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Case Series on Inborn Errors of Metabolism in Neonates: Highlighting the Need for Newborn Screening in India

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Abstract: ***This case series examines the incidence and outcomes of inborn errors of metabolism IEM in neonates admitted to a tertiary care NICU in India. Five cases are presented, each diagnosed with a different IEM. Despite early diagnosis and intervention, the mortality rate was 60%, highlighting the critical need for a national newborn screening program in India. This study underscores the importance of early detection and treatment to prevent adverse outcomes and calls for systematic screening to be implemented nationwide.***

Keywords: Inborn errors of metabolism, Newborn screening, Neonates, India, NICU

1. Introduction

Inborn errors of metabolism (IEMs) are a group of disorders each of which results from deficient activity of a single enzyme in a metabolic pathway. Although IEMs are individually rare, they are collectively common, with an overall incidence of more than 1: 1, 000. More than 500 IEMs have been recognized, more than 100 of which can present clinically in the neonatal period.

IEMs can present in the fetal life, in the neonatal period, or later in childhood and even adult age groups. Most commonly, neonates with IEMs are healthy at birth with signs typically developing in hours to days after birth. The signs are usually nonspecific and may include decreased activity, lethargy, poor feeding, vomiting, respiratory distress, or seizures. These signs are common to several other neonatal conditions, such as sepsis and cardiopulmonary dysfunction. Therefore, maintaining a high index of suspicion is important for early diagnosis and the institution of appropriate therapy which are mandatory to prevent death and ameliorate complications from many IEMs

Screening helps in early diagnosis and initiation of treatment. Early treatment and rehabilitation to the child with IEM prevent premature death and permanent neurological disability.

This case series examines the incidence and outcomes of inborn errors of metabolism IEM in neonates admitted to a tertiary care NICU in India. Five cases are presented, each diagnosed with a different IEM. Despite early diagnosis and intervention, the mortality rate was 60%, highlighting the critical need for a national newborn screening program in India. This study underscores the importance of early detection and treatment to prevent adverse outcomes and calls for systematic screening to be implemented nationwide

2. Aims and Objectives

A prospective observational study to demonstrate the course and disease progression of different Inborn errors of metabolism in NICU setup in a tertiary care hospital and discuss the need for early identification, prevention and treatment of these disorders.

This article aims to present a case series on inborn errors of metabolism in neonates and emphasize the urgent need for a national newborn screening program in India.

3. Materials and Methods

5 patients were studied over a span of 3 months in NICU of a Tertiary Care Centre who were diagnosed with IEMs and required further management. The patients enrolled were diagnosed with the following diseases:

1) Organic Acidemia: Type 1 Citrullinemia
2) Fatty Acid Oxidation Defect: Propionic Acidemia
3) Molybdenum Cofactor Deficiency
4) Galactosemia
5) Congenital Adrenal Hyperplasia: Salt wasting type

The research methods used in the study, which include the examination and followup of five neonates diagnosed with IEMs, are appropriate for the case study design. However, more detail on the diagnostic methods and criteria used would enhance the robustness of the study.

When to suspect inborn errors of metabolism?
Deterioration after a period of apparent normalcy.
Parental consanguinity.
Family history of neonatal deaths.
Rapidly progressive encephalopathy and seizures of unexplained cause.
Severe metabolic acidosis.
Persistent vomiting.
Peculiar odor,

Acute fatty liver or HELLP (hemolysis, elevated liver enzymes and low platelet counts) during pregnancy: Seen in women carrying fetuses with long - chain - 3 - hydroxy acyl - coenzyme dehydrogenase deficiency (LCHAD)

Case 1

A full term male child delivered by normal vaginal delivery, 2nd issue by birth born of 3rd degree consanguineous marriage referred to NICU at 18 hours of life due to Increased Respiratory Distress, Vomiting and Refusal to feed. History of elder female sibling death in NICU on day 4 of life with history of poor feeding and hyperammonemia. Patient had persistent poor activity with convulsion associated with hypoglycemia and was started on Glucose infusion. Patient had persistent distress so ABG was done in this patient which was suggestive of high anion gap metabolic acidosis with hyperammonemia and sepsis screen negative and CXR: NAD. The neonate was suspected to have inborn error of metabolism as per the baseline investigations and basic metabolic profile so TMS was sent. Hyperammonemia was present so ammonia scavenger therapy Sodium benzoate was started for the patient but the patient did not respond to therapy and succumbed on Day 5 of life. TMS report was done which was suggestive of Type I Citrullinemia hence Serum Citrulline levels were done which were elevated indicative of Type 1 Citrullinemia

Citrullinemia Type 1 (CTLN1) is a rare and life - threatening genetic disorder with autosomal recessive inheritence. Two major forms of this condition have been identified. Severe or neonatal form: most common and appears in first few days of life with signs and symptoms of hyperammonemia i. e refusal to feed, vomiting, tachypnea, lethargy, can deeply progress to coma and seizures. Subacute or mild form after 1 year of age with failure to thrive, frequent vomiting, development delay and dry brittle hair.

Case 2

A Full - term female baby, 5th issue of third - degree consanguineous marriage was admitted at 50 hours of life in Neonatal Intensive Care Unit in view of not accepting feeds and poor activity with hypoglycaemic convulsion for which patient was started on Glucose infusion. Basic blood investigations were suggestive of thrombocytopenia with leukopenia. Sepsis screen was negative and CSF analysis was normal. Patient developed tachypnoea and respiratory distress hence oxygen support was started. ABG revealed a high anion gap metabolic acidosis. Metabolic work up was suggestive of hyperammonemia and ketonuria and as sepsis was ruled out , TMS was sent for the patient which showed elevated level of propionyl carnitine and glycine indicating Propionic Acidaemia. Patient was given ammonia scavenger therapy and supportive management but patient succumbed on Day 5 of life.

Propionic acidemia is a rare autosomal recessive metabolic disorder with incidence of 1/20, 000 to 1/250, 000 individuals. It is characterized by deficiency of propionyl - CoA carboxylase, the enzyme converting propionyl - CoA to methyl malonyl - CoA in the metabolism of essential amino acids valine, methionine, isoleucine, and threonine. This enzyme deficiency leads to accumulation of propionyl - CoA which gets converted into propionic acid, leading to multiorgan complications.

Neonatal - onset Propionic acidemia is the most common form in which the baby appears normal at birth and later presents with refusal to feed, lethargy, vomiting, hypotonia, hypoglycemia and seizures in the first week of life. Blood investigations reveal thrombocytopenia, leukopenia, high anion gap metabolic acidosis, ketonuria, hyperglycinemia, hyperammonemia and elevated plasma propionyl carnitine.

Case 3

A full - term male baby delivered by LSCS, 1st issue born of 3rd - degree Consanguineous marriage was admitted to NICU at 72 hours of life in view of refusal to feeds, poor activity and hypoglycemic convulsions for which the baby was started on glucose infusion drip. The Sepsis screen was negative. In view of dysmorphic facies, hypotonia and interactable seizures workup for Inborn errors of metabolism was done which was suggestive of ABG and serum ammonia within normal limits and urine ketones and reducing substances negative and as the suspicion was towards mitochondrial disorders, peroxisomal disorders, WES was sent and Whole Exome sequencing report: Pathogenic variant of MOCS2 gene detected so later Serum Uric acid level was sent which was low. Baby deteriorated rapidly and inspite of all resuscitative measures baby succumbed at 96 hours of life.

Molybdenum Cofactor Deficiency is an extremely rare Autosomal Recessive Inherited Condition characterised by brain dysfunction that worsens over time. Mutations in MOCS1, MOCS2, and GPHN lead to Type A, B, C type of Molybdenum Cofactor Deficiency respectively. These gene mutations impair molybdenum cofactor biosynthesis leading to loss of enzyme activity of 1. Xanthine oxidase/reductase 2. Aldehyde oxidase 3. Sulfite oxidase Leading to build - up of certain chemicals including sulfite, Sulfocysteine, Xanthine, and Hypoxanthine. These patients appear normal at birth but within a week they develop difficulty in feeding, intractable seizures due to VitB12 deficiency, hypotonia, facial dysmorphism and early death. Tests reveal a low level of uric acid in blood and urine and an MRI brain reveals severe encephalomalacia with ophthalmic examination revealing lens dislocation if the patient survives into infancy. Incidence: 1 in 2, 00, 000 newborns worldwide. Only 100 cases have been reported in literature.

Case 4

A full term female child, 5 th issue of 3rd degree consanguineous marriage was admitted to NICU at Day 13 of life in view of icterus upto leg with episodes of vomiting present. Significant previous family history s/o 1 sibling death at 28 days of life which was diagnosed as galactosemia and second sibling death at Day 21 of life in view of suspected liver dysfunction with no workup done for child

Patient's investigations were suggestive of direct hyperbilirubinemia with elevated transaminases, urine for reducing substances positive and USG screening showing increased echogenecity of liver with gall bladder visualised a d patient's stool colour normal so patient's enzyme study for

GALT was sent which had deficiency of GALT enzyme. Patients ophthalmology call was given in view of cataract which was absent at present. Sepsis screen was negative and as per Paediatric hepatologist opinion patient was advised to start lactose free and fructose free diet with soy-based formula feeds and plan EXOM sequencing on follow up.

Galactosemia is an autosomal recessive disease due to the deficiency of galactose - 1 - phosphate uridyltransferase (GALT) which functions in the catabolism pathway of galactose. Typical symptoms of galactosemia in the newborn develop after ingestion of lactose (glucose - galactose disaccharide) through a standand lactose - containing formulas or breast milk. Clinical manifestations include vomiting, diarrhea, feeding difficulties, failure to thrive, hypoglycemia, jaundice, hepatomegaly, elevated transaminases, coagulopathy, ascites, liver failure, renal tubulopathy, lethargy, irritability, seizures, cataracts, and increased risk Escherichia coli neonatal sepsis.

Case 5

A 24-day old male child, 2 nd issue of 3rd degree consanguineous marriage was admitted to NICU due to poor activity, refusal to feed, and poor weight gain, on investigating patient had hypoglycemia and was started on Glucose infusion rate. His genitalia were examined and were normal male genitalia with scrotal hyperpigmentation. Serum electrolytes showed hyponatremia (Serum sodium - 125mmol/L), hyperkalemia (Serum potassium - 5.9mmol/L, hypochloremia (Serum chloride - 84 mmol/L). Sodium correction was started with 3%Nacl infusion and inj calcium gluconate and salbutamol given for hyperkalemia. Despite treatment, the patient had refractory hypoglycemia, hyponatremia and hyperkalemia and as patient had previous history of NICU stay for 18 days ivo refractory hypoglycemia and sepsis screen was negative with sterile blood culture reports so provisional diagnosis was Congenital Adrenaline hyperplasia with salt wasting crisis and patients USG abdomen was within normal limits and Serum 17hydroxyprogesterone (17 - OHP) was >2000ng/ml - highly suggestive of CAH. So confirmatory tests were sent: Serum aldosterone was normal (141.70pg/ml) but Serum cortisol level was low (99.07nmol/L) and plasma Renin was high (46.09pg/ ml). Serum testosterone (0.46nmol/L) and ACTH (54.12pg/ml) was high. Urinary sodium concentration was high (67meq/l). So the diagnosis of CAH (classic, salt - losing variety) was made. Then he was started on replacement therapy (hydrocortisone 100 mg/m2/day, fludrocortisone 150 µg/day). Within 5 days of therapy there was significant improvement both clinically and biochemically.

Parents were counseled about the disease and an instruction to his parents was given to double the dose of his oral hydrocortisone if the child has intercurrent illness.

4. Result

In this case series, out of the 5 cases of Inborn errors of metabolism, 3 succumbed and 2 patients survived so the mortality rate is 60%.

Most commonly, neonates with IEM are healthy at birth with signs and symptoms typically developing in hours to days after birth.

The presentation is non- specific and may include decreased activity, lethargy, poor feeding, vomiting, respiratory distress, seizures, hypoglycemia, failure to thrive etc.

The most common presentation of IEM in this case series is refractory hypoglycemic convulsions.

The baseline metabolic screen: ABG, AMMONIA, URINE KETONE, BLOOD SUGAR, CBC, URINE FOR REDUCING SUBSTANCES, LIVER FUNCTION TESTS, SERUM LACTATE is done and according to the results the further screening tests such as Tandem mass spectrometry, Enzyme studies, Whole Exome sequencing can be done and followed by specific diagnostic investigations.

This study is significant as it highlights the high mortality associated with inborn errors of metabolism in neonates and the potential lifesaving benefits of early detection through newborn screening.

5. Conclusion

India, the second - most populous nation in the world, lacks a national newborn screening initiative as part of its health care strategy. This case series reinforces the need for having a national newborn screening programme for inborn errors of metabolism. Diagnosis is important not only for treatment and prognostication but also for genetic counselling and antenatal diagnosis in subsequent pregnancies 'NEWBORN SCREENING IN INDIA: NEED OF THE HOUR'

Screening helps in early diagnosis and initiation of treatment. Early treatment and rehabilitation to the child with IEM prevent premature death and permanent neurological disability.

This case series highlights the critical need for a national newborn screening program in India. With a 60% mortality rate among neonates diagnosed with inborn errors of metabolism, early detection through systematic screening could significantly reduce mortality and improve long- term outcomes. The implementation of such a program is essential for advancing neonatal healthcare in India.

As Inborn errors of metabolism present with non- specific findings such as poor feeding, drowsiness, lethargy, failure to thrive and hypotonia, a high degree of clinical suspicion should be kept for IEM in certain high risk scenarios such as refractory hypoglycemia, persistent altered sensorium after ruling out the common causes such as sepsis, HIE, congenital infections, refractory seizures, history of previous sibling death and bad obstetric history.

So, a NATIONAL NEWBORN SCREENING PROGRAMME FOR IEMs covering the common disorders such as;

a) Congenital Hypothyroidism
b) Congenital Adrenal Hyperplasia
c) G6PD deficiency

d) Galactosemia
e) Phenyketonuria
f) Biotidinase deficiency could be initiated in India in the public sector.

This is already being implemented by the state governments of KERELA and GOA and the private sector across India.

INDIA being a developing country with cost restrains present, even if newborn screening for all neonates is not possible at least screening of high risk neonates as mentioned above should be undertaken.

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