CASE REPORT

Inborn error of metabolism disgusing as sepsis

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ABSTRACT

Inborn errors of metabolism (IEM) are a genetically inherited disorder that has led to significant morbidity and mortality in the newborns and infant age group. The true prevalence of IEM in India is not known. Havingnon-specific clinical presentation and lack of a routine screening program for newborns in India, it mostly remain undiagnosed and under-reported. With a wide spectrum of nonspecific symptoms,misdiagnosis or delayed diagnosis is common, so our objective is toenhance knowledge and create awareness regarding the red flags of IEM among clinicians so that even slight suspicion of clinical symptoms should be followed by biochemical evaluation.

Many IEM presents with clinical features resembling sepsis but detailed investigations and through history can help us think beyond sepsis. Workup for IEM in our case was suggestive of Propionic acidemia (PA) and Methyl malonicacidemia (MMA).We provide a clinical approach for such critically ill newborns diagnosis. If these cases are detected early and given timely treatment, clinical outcomes can be improved.

Keywords:-Methyl malonicacidemia, propionic acidemia, inborn error of metabolism, sepsis.

INTRODUCTION

Inborn error of metabolism remains a diagnostic difficulty for clinicians and is often missed in infants leading to life threatening complications later in life. [1]We report a case of a two-month old male child who presented with a diagnostic dilemma but after through investigations and following a diagnostic clinical approach was found to have methyl malonic and propionylacidemia. MMA and PA are two genetic inherited disorders due to defiency of mitochondrial located enzyme methyl malonyl CoA mutase and Propionyl CoA carboxylase. [2]Fifty percent cases of MMA respond to vitamin B12 supplementation as half of them are caused due to deficit or metabolic dysfunction of coenzyme dependent on B12, remaining fifty are caused due to specific mutasedefiency.[3]Sass et al in his study on PA and MMA reported that 86% of their patients presented within first 90 days of life,[4] so a sensitization of clinicians regarding diagnostic approach, symptomatology and treatment of IEM is mandatory to have better clinical outcomes.

CASE REPORT

A two-month-old male child born out of a non-consanguineous marriage with normal antenatal, perinatal history presented to the emergency department with complaint of fever, vomiting, abdominal distension and lethargy for two days. The child was on term, with birth weight of 2.8kg now presenting with a weight loss of 400 grams and a history of recurrent admissions since birth. Child was being fed on cows' milk. On admission, child was irritable, pale with sparse hairs, loose skin folds and delayed skin turgor.Vitals recorded were heart rate of 137/min, respiratory rate of 46/min and no fever. Systemic examination revealed abdominal distension, hypotonia and lethargy with rest of the examination unremarkable.

Child was thoroughly investigated due to repeated hospital admissions. Complete blood count revealed hemoglobin of 8 g/dl, total leucocytic count of 7000 per cumm, differential counts of 78.4% polymorphonuclear cells; platelet counts of 250 000 per cumm. Laboratory investigations reported C-reactive protein of 2.9 with normal parameters of blood sugar, liver function test. Lumbar puncture was done and cerebrospinal fluid examination revealed 5 cells per cumm with lymphocytic predominance, total protein 66 mg/dl and glucose 55 mg/dl. CSF culture was sterile. Blood gas analysis suggestive of persistent metabolic acidosis with PH=7.24, 7.22, 7.24, 7.2 on day 1,2,3,4 respectively with arterial lactate =2.68 (N= 1.5-2).Urine for ketones sent due to high lactate levels and was positive. Renal parameters were also deranged.

RFT	DAY1	DAY3	DAY5
Blood urea	60	73	55
Na/K	136/5.7	135/5.8	136/5.7
Creatinine	0.5	0.4	0.4

Among radiological investigations chest x-ray was normal, ultrasound whole abdomen s/o bowel gases.

Working differentials for failure to thrive with persistent metabolic acidosis and dyselectrolemia were made due to 1.faulty feeding with sepsis 2. Metabolic disorder 3.Renal tubular acidosis 4.CAH (Congenital adrenal hyperplasia)

Faulty feeding and sepsis were ruled due to negative septic report and positive urine for ketones and high lactate. Urinary PH>5.5 and ketones excluded the possibility of renal tubular acidosis. Age of presentation along with lethargy, vomiting, dehydration, weight loss and borderline sodium with hyperkalemia pointed towards CAH but no hyperpigmentation of the genitals was against the diagnosis.Pointers in favor of metabolic disorder were vomiting, failure to thrive, lethargy, acidosis, hypotonia, increased lactate levels, dehydration and positive urine for ketones.

With a high suspicion of metabolic disorder serum ammonia levels were sent and reported to be in normal range. Metabolic acidosis with ketosis and lactic acidosis, possibility of organic acidemia and mitochondrial disorder were high.Blood TMS suggestive of propionic acidemia, methyl malonicacidemia and vitamin B12 deficiency. Urine chromatography pointed out increased excretion of methyl malonic acid and borderline excretion of methyl citrate. Repeat urine test was done after vitaminB12 supplementation still suggestive of methyl malonicaciduria.

Table 2: Chronic complications of MMA & PA

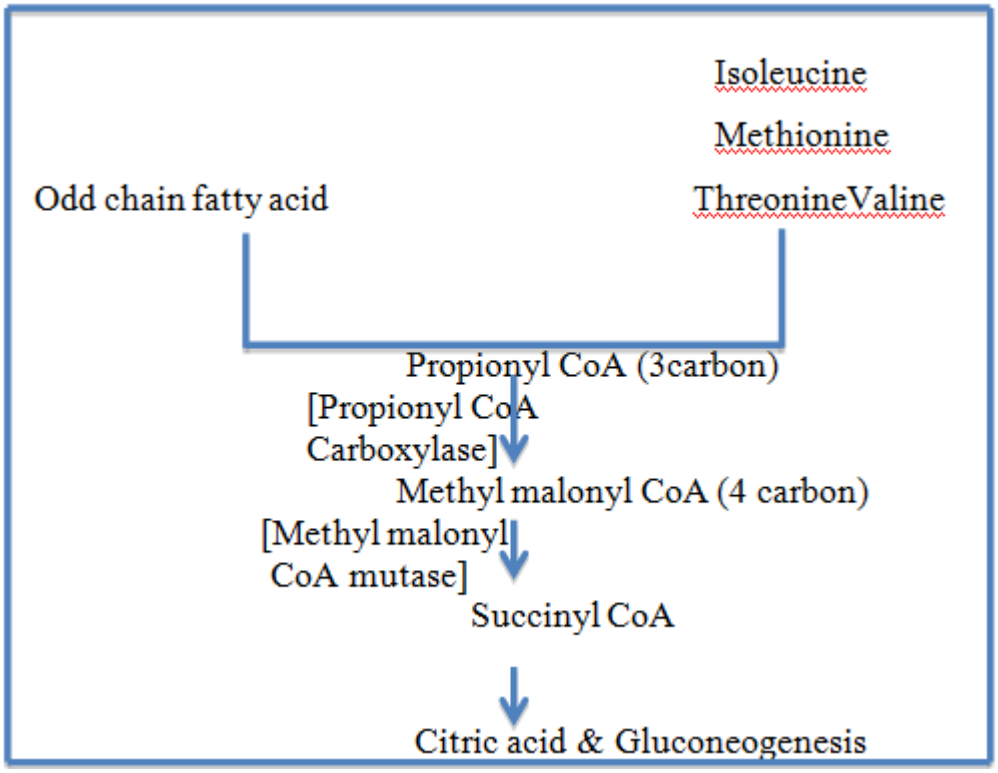
SYSTEM	MANIFESATION	PA	MMA
1.CNS	1.1 Movement disorder (spastic/quadriparesis)	++	++
	1.2 Stroke	++	++
	1.3 Variable intellectual disability	++	+
2.Opthalmological	Optic Nerve atrophy	+	++
3.Gastrointestinal	Pancreatitis	++	+

4.Renal	Tubulointerstitial	-	++
	Chronic Renal failure	+	++
	End stage renal disesase	+	++
5.CVS	Arrthymia	++	+
	Prolonged Qtc	+	-

DISCUSSION

Diagnosing a case of inborn error of metabolism requires high index of suspicionas these disorder have high risk of mortality and long-term neurological disability.[1]MMA methyl malonicacidemiaand propionic acidemia (PA) are rare autosomal recessive metabolic disorder.[5] MMA occur due to genetic defiency of Methyl Malonic Co-enzyme A mutase which is a vitamin B12 dependent enzyme. It is a classical type of organic acidemia. Propionyl CoA carboxylase defiency, a biotin dependent enzyme causes PA. In MMA and PA, there is a defective mitochondrial metabolism of Coenzyme A activated carboxylic acid, which is mainly derived from metabolism of branched chain fatty acid and proteins.[3][flow chart1]There is a wide spectrum of clinical manifestation spanning from neonatal period to adulthood. [6]

Flow chart 1



Acute illness and chronic complications are caused by accumulation of toxic products proximal to metabolic block, altered mitochondrial pathway and oxidative stress. [7] Clinical manifestation of MMA varies with age, severity and B12 supplementation. Disease manifesting early in infancy is the most common, severe form and is least responsive to B12 supplementation.[3]Acute attack causes anorexia, vomiting, dehydration, altered conscious level, encephalopathy or stroke.Chronic complications can manifests as systemic involvement.[8,9] [Table1] Workup of any suspected case should include estimation of blood glucose, serum electrolyte, ammonia, stool for reducing sugar and urine for ketones.

There is no cure, so the aim of the treatment is to reduce formation of toxic products by decreasing the substrate (low protein diet) and supplementation of nutrients. We treated our patient with large dose of vitamin B12 for the acute attack and advised low protein diet, L-

Carnitine, Biotin, Vitamin B12 and alkaline therapy for the long term along with supportive care like maintainingeuglycemia, fluid and electrolyte balance, normothermia, treatment of infections.[10]MMA and PA both have a poor prognosis, even with substrate reduction and supportive treatment 50% of the individual diagnosed in infancy die in early childhood. [3,4]Due to lack of a neonatal screening program in resource poor countries like India, large multicenter studies are needed to understand the disease spectrum better.[11]

LESSONS LEARNT

1. Early and prompt recognition of IEM can prevent long-term disability and morbidity.
2. With a better understanding of pathophysiology of the metabolic disorder, further drug targeting can be improved.
3. Genetic counseling and prenatal diagnosis is essential for parentswithhistory of IEM in family or unexplained sibling death.

REFERENCES

1. Choudhry S, Khan M, Rao HA, Jalan A, Khan EA. Etiology and outcome of inborn errors of metabolism. J Pak Med Assoc. 2013 Sep;63(9):1112-6.
2. Richard E, Jorge-Finnigan A, Garcia-Villoria J, Genetic and cellular studies of oxidative stress in Methylmalonicaciduriacobalamin deficiency type C (cb1C) with homocystinuria, Hum Mutat, 2009, 30(11):1558-156
3. Singer C, Coşoveanu S, Puiu I, Al-Khzouz C, Dumitra G, Doşa M, Marinău L, PopescuM.methylmalonicacidemia in children–case presentation. Revistasoceita ŢII romane de chirurgiepediatrica.2016 :65-67
4. Sass JO, Hofmann M, Skladal D, Mayatepek E, Schwahn B, Sperl W. Propionic acidemia revisited: a workshop report. ClinPediatr (Phila). 2004 Nov-Dec;43(9):837-43.
5. Zhou X, Cui Y, Han J. Methylmalonicacidemia: Current status and research priorities. Intractable Rare Dis Res. 2018 May;7(2):73-8.
6. Fraser JL, Venditti CP. Methylmalonic and propionic acidemias: clinical management update. CurrOpinPediatr. 2016 12;28(6):682-93.
7. Yanfei Li, Tao Peng, Xiaohan Wang et al, A primary study on down-regulated miR-9-1 and its biological significances in MethylmalonicAcidemia, J MolNeurosci (2014), 53:280-286.
8. Deodato F, Boenzi S, Santorelli FM, Dionisi-Vici C. Methylmalonic and propionic aciduria. Am J Med Genet C Semin Med Genet. 2006 May 15;142C(2):104-12.
9. Martinez Alvarez L, Jameson E, Parry NR, Lloyd C, Ashworth JL. Optic neuropathy in methylmalonicacidemia and propionic acidemia.Br J Ophthalmol. 2016 Jan;100(1):98-104.
10. Baumgartner MR, Hörster F, Dionisi-Vici C, Haliloglu G, Karall D, Chapman KA, et al. Proposed guidelines for the diagnosis and management of methylmalonic and propionic acidemia. Orphanet J Rare Dis. 2014 Sep 2;9:130.
11. Dionisi-Vici C, Deodato F, Röschinger W, Rhead W, Wilcken B. 'Classical' organic acidurias, propionic aciduria, methylmalonicaciduria and isovalericaciduria: long-term outcome and effects of expanded newborn screening using tandem mass spectrometry. J Inherit Metab Dis. 2006 Apr-Jun;29(2-3):383-9.