrations.
The usual dose of magnesium is 0.15 – 0.3mmol/kg/day (infants), 0.1 – 0.15 mmol/kg/day (children) delivered as the sulphate. The dose is adjusted if clinically significant hypo or hyper magnesaemia is detected.

Note: Be sure to check a serum magnesium level before starting magnesium in the PN solutionon any small infant whose mother was treated for hypertension or pre-eclampsia. The serum levels in these babies are often 3 or greater at birth if Mg treatment was given to the mother.Since renal clearance of magnesium is poor during the first few days of life, neonates may accumulate magnesium given in the PN solution and reach even higher levels with no warning.Significant hypermagnesaemia is uncommon unless due to excessive supplementation. Hypomagnesaemia is most commonly due to diuretic therapy. Other causes include malabsorption and renal tubular disorders.

Vitamins

The vitamin requirements of the premature infant or newborn are met by the addition Solvito(water soluble vitamins) and Vitlipid (lipid soluble vitamins) to the PN solution.

Trace Elements

The trace elements that have been adequately studied and are known to be important in premature and term infants include:
Copper: Important in transferrin production, leucocyte production, bone formation. Normal neonatal value in plasma: 20-70 mcg/dl. Signs of deficiency: anaemia, and rickets-like bone changes. Signs of overdose: diarrhoea, hypotonia, behaviour changes, photophobia, peripheraloedema.
Manganese: Cofactor in many enzymes (e.g. cholinesterase, pyruvate carboxylase). Normal neonatal value in plasma: unknown. Signs of deficiency: nausea, vomiting, weight loss, dermatitis. Signs of overdose: toxicity has not been reported.
Selenium: An important component of glutathione peroxidase, so helps prevent hydroxyl radical formation and protects biological membranes. Normal neonatal value in plasma: 70-120mcg/dl. Signs of deficiency: haemolysis, Keshan's disease (cardiomyopathy). Signs of overdose: pallor, indigestion, irritability, loss of hair.
Zinc: Cofactor in about 70 enzymes; helps to maintain normal growth, hydration of skin, touch and smell senses. Normal neonatal value in plasma: 88-112 mcg/dl. Signs of deficiency: decreased growth, hypogonadism, parakeratosis, dermatitis, alopecia, hypogeusia, anosmia. Signs of overdose: nausea, vomiting, abdominal pain, dehydration, electrolyte imbalance, dizziness, lethargy, incoordination.
Chromium: Mediates insulin reactions, important for peripheral nerve function. Normal neonatal value in serum: 5-17.5 ng/ml. Signs of deficiency: hyperglycemia, peripheral neuropathy, ataxia, and confusional state. Signs of overdose: Nausea, vomiting, renal and hepatic damage, convulsion, coma. However, chromium is not contained in the commonly used trace element replacement solutions available in Europe (Peditrace).

Element (µg/kg/day)	Preterm	Infant	Children
Zinc	100-500	50-100	50-80
Copper	30-60	20-50	20
Selenium		2-5	2
Manganese		1	1
Iron	100-200	20-100	100

Zinc, chromium and selenium are excreted mainly via the urinary tract. Therefore, toxic levels of these elements may accumulate if the infant has decreased renal function, and they shouldbe omitted from the IV solution if the serum creatinine is >1.2 mg/dl. Copper and manganese are excreted primarily via the biliary tract; so the intake of these two elements should be decreased or discontinued if the infant develops cholestatic liver disease (direct bilirubin >2mg/dl).
Zinc and copper may be ordered separately in those situations where intake of other trace elements is not recommended; the usual doses are zinc 150 mcg/kg/day if less than 14 days old or 400 mcg/kg/day if 14 days or older, and/or copper 30 mcg/kg/day. Manganese, chromium, and selenium cannot be ordered separately.
Blood levels of copper, zinc, and selenium should be monitored monthly, beginning 4 weeks after the initiation of parenteral . A special tube is required; contact the lab before drawing theblood. In conditions of cholestasis, renal failure, or suspected deficiency or toxicity, trace element levels may need to be monitored more frequently.

Iron is not routinely provided as a supplement as there is minimal excretion of this metal. Supplementation is usually enteral although some new PN solutions contain iron.

Complications of parenteral nutrition

Catheter related:
At time of insertion-(e.g. malposition, bleeding, pneumothorax) Late e.g. infection, occlusion, thromboembolism)
PN-related cholestasis:
Multifactorial aetiology includes absence of enteral feeding, overfeeding, prematurity, surgery and sepsis. Correlated with duration of PN, and negatively correlated with age. Early institution of enteral calorie intake is the single most important factor in preventing or reversing PN associatedcholestasis

Recommendations for monitoring of critically ill children receiving Parenteral Nutrition

Parameter	Monitoring frequency	Comments
GENERAL MONITORING		
Weight	Daily	Weigh daily if possible. Chart weights daily Aims: to detect a) Fluid retention, b) Growth
Head circumference	Weekly	
Inspect central IV line site	daily	Aims: to detect skin site infection early
HAEMATOLOGY		
Full Blood Count	Weekly	
BLOOD BIOCHEMISTRY		
Glucose	Daily 6 hourly in unstable ICU patients	
Sodium Potassium	Daily	Most biochemistry. parameters should be measured daily in critically ill, unstable patients; twice weekly during step-up /down care and weekly in stable long-term care
Calcium Magnesium Phosphate	Daily	Recommendations here relate principally to critically ill / unstable patients
Urea Creatinine	Daily	
Protein Albumin ALT, AST, AP Bilirubin	Daily	Request direct+ indirect bilirubin in jaundiced neonates
Triglycerides	Daily during build up Then twice weekly	
Acid-base	Daily	
Copper, Manganese Zinc, Selenium Vitamin A, E	Monthly Monthly Monthly Monthly	? accumulate hepatic failure / jaundice ? accumulate renal failure Vit A can cause toxicity if levels increase
URINE BIOCHEMISTRY		
Glucose	Daily during build up	
Electrolytes	As indicated	To calculate accurate losses

IMAGE QUIZ

Dr Krishna Prasad M CICU Consultant

A 6-week old baby boy is admitted under the surgeons with an incarcerated inguinal hernia.In the background: he was born at 38 þ 1 weeks, weighing 2.23 kg and required admission to SCBU for difficulty in feeding, hypoglycaemia and jaundice requiring phototherapy. G6PD status is checked due to maternal deficiency and he is also found to be deficient. Apart from ongoing minor problems with feeding and weight gain, he has been well. The hernia is manually reduced with morphine and he then goes to theatre for surgical repair. Post-operatively, he is noted to have intermittent low blood glucose levels. He is commenced on IV 10% dextrose infusion. Bloods are taken which show: Na 134 mmol/litre, K 4.9 mmol/litre, Cl 105 mmol/litre, urea 2.4 mmol/litre, creat 51 umol/litre, random cortisol: 153 nmol/litre (160e550), Insulin e undetectable, glucose 2.1 mmol/litre, growth hormone 0.8 nmol/litre. A synacthen test is done which shows: baseline cortisol: 251 nmol/litre, 30 minutes post-synacthen: 275 nmol/litre, 60 minutes post-synacthen: less than 20 nmol/ litre. ACTH: 13.4 ng/litre (low)

A. How would you interpret the results of the synacthen test (pick one)?

1. Normal response
2. Cortisol deficiency e primary adrenal pathology
3. Cortisol deficiency e pituitary/hypothalamic pathology
4. Cortisol deficiency e could be adrenal or pituitary pathology

B. What treatment would you start for this?

1. No treatment required
2. Start sodium chloride supplements
3. Start prednisolone according to surface area
4. Start hydrocortisone
5. Start hydrocortisone and fludrocortisones (replacement dose)

He is seen by the paediatric endocrinology team and further tests are done:

Free T4: 12.4 mmol/litre (9-26), TSH: 4.82 U/litre (0.3-4.2), prolactin 3569 nmol/litre (75-375), LH: 2.4 U/ litre (2-12), FSH: 1.9 U/litre (1.7-8), 17-OH progesterone: 10.7 nmol/litre (0.5-20), IGF-1 less than 3.3 nmol/ litre (3-36).

An MRI scan of the brain and pituitary is undertaken (Figure 1).

C. How would you interpret the laboratory and radiological investigations? (Pick 3)

1. Ectopic bright spot of posterior pituitary
2. Small anterior pituitary
3. Absent pituitary stalk
5. Absent corpus callosum
6. Hypoplastic optic nerves
7. Absent corpus callosum
8. Raised prolactin due to disordered hypothalamic control

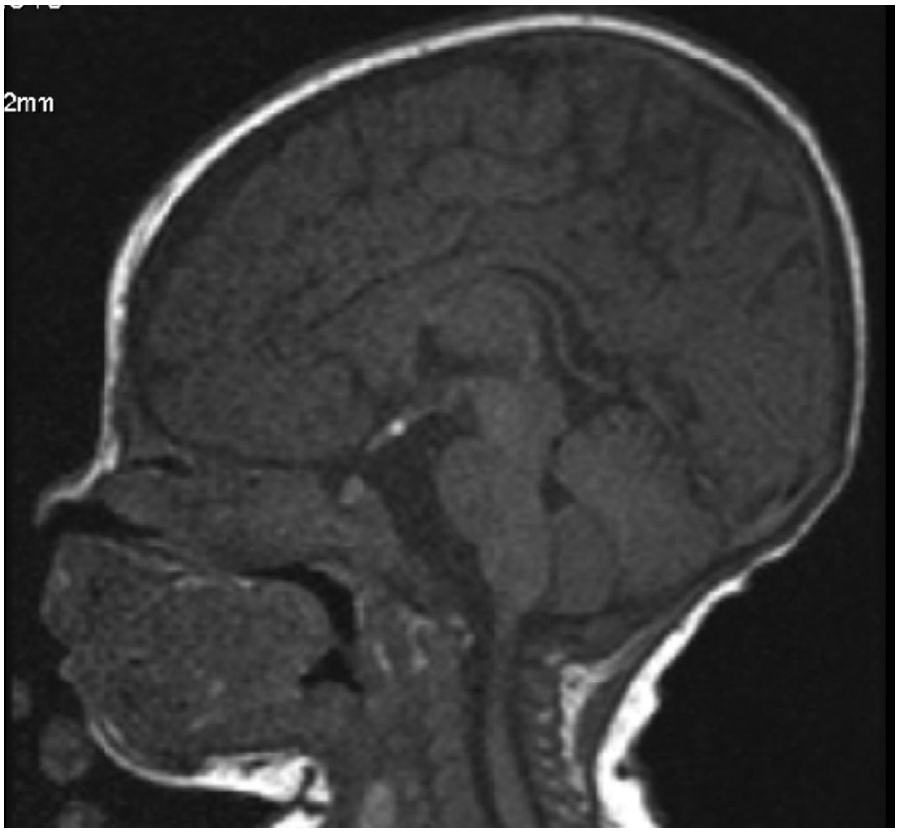

Figure-1

D. What is the most likely underlying diagnosis? (Pick one)

1. Pituitary stalk interruption syndrome
2. Developmental abnormality of the pituitary gland
3. Craniopharyngioma
4. Langerhans cell histiocytosis (LCH)
5. Holoprosencephaly

E. How would you manage this patient (true or false)?

1. Refer to dieticians
2. Refer to neurosurgery for trans-sphenoidal resection of tumour
3. Refer to oncology for consideration of chemo- and radiotherapy
4. Consider growth hormone replacement therapy when baby is older
5. Start thyroxine
6. Stop fludrocortisone and continue hydrocortisone
7. Give parents advice about diabetes insipidus symptoms and tell them to come to hospital immediately if these should occur
8. Advise parents that this carries a very poor prognosis
9. The patient will be on steroid replacement for life
10. Watch for evolving pituitary hormone deficiencies

ANSWERS:

A. 3
B. 5
C. 1, 2, 8
D. 2
E. T, F, F, T, F, T, T, F, T, T

In this case, the cortisol response to synacthen was poor (normal response: peak of 550 nmol/litre or an increment of 200 from baseline). One would expect an abnormally elevated ACTH in adrenal pathology which was not the case here. Therefore a pituitary abnormality was more likely. Moreover the electrolytes remained normal indicating normal mineralocorticoid activity again pointing to a central cause. Whilst the diagnosis is uncertain and waiting for results it is best to treat with hydrocortisone and fludrocortisones replacement doses. In this case there was no salt loss and fludrocortisones was stopped soon after. Sodium chloride supplements are needed in adrenal pathologies like CAH and Addison disease. Vasopressin granules in the posterior pituitary are seen as a bright spot on an MRI scan of the brain.

An ectopic posterior pituitary at the level of hypothalamus or the stalk indicates abnormal neuronal migration and is highly indicative of a developmental abnormality of the pituitary gland. A number of mutations in signalling molecules and transcription factors have been described causing hypopituitarism. In conditions like septo-optic dysplasia, the additional abnormality of a hypoplastic optic nerve may be seen on MRI. Minor abnormalities of prolactin and thyroid function are described with no clinical effect. Prolactin also goes up significantly in conditions affecting the pituitary stalk like LCH. Evolving endocrinopathies (growth hormone and gonadotropin deficiencies) have been described with developmental abnormalities of the pituitary and hence it is important to lookout for these. Diabetes insipidus (DI) may be masked until cortisol replacement therapy is initiated. A normal cortisol status is required for excretion of a waterload. Therefore it is important to lookout for DI symptoms in these children when hydrocortisone treatment is started. Hypoglycaemia in neonates and children should always be investigated especially if persistent.

Endocrine investigations in a hypoglycaemia screen should include true glucose, insulin, cortisol and growth hormone. Deficiency in the latter two can present early with hypoglycaemia. Other key metabolic investigations include ketone bodies, acylcarnitine and carnitine profile, lactate, ammonia and a blood gas. One should also perform a synacthen test (standard or physiological) to rule out cortisol deficiency, either of adrenalor pituitary origin, as cortisol levels are difficult to interpret in the neonatal period and low random levels are not uncommon. Cortisol deficiency may also result in both unconjugated and conjugated hyperbilirubinaemia as occurred in this case. Measurement of 17-hydroxy progesterone should be done if an adrenal pathology, such as congenital adrenal hyperplasia, is suspected. Clues to a pituitary origin like midline facial defects; single central incisor, optic nerve hypoplasia, cleft lip or palate as well as microphallus or undescended testicles and inguinal hernias should be actively sought for by the astute clinician.

NEUROBLASTOMA WITH PARANEOPLASTIC MANIFESTATIONS – A CASE REPORT

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Abstract

The ataxia and horizontal nystagmus can occur as a single neurological event in children with paraneoplastic syndrome in a low degree neuroblastoma. We report a case of Kinsbourne syndrome in a 15 -old-child and, literature review focused on the diagnosis and therapeutic alternatives. This report emphasizes the need for Neurologists and Pediatricians to suspect the hypothesis of an indolent neuroblastoma in patients presenting with paraneopolastic manifestations with no neuroimaging changes. The high percentage of neurocognitive sequelae and permanent deficits is a challenge in the search for new and more aggressive treatment options.

Introduction

The opsoclonus-myoclonus-ataxia syndrome (OMAS) also known as Kinsbourne syndrome can occur as a single neurological event in children with paraneoplastic syndrome in a low degree neuroblastoma . The syndrome occurs most frequently in young children - 3 to 6 years old - and accounts for 2 to 3% of children with neuroblastoma, with an estimated incidence of 1:5 million. It presents with rapid, irregular, involuntary, horizontal and vertical eye movements with no intersaccadic interval (opsoclonus), myoclonus, irritability and cerebellar ataxia .50% of patients have an indolent neuroblastoma. This syndrome manifests itself in small tumors (stage I or II) with favorable histology and without N-myc gene amplification. These tumors rarely recur after resection and the survival is higher than children who do not have neurologic manifestations. Other causes would be idiopathic, associated with viral infections, metabolic and autoimmune diseases .It is accepted that the neurological paraneoplastic syndrome occurs when there are similar antigens between tumor cells and neurons. Despite treatment with corticosteroids, corticotropin (ACTH) and intravenous immunoglobulin, many children with ataxia remain with a residual deficit even after the tumor resection and in some cases there may be severe cognitive deficits as OMAS sequel. We report a 15 month old child, who presented with OMAS as a unique manifestation of an indolent neuroblastoma, focusing on the diagnostic and therapeutic update,

Case Report

A 15 month old, previously fit and well male child had presented to our ER with H/O recurrent falls and abnormal movement of both eyes for 15 days. Mother denies history of fever, altered sensorium or any recent viral infections, no history of trauma. At the time of admission, child was hemodynamically stable with no gross abnormality on general examination .on systemic examination, he had cerebellar signs including, nystagmus, hypotonia, truncal and limb ataxia, and intention tremors. His power was more than 3/5 in all limbs and had DTR of 1+ with normal superficial reflexs.His abdominal system examination revealed a palpable mass extending from the epigastrium to the left renal area. Abdominal ultrasound examination showed a left suprarenal mass measuring 6.5x7 cm. A MRI abdomen demonstrated a large left supra renal mass lesion showing minimal internal echotexture raising the possibility of a neuroblastoma in view of the presenting age (Fig-2). MRI of the brain and spinal cord were done to exclude neoplastic and infectious process within the CNS. PET CT scan had shown a well circumscribed mildly enhancing soft tissue attenuation mass with epicenter in the left suprarenal region.(5.6X4.9X7.5 cm) without any metastatic lesion with low grade metabolically active lesion suggesting a left adrenal neuroblastoma .Subsequently, a Laparoscopic tumour resection (Fig-1) was performed. Child was planned for Chemotherapy and regular follow up depending on the Histo-pathological report of the tumor.

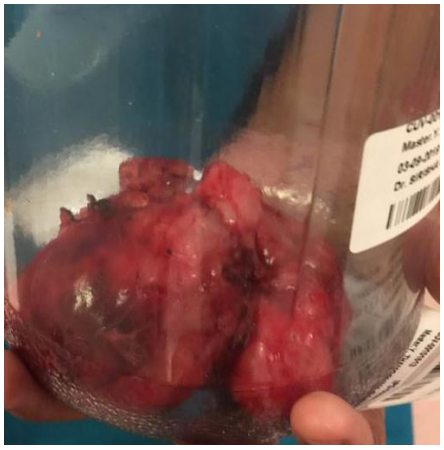

Fig 1: Tumor resected on Laparotomy

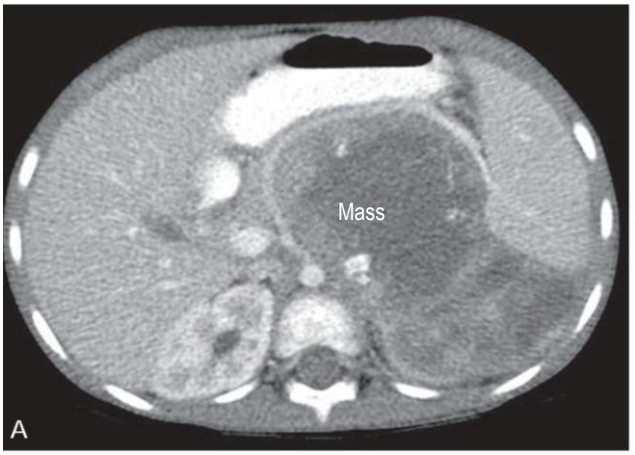

Fig 2: MRI abdomen showing the Left supra renal mass

Discussion

Paraneoplastic neurological syndromes are rare but important in clinical practice. These syndromes are examples of naturally occurring tumour immunity. Tumours causing paraneoplastic neurological syndromes express onconeural antigens which activate an immune response that sometimes successfully suppresses tumour growth. Some of them are associated with presence of onconeural antibodies in serum and cerebrospinal fluid. OMA is a rare neurological condition with an acute onset of myoclonus, opsoclonus, and ataxia. In children, this rare syndrome is typical for neuroblastoma and was first described by Kinsbourne in 1962. The first neurological symptoms of OMA usually appear between 18 and 24 months of age, but this disease can affect children of all ages. Children with OMA do not improve spontaneously and in order to improve their neurological status treatment with steroids or immunosuppressive or cytotoxic drugs is required.

OMA syndrome very rarely can also develop in association with viral infections or vaccination or without any noticeable reason. In idiopathic cases it is assumed that the syndrome could have developed in the course of neuroblastoma which had undergone a complete spontaneous regression. In most OMA cases the tumour is of a small size, without any clinical symptoms related to its primary location. Neurological symptoms of OMA syndrome need to be differentiated from encephalitis, brain tumour, acute cerebellar ataxia and toxic injury. In contrast to OMA, acute post-infectious cerebellar ataxia is never accompanied by either myoclonis or opsoclonus and rarely by irritability. The clinical course of OMA is related to the prodromal phase manifested by changes in the child's behaviour: extreme irritability, inconsolability and insomnia. The symptoms of the disease augment within just a few days. Throughout the acute neurological phase the child suffers from coordination disturbances and frequent falls, accompanied by a decline in neurological status, the loss of ability to sit and stand, fits of anger, blurred speech, hypotonia , tilting of the head, Horner's syndrome, deep tendon reflex disorders or seizures . The course of the disease has periods of exacerbations and remissions, but it is not progressive. In Klein's study, concerning ten patients, remission was achieved within a period of 5 months in seven patients and relapses were present in seven [9]. In some of these patients an MRI examination revealed bilateral cerebellar atrophy. Complete recovery in OMA was seen in only 12-38% of the children Neuroblastic tumours in patients with OMA are less aggressive, have a tendency to involute spontaneously or mature, and are associated with a good prognosis . In 90% of neuroblastomas no metastases are found and the results of oncological treatment are usually very good.

Neuroblastic tumour with OMA is usually a ganglioneuroblastoma or differentiating neuroblastoma, characterized histologically by the presence of diffuse, intense lymphocytic infiltrations and lymphatic lumps. These tumours are usually in the low-risk group according to Shimada and INPC criteria – neuroblastoma with maturation, low MKI, aneuploid, with no MYCN oncogene amplification . In the inflammatory intratumoural infiltrates T-cell lymphocytes predominate. The presence of lymphocytic follicles in the tumour tissues suggests that B lymphocytes play a role in the production of combined antibodies directed at both neuroblastoma cells and neurons in the CNS . Tumour differentiation as well as apoptosis may possibly be caused by chemokines released by stromal cells due to an inflammatory reaction . Neuroblastic cells can present surface antigens – GD2, NCAM, MAG, BAGE, GAGE. However, neither specific or common autoantigens, nor specific antibodies against these antigens were detected in NB patients showed that the majority of the children with OMA have autoantibodies which bind to the surface of isolated rat cerebellar granular neurons . These antibodies inhibited the proliferation of NB-cells in vitro, and were able to induce apoptosis in NB cells, suggesting a humoral autoimmune pathogenesis of the process. The autoantibodies in OMA, both intracellular and surface binding, belong mainly to the IgG3 subclass. In some NB patients antibodies of type Ri-Ab (ANNA2-Ab) and Hu-Ab (ANNA I-Ab) were detected. However, the contribution of antineuronal antibodies to the pathogenesis of distant neurobehavioural disorders in children with neuroblastoma and OMA is controversial.

In our case, the child had opsoclonus and occurred parallel to ataxia and balance impairment. This child hasn't had symptoms related to the primary localization of the tumour, and OMA was the only symptom of the neoplastic disease.Immunohistochemistry showed CD8 cytotoxic lymphocytes and CD56- positive NK cells were the predominant inflammatory cells infiltrating and destroying neuroblastic and ganglioid cells. This supports the results of the Gambini and Cooper group pointing to the prominent cellular immune response within the tumour. On the other hand, CD8 cells are the basic population in inflammatory infiltrates of paraneoplastic encephalomyelitis .

We have no knowledge about the pathological changes within the brains of children with OMA. Autopsy-based studies on paraneoplastic neurological syndromes revealed that the main components of cerebellopathy are neuronal loss of Purkinje and granular cells. What is more, demyelination and lymphocytic infiltrates were described [6]. During the rapid onset of the syndrome, activated T-cells are capable of crossing the blood-brain barrier, whence they enter the brain and attack neurons . Pranzatelli found that in the acute phase of OMA a cell-mediated immunological response dominated . Moreover, increased protein levels in CSF of OMA patients are caused by the intrathecal synthesis of antibodies . In paraneoplastic encephalopathy Dziewulska et al. found increased PECAM-1 expression in blood vessels . PECAM-1 facilitates transendothelial lymphocytic migration. In chronic phases a beneficial fragile immunological balance causes inactivation of the central process; however, it can be destroyed by viral infections. This may explain the periodic recurrence of symptoms , since the viral antigens may provoke similar presentation of antigens as onconeural antigen.This intratumoural immunological reaction triggers the paraneoplastic process against the central nervous tissue components. Children with OMA and neuroblastoma often present permanent neurological and developmental deficits despite a good oncological prognosis, and are in need of specialist medical care, rehabilitation, and psychological and social care.

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