Metabolic Disorders Associated with Unexplained Hypoglycemia in critically ill newborns

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Background : Hypoglycemia is an abnormally diminished content of glucose < 2.6 mmol/L (45 mgm %) in the blood[1]**.** After ruling out severe sepsis, systemic illness, IDM and SGA, several metabolic disorders responsible for severe hypoglycemia need systematic evaluation[2].

Objective and design : Our objective was to find the metabolic disorders associated with unexplained severe hypoglycemia in critically ill new born in a retrospective study.

Materials and method : Out of **483 CINB** cases we analyzed over the past **5 years (Jan 2007 - Oct 2012**); **46** cases had unexplained severe hypoglycemia as a presenting feature. Specific tests were performed which included ammonia, lactate, LFT, urinary ketones, blood gases and calculated anion gap, free fatty acids, GC-MS of urine for organic acids, carnitine / acyl carnitine profile by TMS, VLCFA, plasma amino acids and Sr, Insulin[2].

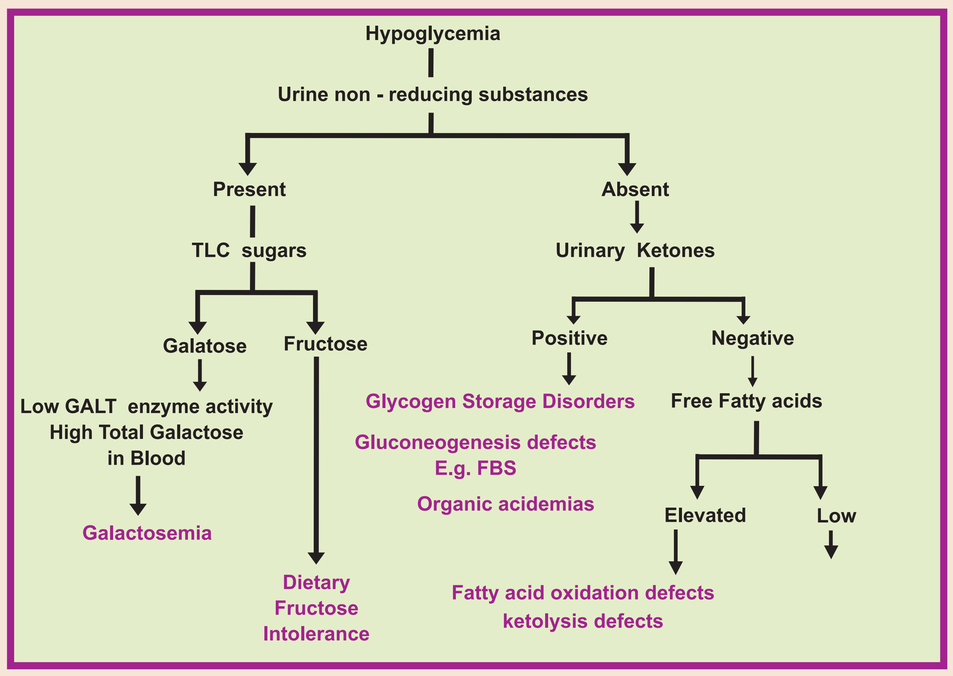
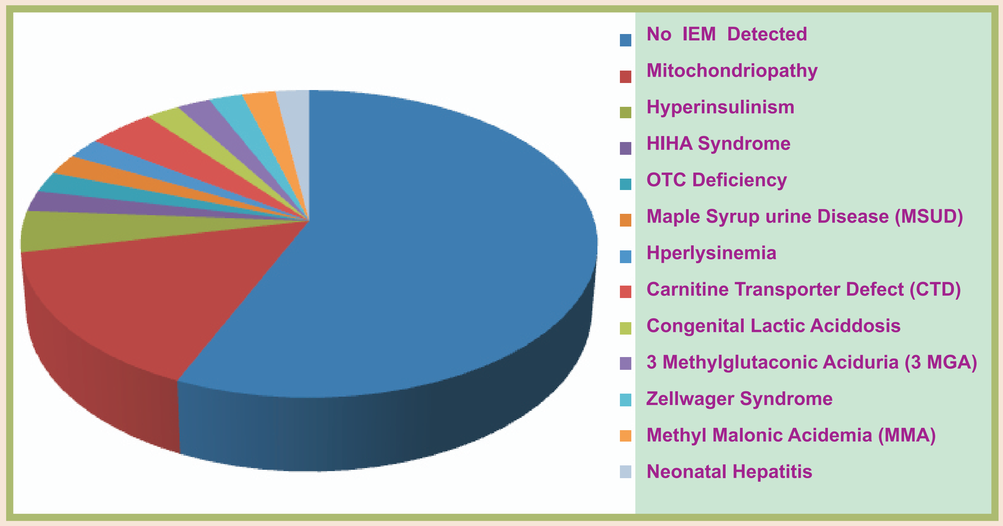


Fig : Flow - chart for metabolic work - up of cases presenting with unexplained hypoglycemia.

Result : In our cohort the commonest disorder was **Mitochondriopathy** (7/46) followed by **Hyperinsulinism**(3/46

		n = 46
1	No IEM Detected	1
2	Mitochodriopathy	2
3	Hyperinsulinism	3
4	HIHA Syndrome	4
5	Ornithine Transcarbamylase Deficiency	5
6	Maple Syrup urine Disease (MSUD)	6
7	Hyperlysinemia	7
8	Carnitine Transporter Defect (CTD)	8
9	3 Methylglutaconic Aciduria (3 MGA)	9
10	Zellwager Syndrome	10
11	Methyl Malonic Acidemia (MMA)	11
12	Neonatal Hepatitis	12



Discussion : - The commonest condition associated with unexplained hypoglycemia is Mitochondriopathy and second most common is Hyperinsulinism. Babies needing glucose supplementation in excess of 10-12 mgm/kg/min should be considered to have Hyperinsulinism. Serum insulin measurement during hypoglycemia often reveals low insulin levels at the time of hypoglycemia and is therefore less sensitive but ***any measurable insulin is suggestive of Hyperinsulinism*.** The diagnostic tests are Genetic analyses – *ABCC8 (SUR1), KCNJ11 (Kir6.2), GLUD1, GCK, HADH, HNF4A, SLC16A1, UCP2*[3]. 18FDOPA PET scan for pancreatic nodules is also very helpful in diagnosing localized hyper secretion of insulin[3]**.** Treatment with Diazoxide may be tried in the dose of 5-15 mgm/kg/day[4]. Mild to moderate hypoglycemia is associated with many disorders but discussion of these is beyond the scope of this poster.

Conclusion : Many inborn errors are responsible for unexplained severe hypoglycemia and they should be systematically investigated. We here with provide a protocol that we follow at our clinic to investigate a case of severe unexplained hypoglycemia.

Abbreviations : IDM- Infant of Diabetic Mother, SGA- Small for Gestational Age**.** LFT- Liver Function test, GC-MS- Gas Chromatography and Mass Spectrometry, TMS- Tandem Mass Spectrometry, VLCFA- Very Long Chain Fatty Acid, HIHA- Hyperinsulinemia Hyperammonemia,

Acknowledgement : We are highly grateful to Dr. Adolf Muehl for his immense contribution and guidance in diagnosing the disorders.

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1. Zschocke J, Hoffman G. Vademecum Metabolicum, 3rd Edition
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Neonatal Jaundice: Approach to diagnosing IEMs

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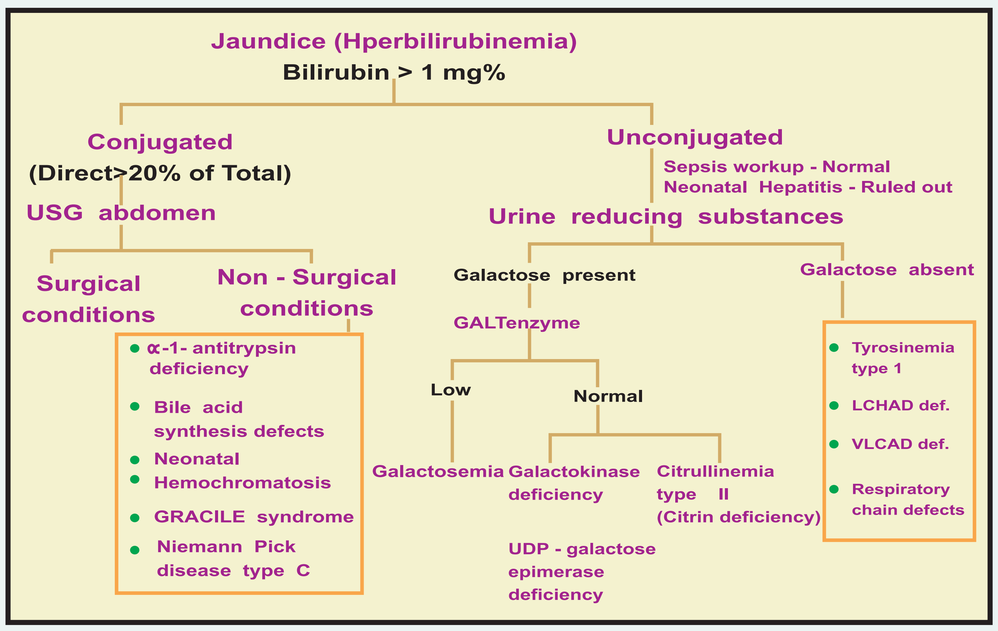
Introduction : Jaundice is one of the most common presentations in critically ill newborns. Causes of neonatal jaundice are many ranging from physiological jaundice, sepsis, hepatitis or inborn errors of metabolism. The present study reviews the approach to neonate with jaundice to identify inborn errors of metabolism.

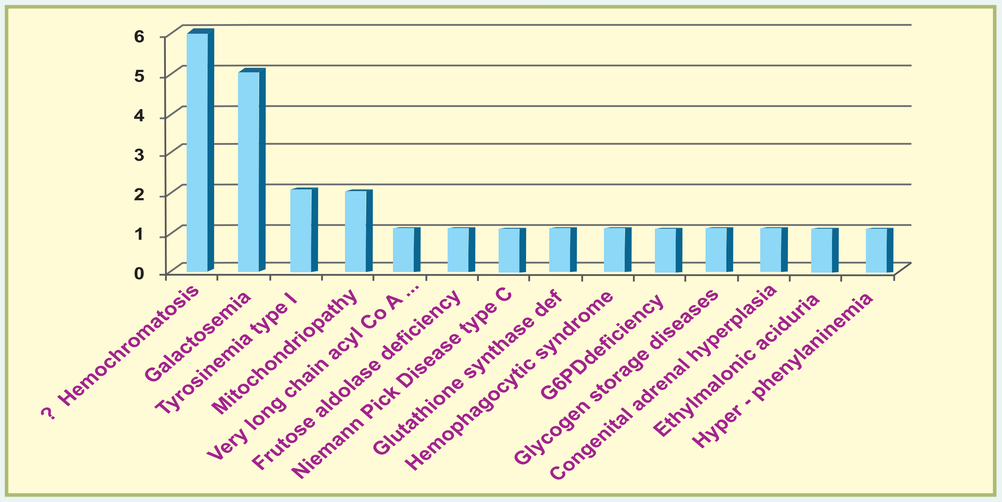
Objective : To put forward a guideline to work up a case presenting primarily with jaundice. To identify inborn errors of metabolism in critically ill newborns presenting with unexplained jaundice.

Material & Methods : Total **483** patients were studied from the year 2008 -June-2012 visiting our clinic. Among these **57** patients presented jaundice in newborn period. Blood and urine samples of these patients were analysed for ammonia, lactate, bilirubin, SGPT, GGT, AFP, amino acids, organic acids, GALT enzyme, Total Galactose, G6PD enzyme, quantitation of succinylacetone, anti - oxidants like glutathione, serum ferritin, total bile acids, bile acid analysis for bile acid conjugates by tandem mass spectrometry, free fatty acids, carnitine/ acyl carnitine profile. Whenever required gene studies were also performed for confirmation.



Results : In our cohort of **57** patients presenting with jaundice we found **26** with inborn errors of metabolism. Since our centre is a specialized metabolic centre, there is a referral bias for metabolic cases. We also had one case of Down's syndrome that presented with prolonged jaundice. The commonest metabolic disorder observed was Galactosemia followed by Tyrosinemia type I. Mitochondriopathy and Hemochromatosis were strongly suspected in 2 and 6 cases respectively, based on biochemical results but need more specialised biopsies and genetic testing than available currently.

Metabolic Disorders	n=25	%
Galactosemia	**5**	**8.77%**
Tyrosinemia type I	**2**	**3.51%**
Mitochondriopathy	**2**	**3.51%**
Very long chain acyl Co A dehydrogenase def	1	1.75%
Fructose aldolase deficiency	1	1.75%
Niemann Pick Disease type C	1	1.75%
Glutathione synthase def	1	1.75%
Hemophagocytic syndrome	1	1.75%
G6PD deficiency	1	1.75%
Glycogen storage diseases	1	1.75%
Congenital adrenal hyperplasia	1	1.75%
Ethylmalonic aciduria	1	1.75%
Hyper- phenylalaninemia	1	1.75%
? Hemochromatosis	**6**	**10.52%**



Discussion : The 2 commonest metabolic disorders in critical babies presenting with jaundice are **Galactosemia (8.77%) and Tyrosinemia Type I (3.51%)**. Galactosemia and Tyrosinemia type1 are the commonest metabolic disorders associated with jaundice in critical babies[1].

Six babies had significantly elevated ferritin with abnormal PT/PTT, not so significantly elevated or normal SGPT, normal GGT and grossly elevated AFP, suggesting a very strong possibility of **Neonatal Hemochromatosis (NH)**. However further confirmatory studies like MRI and biopsy were not available in all six cases as babies expired early in the course of disease. Studies of iron status often show hyper saturation of available transferrin, with hypo- transferinemia and hyper ferritinemia (>800 ng/ml), which though characteristic in NH are non-specific in liver disease of new born infant[2]. Hence a high index of suspicion and early investigation in a critical baby with jaundice for Hemochromatosis is essential. One new born presented with features of Neonatal Hemochromatosis however, MRI did not reveal any extra- hepatic iron deposition, serum triglyceride levels were markedly elevated and bone marrow biopsy confirmed Hemophagocytic Syndrome (HLH).

Mitochondriopathies, especially mitochondrial DNA depletion syndrome also can present with liver cell failure and jaundice in early neonatal period. Molecular studies (***DGUOK* and *MPV17***) are available for confirmation[3]. However biochemical analysis like GC/MS of urine, lactate amino acids in plasma etc. can give a clue. Some disorders, though usually not associated with jaundice, may present with critical illness and mild to moderate hyperbilirubinemia as we found in Congenital Adrenal Hyperplasia, Ethylmalonic Aciduria, and Hyper-phenylalaninemia.

Conclusion : Galactosemia and Tyrosinemia are always considered the most common disorders in newborns presenting with jaundice, however in the present study we found that even though rare, there are other disorders that present with jaundice in neonates. These disorders should also be considered while investigating the cause of jaundice, so that they are not missed out. We provide guidelines for investigation of metabolic disorders in a case with jaundice. Mitochondriopathy and suspected Hemochromatosis cases need specialised biopsies and genetic studies.

Acknowledgement : We are highly grateful to Dr. Adolf Muehl for his immense contribution and guidance in diagnosing the disorders.

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1. Jalan A. Metabolic liver diseases in IEMs in critically ill new borns. Nobel Publisher, 1st Edition. 2011, 93-104.
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APPROACH TO HYPERAMMONEMIA IN NEONATES

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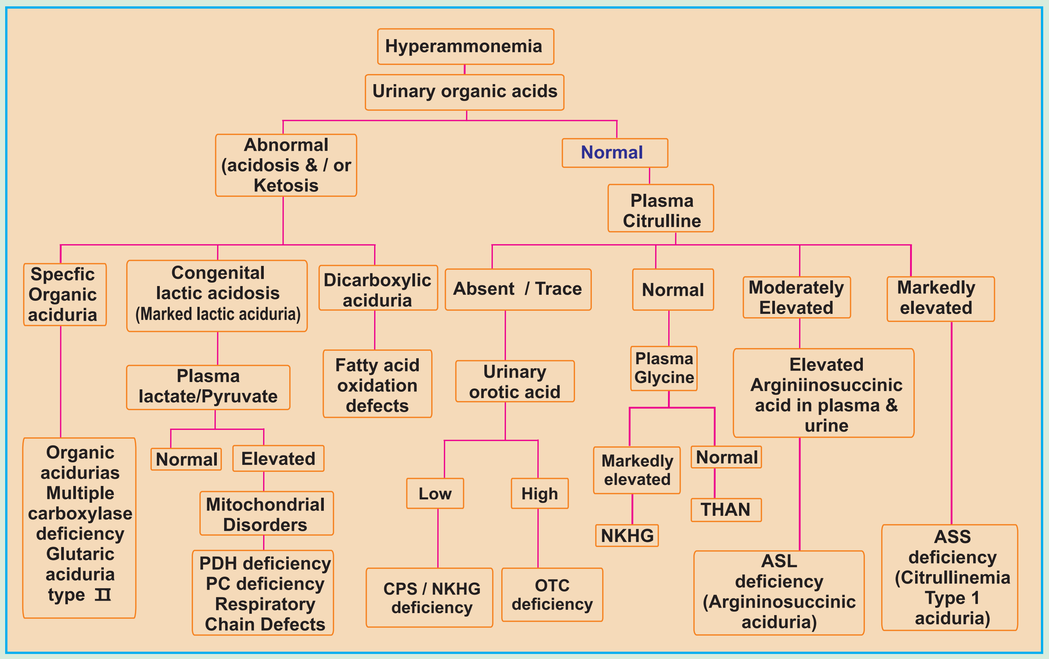
Introduction : A metabolic disorder should be strongly suspected in all term babies with ammonia >200 µmol/L. As treatment differs for different causes of hyperammonemia, it is important to reach the exact diagnosis in these cases as early as possible.[1]

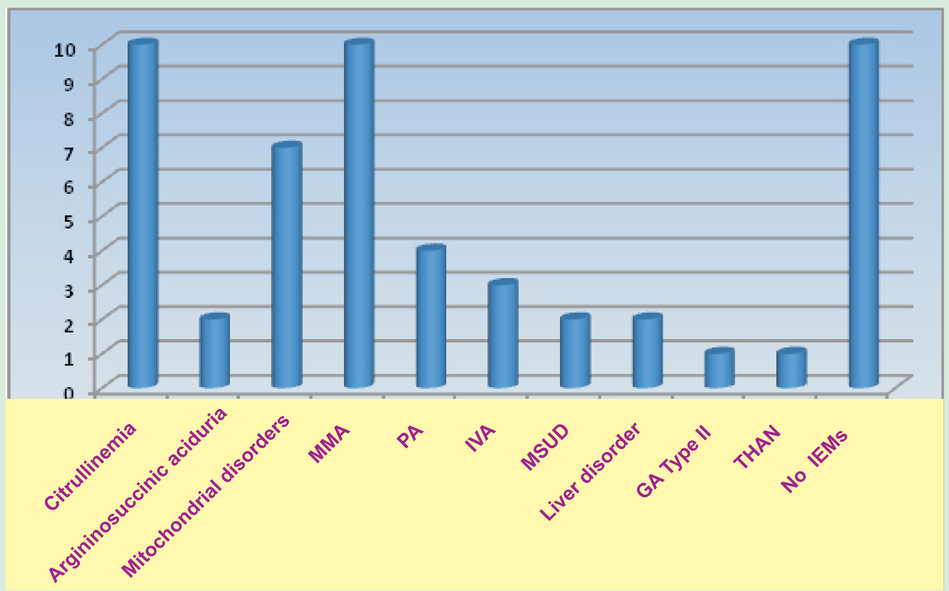
In this retrospective analysis we determine the most common metabolic disorders associated with hyperammonemia. We also attempt to chart a systematic approach to be followed for the early and exact diagnosis in newborns presenting with hyperammonemia.

Materials and Methods : In the present study we analyzed a total of 483 Critically Ill Newborns from Jan, 2008 to June, 2012. Among these, 53 patients presented chiefly with hyperammonemia. Basic laboratory investigations like blood glucose, ammonia, acid- base status, lactate and urinary ketones was followed by a series of specialized tests such as organic acids and orotic acid in urine, amino acids in plasma and urine and acyl carnitines in blood spots. A systematic sketch of the protocol followed at our institute to work-up a hyperammonemia case is given below.



Result : Our results showed hyperammonemia to be a primary presenting symptom in various Urea Cycle Defects among which Citrullinemia constituted the principle differential. Organic acidurias and mitochondrial disorders also represented a major group of disorders apart from Urea Cycle Disorders (UCDs) to present with hyperammonemia.

Metabolic Disorders	Scatter
Citrullinemia	**n= 10**
Argininosuccinic aciduria	n= 2
Mitochondrial disorders	n= 7
MMA	n= 10
PA	n= 4
IVA	n= 3
MSUD	n=2
Liver disorder	n=2
GA Type II	n=1
THAN	n=1
No IEMs	n=9



Discussion : It is essential to measure ammonia early in any sick child in whom a metabolic disorder may be the underlying diagnosis. Blood collected in heparinized or EDTA Vacutainers and kept on ice or analyzed immediately or deproteinized immediately (within 15-20 mins) give accurate results. False elevation of ammonia may be seen otherwise. Also mild hyperammonemia is common and levels of 100-200 µmol/L are commonly seen in a sick child[2].

Nh_3 concentration: µmol/L = µg/dL x 0.59

The most common cause of severe hyperammonemia in our cohort was found to be Urea Cycle Diseases (**Citrullinemia type I** being the principal differential). These newborns presented with progressive or chronic encephalopathy. Respiratory alkalosis and metabolic alkalosis or acidosis was also observed in some cases. The prognosis of a urea cycle disorder is poor if there is prolonged coma (>36 hrs) before specific therapy is started or if the concentration of ammonia remains elevated[1].

32.08% of severe neonatal hyperammonemia cases in our cohort were diagnosed as Organic acidurias. Methylmalonic aciduria, Propionic aciduria, Isovaleric aciduria, etc. presented with hyperammonemia associated with lactic acidosis and ketosis in these newborns. Mitochondrial disorders also presented with acidosis and hyperammonemia.

Emergency management of hyperammonemia by means of extra- corporeal detoxification must be promptly initiated after detection of hyperammonemia. Glucose infusion (6-10 mg/kg/min) with appropriate electrolytes to reduce catabolism and Sodium benzoate / Na. phenyl butyrate[3] for detoxification of ammonia (dose of 250 mgm / kg / day) should be started at the earliest.

Conclusion : Hyperammonemia plays an important role in differential diagnosis of many IEMs. The outcome depends upon early and exact diagnosis and proper management and treatment. We therefore insist upon a systematic approach towards diagnosis in Hyperammonemia.

Acknowledgement : We are highly grateful to Dr. Adolf Muehl for his immense contribution and guidance in diagnosing the disorders.

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1. Zschoke J, Hoffmann G. Vademecum Metabolicum- Manual of Pediatrics, 3rd Ed.
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Clinical Approach to the Spectrum of IEM's in neonates with Convulsions

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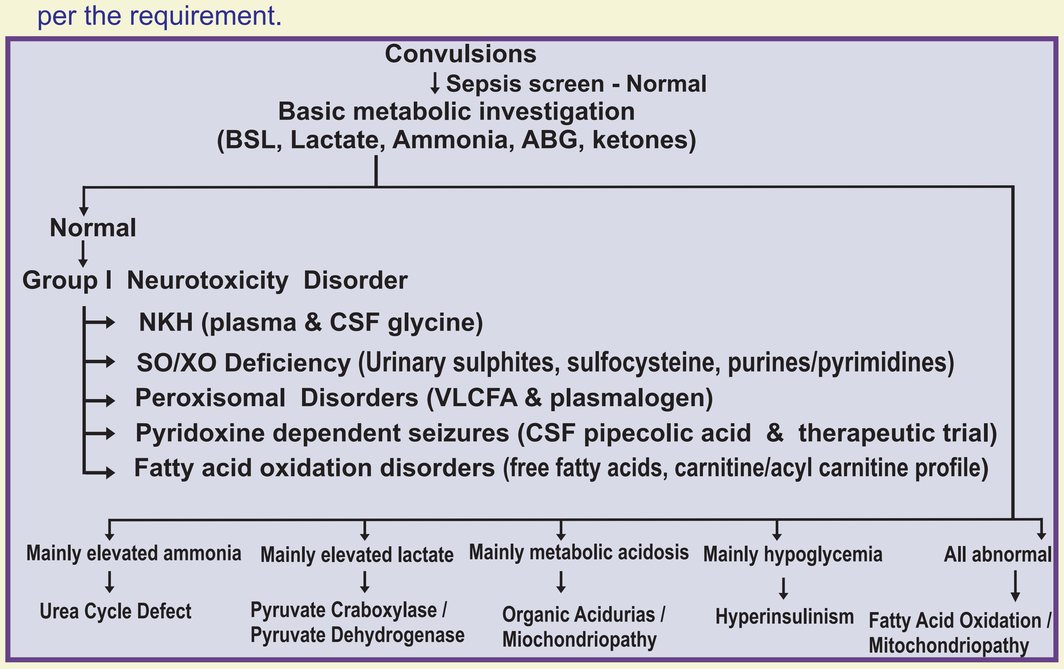
Introduction : Intractable convulsions are a challenging aspect of intensive care of newborns. Inborn errors of metabolism have to be considered in all cases of early onset neonatal convulsions or intractable convulsions. A vast majority of these defects are responsive to treatment and if detected early in the neonatal period will have better outcome.

We herewith present a retrospective analysis of spectrum of IEM's presenting as convulsions and propose a clinical approach to neonates with intractable convulsions.

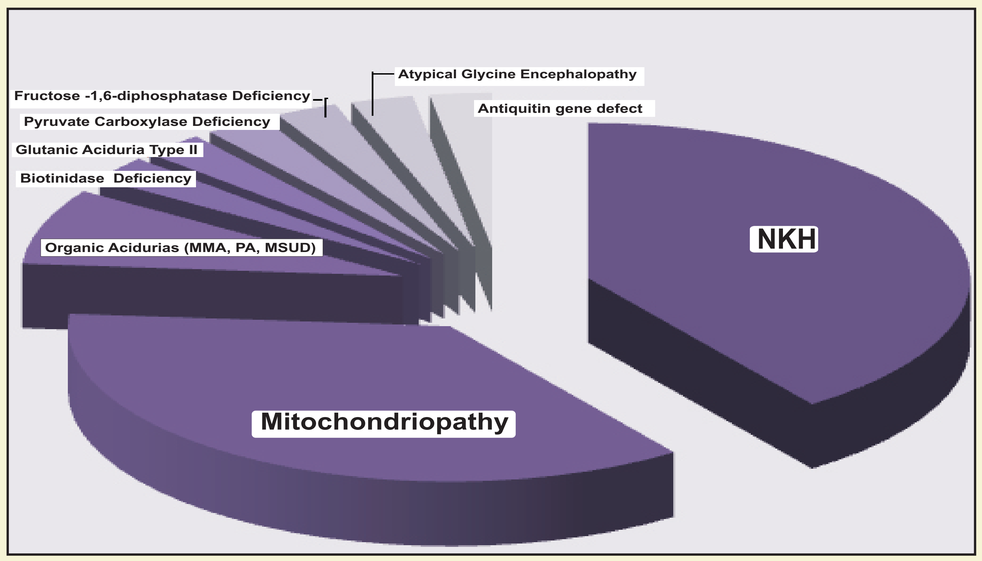
Materials and Methods : Out of the 483 CINB (Critically Ill New Born) cases presented at our institute in the span of 5 years from 2008 to 2012, 72 newborns having intractable convulsions were selected for the study (n=72). The initial screening in these cases (sepsis workup, blood sugar, CSF routine and USG skull) excluded the possibility of sepsis or other CNS pathologies as the primary cause for convulsions.

An array of tests were performed at our institute in an attempt to determine the cause of these convulsions. These tests included blood and CSF lactate and glucose, blood ammonia, LDH, serum free fatty acids, serum biotinidase enzyme activity, transferrin iso-electric focusing, carnitine / acyl carnitine profile in blood and /or serum, urinary organic acids, plasma and CSF amino acids. CSF Neurotransmitter analysis, plasma very long chain fatty acid analysis and CSF and plasma pipecolic acid analysis were performed in a few selected cases as per the requirement.



Result : 21% of the selected newborns having convulsions were diagnosed with Non Ketotic Hyperglycinemia (NKH) (n=15), 19% with Mitochondrial disorders (n=14), 26% with other IEMs (n=19) which included Biotinidase deficiency (n=1), propionic acidemia (n=1), glutaric aciduria type II (n=1). No IEM could be identified in about 33% of the newborns (n=24).

Metabolic Disorder	Distribution
NKH	21% (n = 15)
Mitochondripathy	19% (n = 14)
Organic Acidurias (MMA, PA, MSUD)	4.16% (n = 3)
Biotinidase Deficiency	1.38% (n = 1)
Glutaric Aciduria Type II	1.38% (n = 1)
Pyruvate Carboxylase Deficiency	1.38% (n = 1)
Fructose - 1, 6-diphosphatase Deficiency	1.38% (n = 1)
Atyical Glycine Encephalopathy	1.38% (n = 1)
Antiqutin gene defect	1.38% (n = 1)



Discussion : Neonatal seizures may start within a few minutes after birth to even some days later in life. Initial workup including sepsis workup and CSF routine along with standard line of treatment with IV fluids, calcium and anticonvulsants remains the priority in these cases. Normal findings in routine metabolic screen may suggest a possibility of Group I Neurotoxic Disorders[1]. This group includes Non Ketotic Hyperglycinemia (NKH), Molybdenum cofactor metabolism defect, Peroxisomal Disorders, Pyridoxine / Folinic acid responsive disorders (Antiquitin gene defect) , Pyridoxal – 5 - phosphate dependency and Serine deficiency. **NKH** formed a major group (21%) of IEM's presenting primarily with intractable neonatal convulsions in our cohort. A burst-suppression or hypsarrhythmia on EEG and elevated glycine levels in CSF and plasma may indicate NKH[2].

Mitochondrial disorders formed the second largest group of disorders (19%) associated with convulsions in our cohort. These disorders presented as progressive myoclonic epilepsy and generalized tonic- clonic seizures. Disorders such as Pyruvate carboxylase deficiency (PC), Pyruvate dehydrogenase (PDH) and respiratory chain defects (RCD) can be identified by biochemical investigations and molecular analysis. Gene studies for PHDC, NARP, MERRF, MELAS, and Alper's disease can be undertaken to confirm the etiology in these cases[3].

Many other disorders like Biotinidase deficiency, organic acidemias (Propionic acidemia) and glutaric aciduria also presented with intractable convulsions.

Conclusion : IEM's constituted 67% of the cases presenting with convulsions. Although the most common IEM's found were NKH and Mitochondrial disorders, other disorders also presented with convulsions as a major symptom. In view of the poor prognosis associated with disorders presenting with intractable convulsions, an early and appropriate diagnosis is essential not only for initiation of treatment but also in prenatal screening. We herewith present a systematic approach to diagnose cases with intractable convulsions.

Acknowledgement : We are highly grateful to Dr. Adolf Muehl for his immense contribution and guidance in diagnosing the disorders.

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