## To Our Readers

As you are aware, the Update Series of the CRNSS on "Nutrition in Disease Management" is now available on payment of an annual subscription of RS. 200. We are encouraged by the interest shown by our readers and have also received very positive feedback about some articles in the Series, which they found very informative.

The current issue of the Update Series consists of two very interesting topics. The first of these is a very interesting subject about which there is a lot to learn regarding nutritional management of inborn errors of metabolism. This is even more relevant taking into account that dietary modification is the mainstay of treatment of these disorders. The second article on "Nutritional management in the critically-ill child" highlights the specific problems encountered in nutrition supplementation in the child in the intensive care setting.

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# Dietary Management of Inborn Errors of Metabolism

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Inborn errors of metabolism (IEM) are disorders in which there is a block at some point in the normal metabolic pathway caused by a genetic defect of a specific enzyme. Neuro-metabolic disorders (NMD) are inborn errors of metabolism with neurologic abnormali-ties. There are over 250 such genetic disorders known till date. Most of these are inherited as autosomal recessive disorders but few are X-linked as well. There is definitely a need for early diagnosis, which can help, in specific therapy preventing progres-sion which is an important feature of these disorders and also for genetic counselling. Prenatal diagnosis is possible for many of these defects.

## EXTENT OF PROBLEM

The estimated burden of IEM is 3-4/1,000 live births1. About 20 percent of acute illnesses in newborns in the developed countries is due to IEMS. Indian data on IEMS are scanty. According to an ICMR multicentric study ~ 5 percent of genetic causes of mental retardation are due to IEM2. Other studies have quoted a figure of 0.5-2.5 percent3. In a study at AIIMS, over 2,000 cases were screened for IEMS and 1.9 percent were found to have amino acid disorders. Common disorders reported were homocystinuria, alkaptonuria, maple syrup urine disease (MSUD) and non-ketotic hyperglycenemia (NKH)4.

The disorders in which specific dietary management is the primary management strategy are phenylketonuria (PKU), homocysti-nuria (HCU), pyridoxine non-responsive, maple syrup urine dis-ease and galactosemia. Many others like urea cycle disorders and organic acidurias may require low protein diets along with other treatment modalities. The clinical manifestations of IEMS are variable and non specific most of the times. Table I summa-rises the manifestations and management of some common IEMS.

**Table I: Summary of amino acid and urea cycle disorders**

| Disorders | Amino acid(s)involved | Typical clinical features of untreatedclassical disorders | Dietary regimen tocorrect biochemical abnormality |
|---|---|---|---|
| **Phenylketonuria** Phenylalanine hydroxylase deficiency | Phenylalanine | Mental retardation, fair hair, eczema, convulsions, tremor | Low phenylalanine: +tyrosine supplements |
| Tyrosinaemia - hereditary type I | Tyrosine, phenylalanine ±methionine | Liver & renal dys-function, rickets, chronic 'Fanconi' | Low tyrosine, pheny-lalanine ±methionine cyst(e)ine supplements |
| Tyrosinaemia - tyrosine amino transferase deficiency | Tyrosine, phenylalanine | Skin & eye disorders with or without mental retardation | Low tyrosine, phenylalanine |
| Maple syrup urine disease (MSUD) | Leucine,isoleucine, valine and their keto- acids | Neurological abnor-malities, feeding problems, ketoacidosis Smell of maple syrup in urine Episodic encephapathy particularly with infections Mental retardation | Low leucine, isoleucine and valine Emergency protein- free high-energy regimen during |
| **Organic acidaemias Commonest**<br><br>(a) Propionic acidaemia<br>(b) Methylma lonic acidaemia | Degradation of isoleucine, valine, theonine and methionine | May present :<br>1. Neonate - over-whelming illness neurological abnormalities, acidosis to thrive, vomiting acidosis<br>2. Infancy-failure to thrive, vomiting and retardation<br>3. Older - intermittent<br>4. Mental retardation | Low-protein diet Emergency protein-free high-energy regimen during infections |
| Urea cycle disorders | Protein degradation Hyperammonaemia | May present:1. Neonate - often lethal due to ammonia intoxication<br>2. Infancy-vomiting, anorexia with particularly protein intolerance<br>3. Older - intermittent drowsiness. | Emergency protein-free high-energy regimen during infections |

| | | | |
|---|---|---|---|
| | | behaviourproblems, neurological abnormalities<br>4. Chronic - mental retardation, neurological abnormalities | |
| Homocystinuria - cystathionine synthetase deficiency | Homocystine in blood and<br>urine Methionine | Dislocated lenses Skeletal, abnormalities Thrombosis Mental retardation | (i) Pyridoxine and folic acid in vitamin-responsive disorders<br>(ii) Low-methionine: cyst(e)ine supple-ments plus vitamin B6 and folic acid |

## PRINCIPLES OF THERAPY FOR IEMS5

Dietary management requires an understanding of both normal nutritional requirements and the basic biochemical defect. The principle strategies of management are:

- Dietary reduction of substrates, frequently protein or amino acids, associated with the formation of the toxic metaboli-ties, for example, phenylalanine in PKU, protein restriction in urea cycle defects, galactose/lactose in galactossemia.
- Replacement of essential nutrients that are deficient as a result of the metabolic block, for example, cystein in HCU.
- Co-factor therapy: Pharmacological doses (up to 100 times the nutrient requirement) of specific vitamins to induce non-functional enzyme activity.
- Enhancement of excretion or product utilisation to form non-toxic metabolites like sodium benzoate in urea cycle disorders.
- The choice of therapy depends on the enzyme defect and its consequences but must be constructed to allow the child to grow and develop normally.
- Dietary therapy should be started as early as possible as during the initial years the developing brain is most sus-ceptible to the toxic effects of the substrate and its by products.
- In most situations, dietary therapy has to be continued throughout life.
- The requirement of protein and essential amino acids must normally be provided in the diet. The total nitrogen require-ment may be lower than normal for infants with organic acidaemias and urea cycle defects. Non-essential amino acids should be provided, ideally in the same proportion as in human milk. Table II gives the normal amino acid requirement.
- Frequent measurements of plasma amino acids and other meta-bolites is essential for monitoring deficiencies and control of the disorder.

**Table II : Amino acid requirement in mg/kg body weight per day (Ref 5)**

| | Age in years | | | | |
|---|---|---|---|---|---|
| - | Infants | 2 to 3 | 5 to 6 | 8 to 9 | 11 to 12 |
| (a) Essential amino acids | | | | | |
| L-Histidine | 16-34 | 0 | 0 | 0 | 0 |
| L-Isoleucine | 79-110 | 88.6 | 80 | 71.4 | 60 |
| L-Leucine | 76-150 | 155.0 | 140 | 125.0 | 105 |
| L-Lysine | 90-120 | 121.8 | 110 | 98.2 | 82.5 |
| L-Methionine | 20-45 | 77.5 | 70 | 62.5 | 52.5 |
| L-Cystine | 15-50 | 77.5 | 70 | 62.5 | 52.5 |
| L-Phenylalanine | 40-90 | 132.9 | 120 | 107.1 | 90 |
| L-Tyrosine | 60-80 | 132.9 | 120 | 107.1 | 90 |
| L-Threonine | 45-87 | 88.6 | 80 | 71.4 | 60 |
| L-Tryptophan | 13-22 | 22.1 | 20 | 17.9 | 15 |
| L-Valine | 65-105 | 110.7 | 100 | 89.3 | 75 |
| (b) Probably essential amino acids | | | | | |
| L-Arginine | 50-75 | - | - | - | - |

In the present article, we will discuss some common amino acid disorders, galactossemia and glycogen storage diseases.

## AMINO ACID DISORDERS

The following alterations are commonly made in diets used for amino acid disorders5.

- **Alteration of amino acid pattern of diet:** This type of diet is used when the plasma amino acid pattern is specifically altered by the inborn error. The elevated amino acid is restricted, for example, low phenylalanine in PKU, low leucine, isoleu-cine and valine in MSUD.

  Limiting amino acid is supplied by dietary protein supplements and intake of protein is titrated against the plasma amino acid lev-els.

  Specifically manufactured diets have proteins supplemented with amino acids in the form of protein substitutes specific for the disorder and has a reduced content of the amino acids which cannot be metabolised.

- **Low protein diets:** IEMS of the catabolism of amino acids which lead to the accumula-tion of toxic metabolites such as ammonia not of specific amino acid require restriction in dietary protein along with high energy intake. These patients will usually tolerate the amount of protein which is just adequate for growth. In these situations, an arbitrary protein intake is prescribed and fine control is usual-ly difficult. Alterative means of removing toxic metabolites is to be considered (Benzoate in urea cycle disorders). Protein should normally provide 6 per cent of the total dietary energy except during relapses. In severe forms, adequate protein supplementation may be difficult.
- **Combined low protein diet with supplementary amino acids:** Certain disorders require limitation of total nitrogen intake but need supplementation of amino acids which become essential as a result of metabolic block, for example, argenine in urea cycle defects.

**Table III gives the requirements of diets used in amino acid disorders.**

- 1. At least the minimum requirement of essential amino acids and total nitrogen for growth needs must be supplied, ideal-ly from conventional foods of high biological protein with or without supplementary amino acids in the form of a pro-tein substitute.
- 2. Adequate energy to spare protein from gluconeogenesis, prevent catabolism associated with malnutrition and starva-tion and allow for growth. Replacement of energy normally provided from protein foods is essential.
- 3. Vitamins, minerals, trace metals and essential fatty acids to cover essential requirements and to supply those normally supplied from restricted foods.
- 4. The normal products of the degradation pathway which have an essential function must be provided, for example, cystine in homo-cystinuria, arginine in ornithine carbamyltransferase defi-ciency become essential amino acids.
- 5. Restriction of essential amino acids, for example, leucine, isoleu-cine and valine, in MSUD requires close supervision and biochemical monitoring to ensure that sufficient amounts are provided for growth without exceeding the individual pa-tient's limited but changing capacity to utilise these amino acids.

## PRACTICAL ASPECTS

### Ongoing management

- **Protein:** In low protein diets, protein should be of high biolog-ical value but dietary variety should be kept in mind. In infancy, human milk or whey-based infant formulae are ideal protein sources. Later other foods such as cereals, pulses, milk, etc are introduced. Protein substitutes are available for specific IEMS but essential fatty acids, energy and conventional food are to be supplemented.
- **Fruits and vegetables:** Fruits and vegetables are mostly permitted without measurement except in few disorders like classical MSUD.
- **Energy:** Proteins cannot be utilised for growth unless adequate dietary energy is available. Protein restricted diets are frequently low in energy.

  Energy can be provided by:
  * Measured quantity of natural protein food
  * Low protein or negligible protein food - sugar, fat, butter
  * Fruits and vegetables
  * Other low protein preparations
  Glucose polymers and fat emulsions are necessary at times.

- **Vitamins and minerals :** When natural food is restricted, vitamin deficiencies may result. A complete supplement of all natural vitamins may be given. Vitamins may have to be used as co-factor therapy in various diseases. A number of minerals and trace elements may have to be supplemented. Readymade preparations are available but not in India.
- **Essential fatty acids:** can be supplemented by using vegetable oils.

  * A good parent-child relationship and parental support are essential.

  * Acute illness and metabolic relapse:

  # Precipitating event should be managed and specific manage-ment according to the disease should be done.

  # Temporary omission of protein (or very low 0.25 - 0.5 gm/kg/day) is recommended along with high energy supplements through oral or parenteral route. We have found hepatic coma diet to be useful during these episodes.

- **Phenylketonuria:** PKU is managed by using a controlled low phenylalanine diet. The recommended intake of nutrients (except phenylalanine and tyro-sine) are similar for normal infants. Protein free energy, all vitamins, minerals and trace elements are supplemented. Regular estimates of blood phenylalanine levels is essential. The levels must be maintained between 3-15 mg/dl. Table IV gives the require-ments for dietary management of PKU.

Several low phenylalanine diets are available in the West. None of these is available in India but can be imported. These special diets are very expensive and most parents have problems of affordability.

Based on the phenylalanine content of some common products used in India, dietary exchanges can be calculated and diet can be charted in situations when commercial diets cannot be procured7.

The patient is usually given 1/3 to 1/10th of normal phenylalanine content. The phenylalanine intake varies at different age groups and has to be titrated according to phenylalanine levels.

There can be some relaxation in rigid dietary restriction after three years of age but some restriction has to continue throughout life. A very strict control in PKU girls during pregnancy is mandatory.

**Table IV: Guide to requirements in the dietary management of 'classical' phenylketonuria per kg actual body weight per day. (Ref 6)**

| Age in | Energy | Total protein and amino acids (g) | Theoretical initial intake of phenylalanine from natural protein (mg) |
|---|---|---|---|
| 0 to 1 | 100 to 130kcal | 3 to miximum 4 | 50 to 60 |
| 1 to 2 | 90 to 100 kcal | 2.4 to 3.5 | 30 to 40 |
| 2 to 4 | 80 to 100 kcal | 2 to 3 | 25 to 40 |
| 4 to 6 | 80 to 100 kcal | 2 to 3 | 25 |
| 6 to 8 | 70 to 90 kcal | 2 to 2.5 | 15 to 25 |
| 8 to 14 | 55 to 75 kcal | 1 to 1.5 | As tolerance |
| over 14 | 45 kcal | 1 | As tolerance |
| Pre-conception and pregnancy | - | Minimum 1 (>50g/day) | As tolerance, increasing with the demands of the foetus in the second half of pregnancy |

- **Maple syrup urine disease:** In MSUD the intake of leucine, isoleucine and valine has to be restricted. The levels for leucine are maintained between 100-700 umol/lit and between 100-400 umol/lit for valine and isoleucine.

  This is a very difficult disorder to manage, and more so without availability of commercial diets. A modified Indian diet can be prescribed but there are no long-term experiences available. The intakes should vary at different age groups and the diet needs modi-fication accordingly.

- **Homocystinuria:** A low methionine and high cysteine diet helps in maintaining intellectual development. The introduction of dietary therapy is worthwhile at any age, but is very expensive for the Indian patient, as commercially produced low methionine and high cysteine formulae are

not available and need to be imported. Therefore, most of the times, one has to plan a special diet for patients, using locally available foods. These diets aim to provide 25-45 mg/kg/day of methionine in infants and 8-10 mg/kg/day of methio-nine in teenagers. Plasma levels of methionine are to be main-tained between 0.03-0.1 mmol/1 and cystine levels between 0.037-0.085 mmol/1. Although, ideally, quantitative measurements of plasma methionine are required, the same information can be obtained by paper chromatography after careful standardisation. Table VI gives a list of restricted and unrestricted food items in homocystinuria. Since wheat and pulses are to be restricted, the caloric density of the diet can be increased by mixing sago or arrowroot powder in wheat flour. A prototype diet for a 10 kg child is shown in Table VII. It is difficult to increase the cystine content of this diet without inadvertently increasing its methionine content. Therefore, these diets are not as effective as commercial diets.

Trial of treatment with Pyridoxine and folic acid (1-5 mg/d) is worthwhile in all the cases. Treatment with betaine (trimethylglycine; 6-9 g/d) which serves as a methyl group donor, produces clinical improvement in patients unresponsive to pyridoxine.

**Table V: Dietary exchanges in Phenylketonuria (Ref 7) (Common Indian foods)**

| **Vegetables (cooked)** | **15 mg exchanges** | **Amount (in ablespoonfuls** |
|---|---|---|
| Green beans | | 5 |
| Cabbage | | 8 |
| Carrots | | 5 |
| Cauliflower | | 3 |
| Brinjal | | 1.5 |
| Spinach | | 1 |
| Gourd | | 3 |
| Onions | | 4 |
| Sweet potato | | 4 |
| Fruits | | Number |
| Apple | | 4 (small) |
| Guava | | 1/2 (medium) |
| Mango | | 1 (small) |
| Orange | | 1 (medium) |
| Papaya | | 1/2 (cup) |
| Watermelon | | 1/2 (cup) |
| | | 30 mg exchanges |
| Cereal | | Amount (in tablespoonfuls) |
| Rice (cooked) | | 5 |
| Wheat | | 2 |
| Barley | | 3 |
| Lentils | | 3 |
| **To avoid** | | |
| Meat, fish Chicken, eggs Urad dal | | |
| **To take ad lib (any amount**) Sweets, jam Butter and ghee Sugar and honey Aerated water | | |

- **Galactossemia:** The classical form of galactossemia is caused by galactose 1 phos-phate uridyl transferase deficiency. Other forms occur due to galactokinase and Epimerase deficiency.

**Table VI: Diet for Homocystinuria patients (Ref 8)**

**List A - Forbidden foods**
(a) Meat, chicken, fish, eggs.
(b) Milk, cheese, curd, ice-cream, chocolates, horlicks, oval-tine.
(c) Wheat flour, bajra, maize, barley, jowar, oat meal, bread, cakes, biscuits and pasteries.
(d) Rice and pulses.
(e) Nuts and dried fruits.
(f) Maggi and other soup cubes.
(g) Peas.
(h) Methi, arvileaves.

**List B - Foods to be consumed in moderate amounts**
(a) Beans, beet root, cauliflower, bathua, cabbage, carrot, onion, potatoes, radish, sweet potatoes, lowki, brinjal, cucumber, bhindi, pumpkin, tomatoes.
(b) Banana, grapes, guava, mango, papaya, apple.

**List C - Unrestricted foods**
(a) Arrowroot, cornflour, sago, custard powder.
(b) Sugars, honey, jam, marmalade, jellies.
(c) Butter, cooking fat and oil.
(d) Tea, coffee, squash.
(e) Salt, pepper, vinegar, spices, curry powder.
(f) Lowki, tori, tinda.

Dietary exclusion of galactose and lactose (from which galactose is derived) is necessary almost through out childhood and major sources should probably be omitted throughout life9. A nutritionally adequate galactose/lactose free milk substitute should be used during infancy and later as a supplement to diet. In later childhood occasional lactose free milk and calcium and vitamin supplements may suffice. Monitoring should ideally be done by measurement of galactose 1-phosphate levels in RBCS. Fortunately lactose free formulae are available in our country and this disorder can be managed with relative ease. Some people also recommend restriction of plant foods (pulses, beans, peas, spinach) during infancy and early childhood due to the presence of galactosides and nucleoproteins which are potential sources of galactose but opinions differ10,11.

***Glycogen storage diseases:** These disorders principally affect the liver and have nine different types depending on the enzymes involved. As carbohydrate metabolism in the liver is responsible for glucose homeostasis, this group of disorders presents typically with hypoglycaemia and hepatomegaly (not in all types)

Treatment is designed mainly to maintain normoglycemia and is achieved by continuous nasogastric infusion of glucose or oral uncooked starch. Uncooked starch acts as a slow release form of glucose.12 This is specially useful in Type I, III and VI but is most demanding in Type I.

**Table VII: Low methionine diet for a 10 kg child (Methionine allowance 25-45 mg/kg, Cal: 100-120/kg, Protein 2g/kg) (Ref 8)**

| | Cal | Protein | Methionine (mg) |
|---|---|---|---|
| **Breakfast** | | | |
| Buffalo milk | 115 | 4.0 | 100 |
| 100ml + 1tsf sugar | 20 | - | - |
| Sago khichari (10g sago, 25g Potato, 1tsf oil) | 110 | 1.0 | 6.0 |
| **Lunch** | | | |
| Rice 50g cooked & drained + 1tsf ghee | 220 | 3.5 | 25 |
| Vegetable 1 Katori + 1tsf ghee | 50 | - | 10 |
| Curd 50 ml | 60 | 2.0 | 50 |
| + Fruit 1 | 50 | - | - |
| **Tea** | | | |
| 50 ml milk | 60 | 2.0 | 50 |
| + 1tsf sugar | 20 | - | - |
| 2 arrowroot biscuits | 50 | - | - |
| **Dinner** | | | |
| Rice 50 g cooked & drained + 1tsf ghee | 220 | 3.5 | 25 |
| 1 katori vegetable | 50 | 1.0 | 10 |
| 1 katori dal masur cooked (25g raw) | 70 | 1.25 | 10 |
| Sweet semolina kheer (20g semolina+ 25 ml milk + 1tsf sugar) | 120 | 3.50 | 55 |
| **TOTAL** | **1215** | **21.75** | **341** |

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## NEWS AND NOTES

Readers will kindly note that the official web site for the Nutrition Foundation of India has now been changed to http://www.nutritionfoundationofindia.org/

### INDIAN SOCIETY FOR PARENTERAL AND ENTERAL NUTRITION (ISPEN) SECRETARIAT

The Secretariat for the ISPEN is now located at the Centre for Research on Nutrition Support Systems (CRNSS), C-13, Qutab Institutional Area, New Delhi 110 016, with effect from January 1, 2001. Dr Sarath Gopalan (Executive Director, CRNSS) is currently the Secretary of ISPEN.

### VII ANNUAL CONFERENCE OF ISPEN

The VII Annual Conference of the Indian Society for Parenteral and Enteral Nutrition will be held at Mt Abu from October 12-14, 2001. For further details contact: Dr S.S. Alurkar, MD, Organising Secretary, 301, Arth Complex, Behind Shree Rama Motors, Mithakhali Six Rds, Ahmedabad 380 009 Tel: (O) 079-6426777, (R) 079-6600036; E-mail: alurkar@indiatimes.com