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Review Article

Inherited Metabolic Disease in the Neonatal Period: Approach to Clinical Diagnosis

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Abstract

This review article highlighted the need for clinicians to be alert to the possibility of an inherited metabolic disease (IMD) being the cause of a neonatal illness and provided a systematic approach to clinical diagnosis when IMD is suspected. Inherited metabolic disease (IMD) must be considered in the differential diagnosis of an ill neonate with nonspecific unexplained features, such as poor feeding, lethargy, failure to gain weight/weight loss, coma, apnoea, hyperventilation, seizures and hypotonia. Investigation for IMD should begin with simple urine and blood screening tests. For example, the urine examination includes checking for unusual odours, urinalysis (for ketones, amino acids, and organic acids), and reducing substance in urine, ferric chloride test and dinitrophenylhydrazine test. This is followed by simple blood tests e.g., full blood count, glucose, ammonia, amino acids, urea and electrolytes (Na, K, Cl, P, Ca) levels, creatinine levels, liver function tests, serum lactate/pyruvate ratio and blood gases. In neonates, ketonuria with acidosis is a very important laboratory finding pointing to IMD. Although the prognosis for patients with IMD presenting in the neonatal period is often poor, every effort must be made to establish the diagnosis for parental counselling and in case prenatal diagnosis is possible in future pregnancies. In conclusion, when presented with an ill full-term neonate with nonspecific, unexplained/peculiar features pursue the usual bacterial septicaemia work-up, but in addition, consider IMD and evaluate, timely, for metabolic disease. This approach is very useful since the commonest mistake in the management of a neonate with IMD is a delay in diagnosis or a misdiagnosis, resulting in a delay in starting treatment with catastrophic consequences.

Key words: Inherited metabolic diseases, Inborn errors of metabolism, Clinical diagnosis, Neonatal screening

Introduction

Inherited metabolic disease (IMD) refers to a disorder in which single gene defects cause clinically significant blocks in metabolic pathways[1]. IMD results from mutations in DNA that code for a specific protein, which may act as an enzyme, receptor, transport vehicle, membrane pump or structural element[2,3]. Most IMDs are inherited as autosomal recessive trait and neonates with parental consanguinity are at increased risk[4]. The incidence of individual, IMD is relatively low with an estimate of 1 in 100,000 to 1 in 200,000 live-births[5,6] However, collectively, the estimated incidence of IMD varies from 1 in 1,000 to 1 in 1,500 live birth[7,8.] The precise incidence rates of IMD are difficult to come by because of undiagnosed cases. The prevalence of IMD is determined by the geographical and ethnic composition of the population. For example, among live births, the estimated prevalence are 1 in 1,400 to 1 in 5,000 in the United States[9], 1 in 2,800 in South Korea,[10] 1 in 5,000 in Thailand[11], 1 in 784 in the United Kingdom[12] and 1 in 2,077 in Germany[13]. With the ever-increasing rate at which new ones and variations of old ones are being recognized, IMD is an area of paediatrics that is assuming an increasing role in both private practice and tertiary hospitals referral[14,15] The most common error in the management of neonates with IMD is a delay in diagnosis, resulting in a delay in commencement of appropriate treatment and, sometimes, a rapidly progressive neurologic deterioration, coma and death[9,16]. In this regard, therefore, there is a need for the paediatrician to develop a system for identifying the patient who might have an IMD and, at least, for determining the general category to which the suspected IMD belongs. The key is a systematic approach that recognizes certain

Major Clinical Manifestations of IMD in the Neonatal Period

Generally speaking, IMD usually do not present immediately after birth because the defective metabolic pathway in the fetus is compensated for by the maternal placental unit. Consequently, there is an interval (hours, days or weeks) during which the neonate appears well. Symptoms appear only when the neonate begins to depend on its own metabolism. However, some IMD like glutaric acidaemia type II, pyruvate carboxylase deficiency, Zellweger syndrome and GM_1 gangliosidosis affect the fetus in utero, resulting in advanced disease at birth. Disorders of carbohydrate and protein metabolism as well as disorders of energy production (gluconeogenesis and glycogenolysis) tend to present in the neonatal period and are usually unrelenting and rapidly progressive[3,9].

constellation of signs and symptoms and utilizes simple generally available and affordable tests.

Inherited metabolic diseases (IMD) are revealed either as a result of the mass screening of neonates or by investigation of ill neonates presenting with a constellation of clinical features. Since developing countries cannot afford mass screening programmes, paediatricians in such regions have to depend on evaluation based on signs and symptom complexes to reach a diagnosis, at least tentatively. Many paediatricians feel overwhelmed not only by the number and complexity of IMD, but also, by the interpretation of laboratory tests needed to diagnose these disorders. As a result, the clinician may exhibit lack of confidence when confronted with a neonate requiring evaluation for IMD. The situation is further compounded by paucity of guidance from the literature on the subject of clinical recognition of these diseases[17]. The majority of IMD that occur in the neonatal period are characterized by non-specific signs and symptoms, such as poor feeding, lethargy, failure to thrive, respiratory distress, seizures and coma which in themselves are not useful in making a diagnosis but when observed in combination, without a known cause, are suggestive of such a diagnosis[8,17].

This review article sought to (i) highlight those constellation of clinical findings in the neonatal period that should alert the clinician to the possibility of existence of IMD; (ii) provide a simplified approach to clinical diagnosis of IMD and; (iii) provide an approach to the use of selected simple laboratory tests in neonates suspected clinically of having an IMD.

Classification of inherited metabolic diseases

Inherited metabolic diseases can be simply categorized into three[2,15]: Classification based on: (i) time of onset; (ii) clinical presentation and; (iii) biochemical basis of the disease. A review of the literature revealed that subdividing IMD by clinical presentation is the most useful approach to evaluation and accurate diagnosis of IMD[9,15,17]. This approach was, therefore, followed in this article.

When to suspect IMD[17,18,19]

A. Historical findings. An inherited metabolic disease should be considered if:

1. There is a high rate of consanguineous marriage in the local population since most IMDs are inherited as autosomal recessive trait.
2. There is a family history of unexplained neonatal or infant death (prior siblings or male infants on maternal side of the family).
3. Maternal illness during pregnancy e.g., acute fatty liver of pregnancy, HELLP syndrome (may occur in pregnancies with a fetus with long chain fat oxidation defects).
4. There are persistent unexplained symptoms, such as persistent or recurrent vomiting.
5. Increased fetal movements(in utero seizures)
6. There is family history of unexplained neuropathy or myopathy
7. History of similar illness especially in siblings.
8. The onset of signs and symptoms listed in Table 4 after a period of apparently good health.
9. Symptoms accompanying changes in diet e.g., soy-based formula.
10. Failure to thrive (failure to gain weight or weight loss).
11. Failure of usual therapies to alleviated the symptoms e.g., in hypoglycaemia.

B. Physical findings associated with IMD

1. Abnormal urine or body odour (Table 1)[3,20]

Table 1: Inherited metabolic diseases associated with abnormal urine or body odour.

Disorder	Odour
Glutaric (type II) and Isovaleric acidaemias	Sweaty feet or cheesy
Hyper metioninaemia	Boiled cabbage or rancid butter
Tyrosinaemia	Musty

Disorder	Odour
Phenylketonuria	Musty
Marple syrup urine disease	Maple syrup or burnt sugar
Oasthouse urine disease (methio-nine malabsorption)	Dried malt or hops (yeast-like)
Methylmalonic and propionic acidaemias	Fruity (ketosis) or ammoniacal
Trimethylaminuria	Rotting fish
Hydroxymethylglutaryl CoA Lyase deficiency	Cat's urine
Hawkinsinuria	Swimming pool

3. Hepatomegaly
4. Hypotonia, seizure, coma, lethargy
5. Apnoea or respiratory distress (tachypnoea, dyspnoea).
6. Dehydration.
7. Cataract

C. Laboratory findings indicating a possibility of IMD

1. Severe hypoglycaemia.
2. Ketotic hypoglycaemia.
3. Urine reducing substance positive but negative with clinistix strip specific for glucose.
4. Metabolic acidosis with elevated anion gap.
5. Ketonuria with acidosis
6. Conjugated hyperbilirubinaemia with increased prothrombin time (PT) and partial thromboplastin time (PTT).
7. Lactate/pyruvate ratio of less than 25 makes the possibility of lactic acidosis, organic acidurias, urea cycle defects and disorders of fatty acid metabolism very unlikely.[20]
8. High levels of lactate and pyruvate suggest mitochondrial defects.[20]

Initial (simple) screening tests

Whenever a neonate is suspected of having IMD, simple initial screening tests should be performed immediately. Such an investigation should begin with simple urine metabolic screening tests and blood analysis. First and foremost, start by checking for unusual urine odour (Table 1). Common urine metabolic screening tests are critical, especially in resource poor countries, where sophisticated medical laboratory facilities are not available (Table 2). Although many of these tests are non-specific, a positive result can indicate which specific test(s) should be performed in the evaluation process.

Table 2: Common urinary metabolic screening tests[4].

Urine test	Principal metabolic disorders detected
Ketones (dipstick)	Glycogen storage diseases, organic acidaemias, tyrosinaemia
Reducing substances	Galactosaemia, diabetes mellitus, fructose intolerance, Tyrosinaemia.
Ferric chloride test	PKU, MSUD, tyrosinaemia,
Dinitrophenylhydrazine	PKU, MSUD, glycogen storage diseases types I, III, V & VI, lactic acidosis.
Nitrosonaphthol	Tyrosinaemias, fructosaemia, galactosaemia
Cetylpyridinium Chloride	Mucopolysaccharidosis.
Paper chromatography	Aminoacidopathies, Renal Fanconi syndrome
Gas chromatography	Organic acidurias, lactic acidosis

Advanced (secondary) screening tests

Further investigation depends on the results of the initial simple screening tests.

a. Tandem mass spectrometry.

Availability of tandem mass spectrometry has revolutionized neonatal screening for IMD because it can detect many several disorders of amino acid, organic acid and fatty acid metabolism using a single blood specimen and analytical technique.[21,22] In addition, it may serve as a complementary to immunoassay-based methods for congenital hypothyroidism and congenital adrenal hyperplasia.[21] Chase et al[23] has shown that tandem mass spectrometry is accurate, sensitive with little or no false positives.

b. Biomakers.

Specialized biochemical genetic laboratories utilize some biomarkers, such as carnitine, acylcarnitine, very long chain fatty acids and lysosomal enzymes but require appropriate-age related reference intervals.

c. Magnetic resonance imaging (MRI)[24].

The nature of myelin has been reviewed by Barkovich and the effects of its different components on MRI parameters elucidated leading to better understanding and diagnosis of IMD.[25]

d. Magnetic resonance spectroscopy (MRS).

Using MRS of the brain, Barkovich et al[26] showed that patients with mitochondrial disorders have high levels lactate. Proton nuclear magnetic resonance spectroscopic studies have shown that the technique can detect N-acetylated metabolites in urine[27].

Approach to Clinical Diagnosis of an Inherited Metabolic Disease in the Neonatal Period

1. Acute neonatal presentations

Table 3: Common presenting features of IMD and common differential Diagnoses

Symptom/sign/ laboratory finding	Common non-metabolic differential diagnoses
Hypotonia, seizure, coma	Hypoxic-ischaemic encephalopathy (HIE) meningitis. Exclude with history, CSF examination, cranial ultrasonography.
Persistent vomiting	Intestinal obstruction, bacterial septicaemia. Exclude with routine sepsis work-up, abdominal x-ray (erect and supine).
Metabolic acidosis	Congenital heart disease e.g., hypoplastic left heart, aortic atresia. Bacterial septicaemia. IMD more likely if no response to treatment with bicarbonate. Renal tubular acidosis, if anion gap is normal.
Hypoglycaemia	IMD more likely if no other cause e.g. SGA, IDM, HIE or persistent/recurrent or difficult to treat.
Conjugated hyperbilirubinaemia	Biliary atresia, hepatitis
Ketonaemia/ ketonuria, abnormal urinary odour	Both very suspicious of IMD, especially if combined with acidaemia.
Neutropaenia, thrombocytopaenia	Bacterial septicaemia, DIC (prolonged PT, PTT, thrombin time, increased FDP)

Adapted from Rennie JM, Robertson NRC[28]

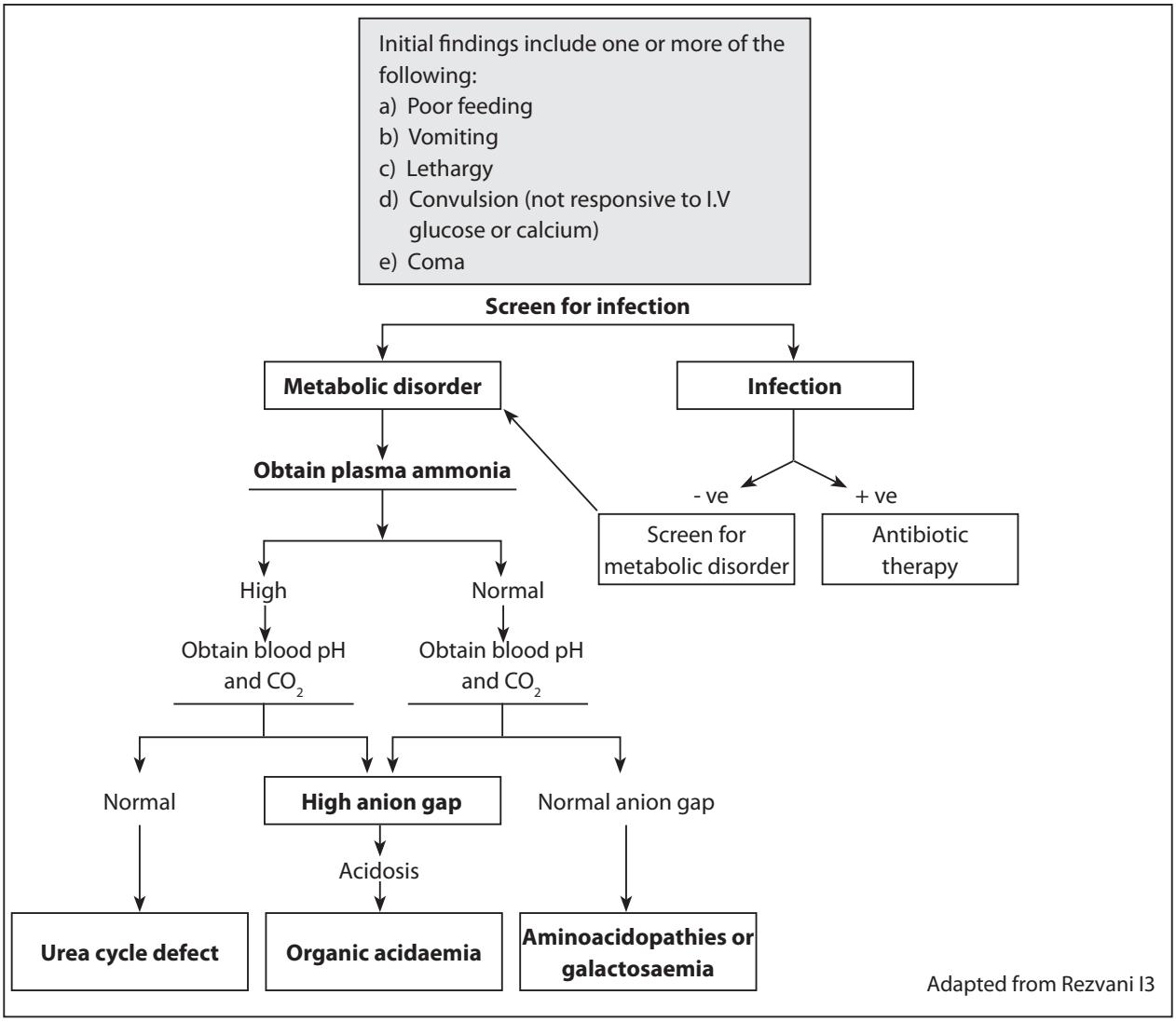

Fig 1: Clinical approach to a neonate with suspected inherited metabolic disease

This schema (Figure 1) is a guide to the elucidation of some of the metabolic disorders in neonates. Although some exceptions to this schema exist, it is appropriate for most cases.

Presentation by symptom complex in the neonatal period

Table 4: Signs and symptom complexes suggesting classes of inherited metabolic diseases.

Signs and symptom complexes	Classes of metabolic disorders to be considered
Neurologic (hypotonia, lethargy, poor sucking, seizures, coma)	Glycogen storage disease, galactosaemia, organic acidaemias, hereditary fructose intolerance, maple syrup urine disease, urea cycle disorders, hyperglycinaemia, pyridoxine dependency, peroxisomal disorders
Hepatomegaly	Lysosomal storage diseases, galactosaemia, hereditary fructose intolerance, glycogen storage disease, tyrosinaemia, Gaucher disease, Alpha-1-Antitrypsin deficiency, Niemann-Pick disease, Wolman disease, fatty acid oxidation defect
Hyperbilirubinaemia	Galactosaemia, hereditary fructose intolerance, tyrosinaemia, Alpha-1-Antitrypsin deficiency
Non-immune hydrops	Gaucher disease, Neimann-Pick disease
Abnormal eye findings: - Nystagmus - Cataract - Corneal clouding - Macular cherry red spot	Zellweger syndrome Galactosaemia, mannosidosis, aspartylglyco saminuria Hurler syndrome, Scheie syndrome, Hunter syndrome, Morquio syndrome Sialidosis, Niemann-Pick disease, Tay-Sach disease Gaucher disease, Gangliosidosis.
Abnormal head findings: - macrocephaly - microcephaly - Large fontanelle	Glutaric acidaemia I, Tay-sach disease mucopolysaccharidoses. Maternal PKU, Smith-Lemli-Optiz syndrome Hypophosphatasia, Zellweger syndrome
Abnormal hair/ alopecia	Biotin deficiency, Argininosuccinic acidaemia
Unexplained haemorrhage	Von Gierke's disease, Tyrosinaemia I, Galactosaemia, organic acidaemias. Gaucher disease
Bone pain	Gaucher disease
Coarse facial features	GM_1 gangliosidosis, Beta-glucuronidase deficiency, I-cell disease, sialidosis
Macroglossia	GM_1 gangliosidosis, Glycogen storage disease Type II (Pompe disease).
Tachypnoea / Dyspnoea	Organic acidaemias, urea cycle disorders
Hypoglycaemia	Galactosaemia, hereditary fructose intolerance, methylmalonic acidaemia, propionic acidaemia. Glycogen stoage disease, MSUD.
Ketosis	Organic acidaemias, Tyrosinaemia
Metabolic acidosis	Organic acidaemias, Glycogen storage disease, MSUD, galactosaemia, hereditary fructose intolerance.
Abnormal odour	See section on clinical presentation of IEM
Bacterial infections	E.coli septicaemia in 25-50% of cases of galactosaemia[2,4] Organic acidaemias due to neutropaenia. Respiratory infection in GSD type I
Cardiomegaly	Pompe disease, fatty acid oxidation defect.

Table 5: Major clinical manifestations of IMD in the neonatal period.

Clinical finding	Associated group of IMD
Failure to thrive, poor feeding	Virtually all IMD
Lethargy	Urea cycle disorders, organic acidaemias
Vomiting	Disorders of carbohydrate metabolism, urea cycle defects, organic acidaemias.
Jaundice	Galactosaemia, hereditary fructose intolerance, glycogen storage disease type IV.
Hypotonia or hypertonia	Urea cycle defects, carbohydrate metabolism disorders.
Seizures	Carbohydrate metabolism disorders, urea cycle defects.

Hepatomegaly	Disorders of carbohydrate and lipid metabolism, mucopolysaccharidosis
Dehydration	CAH, urea cycle defects, propionic acidaemia
Unusual urine odour	Shown in Table 1.
Respiratory distress	Urea cycle defects, congenital lactic acidosis.
Macroglossia	Glycogen storage disease, type II, disorder of lipid metabolism.

CAH = Congenital adrenal hyperplasia

Table 6: Laboratory findings associated with IMD in the neonatal period.

Laboratory finding	Associated IMD
Metabolic acidosis	Organic acidaemias, disorders of carbohydrate metabolism.
Hypoglycaemia	Disorders of carbohydrate and amino acid metabolism
Reducing substances in urine	Galactossaemia, hereditary fructose intolerance, tyrosinaemia.
Ferric chloride test positive in urine (phenistix)	MSUD, PKU, tyrosinaemia, oasthouse urine disease.
Hyperammonaemia	Urea cycle defects, hyperlysinaemia.
Neutropaenia	Organic acidaemias, tyrosinaemia, orotic aciduria, carbamolyphosphate synthetase deficiency.
Thrombocytopaenia	Organic acidaemias, tyrosinaemia

(MUSD = Maple syrup urine disease; PKU = Phenylketonuria)

Table 7: Metabolic disorders that may be associated with reducing substances in the urine.

Metabolic disorder	Reducing compound in urine
Diabetes mellitus	Glucose
Galactosaemia	Galactose
Hereditary fructose intolerance	Fructose
Tyrosinaemia	*p*-Hydroxyphenylpyruvic acid
Renal glycosuria	Glucose
Galactokinase deficiency	Galactose

Confirmatory testing principles[1]

A positive screening test must be followed by specific clinical evaluation and laboratory testing to confirm the disorder. Every protocol for the evaluation of an infant with an abnormal screening result must clarify which patient need to be treated and which one has had a false-positive result. Definitive testing must be carried out promptly and accurately. Parents need to be educated and reassured while testing proceeds because of the intense parental anxiety associated with positive screening tests. Treatment must be commenced immediately the diagnosis is confirmed. If an IMD is excluded, parents need a full explanation and reassurance that the neonate is well.

Diagnostic specimens to be obtained in seriously ill neonates suspected of inherited metabolic disorder

If the condition of a seriously ill neonate is deteriorating and death appears imminent, it is important to gather as much information as possible about the neonate's disorder.

Table 8: Metabolic disorders associated with positive ferric chloride reaction.

Metabolic disorder	Major compound in urine	Colour
DKA	Acetoacetic acid	Cherry red
Conjugated hyperbilirubinaemia	Bilirubin	Green
Phenylketonuria	Phenylpyruvic acid	Green
Tyrosinaemia	p-Hydroxyphenylpyruvic acid	Green, fades rapidly
MSUD	Branched-chain ketoacids	Gray-green
Oasthouse urine disease	a-Hydroxybutyric acid	Purple
Congenital lactic acidosis	Pyruvate	Green-gold

(DKA = Diabetes ketoacidosis; MSUD = Maple syrup urine disease)

Specific diagnostic steps to be taken[15,18]

a) **Blood:** i) Collect 20 – 25ml of whole blood and separate the plasma from the cells and freeze in 1 – 2ml aliquots at –20^{0}C (for quantitative amino acids, carnitine and ketone bodies).

ii) Refrigerate an erythrocyte fraction at 4^{0}C (for enzyme and peroxisomal studies). In addition, refreeze an erythrocyte fraction at –20^{0}C (for enzyme/DNA studies).

b) **Urine:** Collect 20-30ml and store in 5ml aliquots at –20^{0}C (for organic, orotic and amino acid screening).

c) **Vitreous humor (for chemistries)**

d) **Skin:** About 3 – 4mm should be taken as full-thickness sterile biopsy (cleansed with alcohol, not iodine) store in a sterile culture medium (or sterile 5% dextrose in normal saline). Transport immediately to a tissue culture laboratory for fibroblast culture and enzyme/DNA analysis.

e) **CSF:** Store a sample at –20^{0}C.

f) **Liver sample:** May biopsy percutaneously as necessary and store at –20^{0}C.

g) Tissue biopsies of liver, heart, muscle and brain stored at –20^{0}C. Tissue should be evaluated by light and electron microscopy (for peroxisomes, liposomes, mitochondria).

h) Complete autopsy including x-ray films.

Reasons for false-negative results:[1,6,29]

1. In a particular enzyme defect, levels of precursor may not increase at birth until the baby starts an independent existence (metabolism-wise) and this may require commencement of normal feeding e.g. in phenylketonuria, blood phenylalanine is normal but rise to maximum during the first 2 to 3 weeks of life. Screening should, therefore, not be performed before the sixth day of life.
2. The increased concentration of precursors or production of abnormal metabolites, may be dependent on regular feeds and may fluctuate in relation to timing of feeds. It has been shown that the presence of galactose in urine, an observation used frequently to test for galactosaemia, is not a constant feature in all cases of the disease.
3. Some enzyme systems mature weeks or months after birth and if the production of the abnormal metabolites is dependent on this late maturing enzymes, the biochemical signs may be absent in the early stages of life. An example is the late maturation of liver transaminase which converts accumulated phenylalanine to phenylpyruvic acid for excretion in the urine.
4. Common causes of a false-positive test for urine-reducing substances include:

   radiologic contrast dyes, stool contamination, antibiotics (especially ampicillin), pentosuria from pentose-enriched fruits (true positive but non-pathologic) and p-hydroxyphenyl pyruvic acid (tyrosinaemia).

Some practical aspects of newborn screening

In newborn population screening studies, the samples which are easily obtained are:

1. Blood may be obtained at birth from the umbilical cord, and later from capillary samples by pricking the heel. For ease of collection and transportation the blood samples. Many analyses are then performed on these dry blood spots.
2. Urine may be collected conveniently by leaving a filter paper inside the nappy.
3. Blood transfusion gives false-negative results and sample deterioration false-positive results in galactosemia.

Conclusion

It is my hope that the clinical diagnostic guidelines presented in this review article, based on a systematic approach that recognizes a constellation of clinical features and utilizes common and affordable screening laboratory tests will assist clinicians, especially those working in resource poor countries, in the evaluation of neonates for metabolic disorders.

References

1. Thomas JA, Van Hove JLK. Inborn errors of metabolism. In: Hay WW Jnr, Levn MJ, Sondheimer JM, Deterding RR (eds). *Current Diagnosis and Treatment in Pediatrics*, 20th edition. New York, McGraw Hill; 2011:992–1019.
2. Kulkarni ML. Inborn errors of metabolism. In: Parthasarathy A (ed). *IAP Textbook of Pediatrics*, 4th edition. New Delhi, Japee Brothers Medical Publishers Ltd; 2009: 1029-41.
3. Rezvani I. An approach to inborn errors of metabolism. In: Kliegman RM, Behrman RE, Jenson HB, Stanton BF (eds). *Nelson Textbook of Pediatrics*, 18th edition. Philadelphia, Saunders Elsevier; 2007:527-29.
4. Kelley RI. Inborn errors of metabolism. In: Polin RT, Ditmar MF (eds). *Pediatric Secrets*. Philadelphia, Hanley and Belfus Inc; 1989:201-14.

5. Yudkoff M. Metabolic emergencies (Inborn errors of metabolism). In: Fleicher GR, Ludwig S (eds). *Textbook of Pediatric Emergency Medicine*. 2nd edition Baltimore, Williams & Wilkins; 1988:760–71.

6. Crook MA. *Clinical Chemistry and Metabolic Medicine*. 7th edition. London, Edward Arnold (Publishers) Ltd; 2006:368–79.

7. Seashore M. Metabolic disorders. In: Kliegman RM, Marcdante KJ Jenson HB, Behrman RE (eds). *Nelson Essentials of Pediatrics*, 5th edition. New Delhi, Elsevier (publishers); 2006:243–69.

8. Kleinman RE. *Pediatric Nutrition Handbook*, 5th edition. Elk Groove Village, American Academy of Pediatrics Press; 2004:481–90.

9. Gupta A. To err is genetic: Diagnosis and management of inborn errors of metabolism. *Anthropologis*t Special Volume 2007;3:415-23.

10. Yoon HR, Lee KR, Kang S, Lee DH, Yoo HW et al. Screening of newborns and high-risk group of children for inborn metabolic disorders using tandem mass spectrometry in South Korea: a three-year report. *Clin Chim Acta* 2005;354:167-80.

11. Wasant P. Inborn error of metabolism (IBEM) in Thailand. *Southeast Asia J Trop Med Public Health* 1995;26 Suppl 1:109-111.

12. Sanderson S, Green A, Preece MA, Burton H. The incidence of inherited metabolic disorders in West Midlands, UK. *Arch Dis Child* 2006;91(11):896-99.

13. Baric I, Fumic K, Hoffmann GF. Inborn errors of metabolism at the end of millennium. *Croat Med J* 2001; 2(4):379-83.

14. Tasker RC, McClure RJ, Acerini CL. *Oxford Handbook of Paediatrics*. Oxford, Oxford University Press; 2008:925-50.

15. Korson M, Irons M, Levy H. Hereditary metabolic diseases. In: Avery ME, First LR (eds), *Pediatric Medicine*, 2nd edition, Baltimore, Williams and Wilkins, 1994;1013-125.

16. Clarke JTR. *Clinical Guide to Inherited Metabolic Diseases*. Cambridge, Cambridge University Press; 2006.

17. Burton BK, Nadler HL. Clinical diagnosis of the inborn errors of metabolism in the neonatal period. *Pediatrics* 1978;61(3):398-405.

18. Theda C. Inborn errors of metabolism with acute neonatal onset. In: Gomella TL (ed). *Neonatology: Management, Procedures, On-call problems, Diseases and Drugs*, 5rd edition. East Norwalk. Prentice–Hall International Inc; 2004:396-417.

19. Fox G, Hoque N, Watts T. *Oxford Handbook of Neonatology*. London, Oxford University Press; 2010:364-66.

20. Cleary MA, Green A. Developmental delay: when to suspect and how to investigate for inborn error of metabolism. *Arch Dis Child* 2005;90(11):1128-130.

21. Clarke S. Tandem mass spectrometry: The tool of choice for diagnosing inborn errors of metabolism? *Br J Biomed Sci* 2002;59(1):42-6.

22. Marshden D. Expanded newborn screening by tandem mass spectrometry: the Massachusetts and New England experience. *South-east Asian J Trop Med Public Health* 2003;34(Suppl 3):111–20.

23. Chace DH, Kalas TA. A biochemical perspective on the use of tandem mass spectrometry for newborn screening and clinical testing. *Clin Biochem* 2005;38(4):296-309.

24. Lepage N, Li D, Kavsak PA, Bamforth F, Callahan J et al. Incomplete pediatric reference intervals for management of patients with inborn errors of metabolism. *Clin Biochem* 2006;39(6):595-69.

25. Barkovich AJ. Concepts of myelin and myelination in neuroradiology. *Am J Neuroradiol* 2000;21(6):1099-1109.

26. Barkovich AJ, Good WV, Koch TK, Berg BO. Mitochondrial disorders: analysis of their clinical and imaging characteristics. *Am J Neuroradiol* 1993;14(5):1119-137.

27. Engelke UF, Liebrand-van Sambeek ML, de Jong JG, Leroy JG, Morava E, Smeitink JA. N-acetylated metabolites in urine: proton nuclear magnetic resonance spectroscopic study on patients with inborn errors of metabolism. *Clin Chem* 2004;50(1):58-66.

28. Rennie JM, Roberton NRC. *A Manual of Neonatal Intensive Care*, 4th edition. London, Arnold Publishers Ltd; 2002:296-304.

29. Holton JB. *An Introduction to Inherited Metabolic Diseases*. London, Chapman and Hall; 1988:48–73.

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