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A Case Study of Inborn Error of Metabolism (Probable Organic Acidemia)

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ABSTRACT

Rare genetic (inherited) abnormalities known as inborn errors of metabolism prevent the body from properly converting food into energy. We present a case on inborn error of metabolism (probable organic acidemia) to obtain further understanding and gain extensive knowledge. The patient was observed directly; the patient's records presented in this study are available in hard copy and electronic form in the hospital's discharge data set and that were referred. A literature search was done, and the information was summarized along with the case description. An 8-year-old girl born with 3rd-degree consanguineous marriage was brought in with complaints of vomiting for 2 days, fast breathing for 3 hours, an occasional cough, and decreased oral intake. Blood gas done showed high anion gap metabolic acidosis. A complete blood count showed neutrophilic leukocytosis. Serum ammonia was elevated. Serum electrolytes showed hypokalemia. The urine complete picture showed the presence of ketone. Confirmatory tests like GCMS, TMS and DBS were performed. The diagnosis of inborn error of metabolism (possible organic acidemia) was made given the above clinical, analytical and laboratory parameters after excluding other possibilities. She was treated with protein restriction, sodium bicarbonate (to treat acidosis), L-carnitine, vitamins, and other supportive measures. She had improved symptomatically and was hemodynamically stable.

INTRODUCTION

Mutations in the genes that code for proteins essential to metabolism result in hereditary diseases known as inborn errors of metabolism (IEM). They are transmitted as autosomal recessive, and rarely, the inheritance may be X–X-linked and autosomal dominant. They can have an impact on up to 1 in 2500 live births [1]. Etiologic factors include environmental, epigenetic, and microbiome factors, which also occur at any age [2]. It plays a significant role in the metabolic pathway of carbohydrates, fatty acids, and proteins by interrupting their breakdown or storage. By disrupting the carbohydrate metabolism, it causes hypoglycemia. By disrupting protein metabolism, it causes hyperammonemia. By disrupting fatty acid oxidation, it causes acidosis and hypoglycemia [1].

Neurological abnormalities and gastrointestinal symptoms are the most common representations of IEM. Neurological abnormalities include developmental delay, poor tone, seizures, and poor tone. Gastrointestinal abnormalities include dehydration, nausea and vomiting, hepatomegaly, food intolerance, diarrhea, and food aversion [2,3].

The nosological classification includes three broad groups:

1. Intoxication disorders (amino acid metabolism disorders, alteration of carbohydrate metabolism, and others) [4].

2. Energy metabolism disorders (mitochondrial disease, fatty acid beta-oxidation disorders, and others) [5].

3. Storage diseases (lysosomal disease, peroxisomal disease, and others) [6].

When dealing with an acute crisis in patients with an IEM, it is crucial to consider the potential implications of catabolic circumstances (infections, fasting, physical activity, delivery, etc.), the ingestion of food that the patient cannot metabolize (proteins, fatty acids, etc.), or specific medications [7]. Ammonia, lactate levels, a complete hemogram, and ketone bodies in the urine should be obtained. It is recommended to administer treatment using certain cofactors and detoxifiers based on the condition in issue [8]. Here we present a case of inborn error of metabolism (probable organic acidemia) in a pediatric patient.

CASE DESCRIPTION

An 8-year-old developmentally normal girl born with 3rd-degree consanguineous marriage was brought in with complaints of vomiting for 2 days, fast breathing for 3 hours, an occasional cough, and decreased oral intake. She was born by lower segment cesarean section (LSCS) with a birth weight of 3kg. Immunized according to the National Immunization Schedule (NIS). No adverse events following immunization (AEFI). There was no family history of similar complaints previously. She had a history of having similar complaints at 11 months of age and was diagnosed with severe metabolic acidosis with shock. The pedigree of the family is shown in **Fig. 1**.

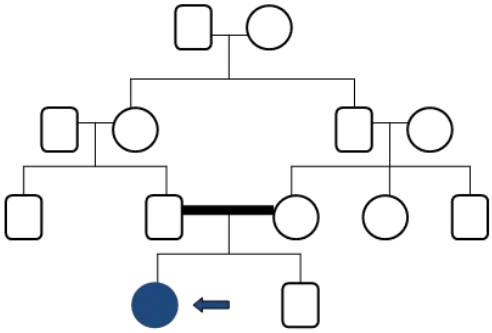

Fig. 1 Pedigree of the Family

Square: male; circle: female; colored arrow; and the circle indicates the 8-year-old female baby affected by IEM.

INVESTIGATION

On examination, the child was afebrile, drowsy, dehydrated, tachycardiac, and had tachypnea with acidotic breathing. She weighs 22kg and is 122cm tall. Systemic examinations were normal. Blood gas analysis showed high anion gap metabolic acidosis (pH 6.9, HCO_3 – 1.9 mmol/L). A complete blood count showed neutrophilic leukocytosis. A liver function test was done and found to be normal. Serum amylase, lipase, calcium, and magnesium were found to be normal. Serum ammonia (216 microg/dl) was elevated. Serum electrolytes showed hypokalemia (2.89 mEq/l). Urine complete picture showed the presence of ketone (3+).

DIFFERENTIAL DIAGNOSIS

High anion gap metabolic acidosis

1. Methanol poisoning: no history
2. Uremia: no
3. Diabetic ketoacidosis: blood sugar was normal
4. Paraldehyde: no history
5. Lactic acidosis: lactate levels 0.98
6. Ethanol: nil
7. Salicylate: no history
8. **IEM**: favors vomiting, hyperammonia, metabolic acidosis, elevated ketone and against normal sugar and normal jaundice.

IEM

1. Maple syrup urine disease: No specific urine odor.
2. **Organic acidemias** (**most likely**): metabolic acidosis (+), elevated ammonia and ketone, no hypoglycemia, lethargy and vomiting.
3. Urea cycle defects: elevated ammonia.
4. Disorders of carbohydrate metabolism: no hypoglycemia, no organomegaly.
5. Fatty acid oxidation disorders (FAOD): elevated ketone.
6. Mitochondrial disorders: no lactic acidosis.

CONFIRMATORY DIAGNOSIS

Acylcarnitine profile and amino acid profile analysis were performed using Tandem mass spectrometry (MS/MS) and liquid chromatography – tandem mass spectrometry (LC – MS/MS).

Acylcarnitine profile and amino acid profile showed Carnitine/acylcarnitine translocase deficiency (CACT), Carnitine Palmitoyl transferase deficiency type 1 (CPTI), Acyl CoA – Dehydrogenase deficiencies, Isovaleric acidemia (IVA), Glutaric acidemia – type 1 (GA – 1), Methylmalonic acidemias (MMA), Propionic acidemia (PROP), Malonic aciduria (MAL), Carnitine uptake deficiency (CUD), argininemia, argininosuccinic aciduria, and carbamoylphosphate synthetase deficiency.

Organic acids were analyzed using Gas Chromatography Mass Spectrometry (GCMS). It showed elevated levels of 3-hydroxybutyric acid, acetoacetic acid, ethylhydracrylic acid suggestive of ketosis. 2-hydroxybutyric acid showed 3.26% (cut off 0.50%), glycolic acid - 15.05% (cut off 3.99%), 3-hydroxypropionic acid – 6.64% (cut off 1.95%), 3-hydroxybutyric acid – 543.63% (cut off 5.28%), 3-hydroxyisovaleric acid – 26.33% (6.10%), ethythydracrylic acid – 16.33% (cut off 6.22%), acetoacidic acid – 23.67% (cut off 0.10%), phosphoric acid – 288.03% (72.70%), phenylacetic acid – 1.24% (cut off 0.62%), glutaconic acid – 0.82% (cut off 0.50%), thioglycolic acid – 0.62% (0.10%), 5-hydroxy-2-furoic acid – 71.67% (9.02%), palmitic acid – 37.59% (cut off 23.3.4%).

The genetic profiling was performed using dried blood spot (DBS) and the results for acylcarnitines were FreeCN – 31.174 µM, C2 – 24.249 µM, C3 – 2.99 µM, C4 – 0.155 µM, C5:1 – 0.014 µM, C5 – 0.059 µM, C4-OH – 0.168 µM, C6 – 0.038 µM, C5 – OH – 0.053 µM, C8:1 – 0.028 µM, C3DC – 0.019 µM, C10:1 – 0.009 µM, C10 – 0.019 µM, C4DC – 0.103 µM, C5DC – 0.019 µM, C12:1 – 0.014 µM, C12 – 0.042 µM, C14:2 – 0.001 µM, C14:1 – 0.057 µM, C14 – 0.086 µM, C16:1 – 0.038 µM, C16 – 1.528 µM, C16-OH – 0.012 µM, C18:2 – 0.101 µM, C18:1 – 0.833 µM, C18 – 0.682 µM, C18:1-OH – 0.012 µM, C18-OH – 0.025 µM.

The results for aminoacids were found to be Gly MRM – 145.85 µM, Ala – 90.629 µM, Val – 91.486 µM, Gln (Glu) – 32.075 µM, Leu-lle – 88.591 µM, Met – 17.975 µM, His – 20.998 µM, SUAC – 0.298 µM, Phe – 47.415 µM, Tyr – 48.245 µM, Asp – 77.394 µM, Glu – 108.64 µM, Ser – 49.51 µM, Orn – 100.061 µM, Cit(119) – 28.451 µM, Arg – 28.483 µM.

The diagnosis of an inborn error of metabolism (possible organic acidemia) was made given the above clinical and laboratory parameters, after excluding other possibilities.

TREATMENT

Patient was admitted for 3 days. Nothing per oral (NPO) was maintained for 24 hours. After 24 hours NPO, she was started on low protein diet. ORS sachet 100ml was given after each loose stool.

Decreased catabolism by infusion of 500 ml dextrose fluid 10% at 80ml/hr and maintenance with 150% DNS for 48 hours. Sodium bicarbonate was infused over 4 hours in 80 ml 5% dextrose. Infusion was initiated at a rate of 40ml/hr for 4 hours tapered to 20ml/hr for 6 hours and later tapered to 6.6ml/hr for 24 hours.

On second day, 10ml of 20mEq potassium chloride was diluted with 415ml 10% DNS along with 85ml 25% dextrose and infused at a rate of 76ml/hr tapered to 15ml/hr and stopped. Inj. Pantoprazole 20mg 1-0-0 was given for 2 days; it was stopped and converted to T. Pantoprazole 20mg 1-0-0 on 3rd day. Inj. Ceftriaxone 750mg 1-0-1 was given for 2 days; it was stopped and Syp. Cefixime 10ml 1-0-1 was given on 3rd day. T. Carnitine 500mg Q8H was given on day 1; it was stopped and changed into a combination drug of Folic Acid (1.5 mg) + L-Carnitine / Levocarnitine (500 mg) + Methylcobalamin (1500 mcg) Q8H for next 2 days.

The child was well tolerated with low protein diet, and was clinically stable. She was discharged with the Syp. Carnisure 500mg/5ml (5ml – 5ml – 5ml), continue till next review; Syp.Cefixime 5ml/50mg 1-0-1 for 2 days.

FOLLOW-UP & OUTCOME

On follow-up after 1 week, she had improved symptomatically and was hemodynamically stable. Syp Carnisure 500mg/ml was stopped. Advised to obtain urgent care when she is experiencing vomiting and fast breathing.

DISCUSSION

A group of hereditary metabolic diseases known as inborn errors of metabolism are brought on by the inactivation of one or more particular enzymes or by problems with the transport of proteins, which block the metabolism [9]. A group of diseases marked by the excretion of non-amino organic acids in the urine are referred to as "organic acidemia" or "organic aciduria" (OA) [10]. Children have a potentially fatal bout of metabolic acidosis which is marked by an increased anion gap [11]. The patients received treatment plans based on protein restriction, sodium bicarbonate (to treat acidosis), L-carnitine, and vitamins [12]. In this patient, on examination, lethargy, vomiting, hyperammonia, presence of ketone, high anion gap metabolic acidosis favors inborn error of metabolism most likely organic acidemia.

The patient in our study was born to a consanguineously married couple. Parental consanguinity is known to raise the likelihood of autosomal recessive IEM. [14].This study had certain limitations. The diagnosis was made on the basis of clinical presentation, analytical tests and other laboratory tests, though these tests do suggest the diagnosis, final

confirmation made using genetic tests. The use of LC-MS/MS during the past decades has led to a remarkable increase in screening of IEMs. LC-MS/MS, GCMS techniques may play a vital role in screening and diagnosis of IEMs in newborns and this may help facilitate timely therapy of treatable IEMs. This study also highlights the fact that findings from advanced testing, such as GC/MS and TMS, are not widely available in many regions of the country. This is especially crucial in underdeveloped nations because general pediatricians are ignorant about IEM due to a lack of suitable facilities.

The first line investigation for IEM should include – Complete blood count, complete Urine analysis, Arterial blood gas analysis, Blood glucose, electrolytes, liver function test, renal function test, and other required laboratory tests. Confirmatory tests like spectroscopy, chromatography, and enzyme assays can be performed.

The treatment aims to reduce formation of toxic metabolites, to enhance excretion of formed toxic materials, to treat co-morbities, to initiate supportive treatment, and to give enough calories. Dietary treatment, enzyme replacement therapy and cofactors replacement therapy can also be performed in few forms of inborn error of metabolism [15].

CONCLUSION

The rate of this diagnosis is strongly correlated with clinical decision, prompt and effective therapy can make a vital difference. The nature of inborn metabolic errors is expected to change as more sophisticated lipid metabolic pathways and other cellular processes are comprehended and the impact of epigenetics is investigated [13]. Metabolic disorders can be difficult to understand due to their rarity and the multiplicity of conditions. Prenatal IEM diagnostic and screening programs will be very helpful in genetic counseling and prevention.

DECLARATION

ETHICS APPROVAL

Not applicable.

CONSENT TO PARTICIPATE

Verbal consent was obtained from the patient’s parents.

CONSENT FOR PUBLICATION

Verbal consent was obtained from the patient's parents.

CONFLICT OF INTEREST

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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AVAILABILITY OF DATA AND MATERIALS

The patient's records presented in this study are available in hard copy and electronic form in the hospital's discharge data set.

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