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Review Article

EPIDEMIOLOGY, PATHOPHYSIOLOGY, AND HINDRANCE OF UREA CYCLE ERROR OF METABOLISM

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ABSTRACT

Inborn errors of metabolism (IEMs) are a class of genetic disorders that are rare individually, but collectively they occur in common terms exhibiting an average prevalence of 1 in 1000 individuals. One of the most commonly occurring IEMs is the urea cycle disorders (UCDs), which are a group of unusual disorders that have an effect on the urea cycle, a sequence of metabolic processes through which nitrogen is transformed into urea and expelled from the body by the urine. These diseases are the primary cause of hereditary hyperammonemia, and they can result in developmental disabilities, epilepsy, loss of psychomotor control, and death. UCDs are most commonly diagnosed during infancy, although certain infants do not exhibit symptoms until they are in their early childhood. IEMs are precisely diagnosed and recorded through tandem mass spectroscopy-based newborn screening. Recent advances in IEMs include new therapies based on dietary modification, enzyme replacement therapy, development of novel compounds, and diagnosis involving untargeted metabolomics and whole-exome sequencing are also widely being used in new disease discovery. Modern improvements in diagnosis and care have increased the prognosis significantly for a lot of children with IEM. It has been suggested that expanded access to awareness of IEMs is the most significant change leading to better treatment. The purpose of this review is to provide an overview on IEM and present in-depth knowledge about the UCDs including their subtypes.

Keywords: Inborn errors of metabolism, Urea cycle disorders**,** Urea cycle disorders classification, Management of urea cycle disorders.

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INTRODUCTION

Given the existence of conventional biochemical technologies in the 20th century, the inborn metabolic errors originally identified were usually diseases of intoxication manifesting in the central nervous system or different end-organ consequences [1]. Inborn errors of metabolism (IEM) are inherited single gene defects caused by a malfunction or abnormality in a transporter, an enzyme or its cofactor, leading to substrate aggregation or the product deficiency. Sir Archibald Garrod described these diseases for the first time in 1908 and submitted his study titled "Inborn Errors in Metabolism" to the Royal College of Physicians as the Croonian Lectures [2-4]. More than 700 IEMs were known till date [5]. IEM is rare, but their overall occurrence is greater than 1:1000 and is responsible for a considerable portion of disability and deaths during childhood [6]. Most of the IEM disorders are autosomal recessive type, but X-linked and autosomal dominant disorders are also existent. Since neonates with IEMs typically present with nonspecific symptoms [7], a high note of suspicion is critical for early detection of IEMs. Hence, any previous records of paternal affiliation or a formerly infected sibling may indicate the possibility of IEMs.

The IEMs can be classified into two categories: Those caused by abnormalities in energy sources metabolism such as proteins, carbohydrates, or lipids and those caused by disruption in pathways occurring within cell organelles such as peroxisome, mitochondria, and lysosome. Urea cycle disorders (UCDs), chemical acidemias, and amino acidopathies are examples of metabolic disorders affected by protein metabolism disorder. Defects of fatty acid b-oxidation and the carnitine shuttle are examples of lipid metabolism disorders. Among the carbohydrate diseases are galactosemia and glycogen storage disorders. The storage disorders of lysosomes are caused by disability to digest or recycling of complex large macromolecules and might manifest with a variety of symptoms, based on the enzymatic block. Of the most significant laboratory outcomes associated with inborn metabolic errors, urea cycle defects [8], and certain organic acidemias are at the top.

UCDs are a type of inborn error in hepatic metabolism [9] caused by the lack of enzymatic activities that control the transfer of nitrogen from ammonia to urea. With an average prevalence of at least 1 in 2500, these conditions often lead to lethal hyperglutaminemia and hyperammonemia [10,11]. The manifestations of UCDs vary with independent of the age, although they are most probably to appear during the late infancy, neonatal stage, and at the time of puberty. Early signs are generally nonspecific, so it is crucial to regularly screen for hyperammonemia to determine a diagnosis rapidly and avoid complications. A disorder known as transient hyperammonemia of the newborn is of the differential diagnosis in neonates, while in older infants the defects of fatty acid oxidation may be taken into consideration [12,13]. The toxic ammonia is eliminated by the urea cycle through renal excretion which is generated by the amino acid deamination by transforming it into nontoxic urea. If the urea cycle fails to function, ammonia builds up in the blood and thus causes impaired mental state, fatigue, cerebral edema, lethargy, and eventually, coma, and death [14].

The metabolic condition hyperammonemia is characterized by increased ammonia levels, a potent neurotoxin. Hyperammonemia is most often represented by neurological signs and symptoms, which can be acute or chronic, based on the repressed abnormality [15]. To avoid permanent neurological damage, hyperammonemia should be detected early and treated promptly. Aside from ammonia, urinary organic acids and plasma amino acids are necessary to determine the form of UCD [16]. It should be recognized that metabolic disorders can be variable and inconsistent. Hence, to validate the diagnosis, enzymatic, or molecular analyses are required. In IEMs, early diagnosis and administration of adequate therapy are needed to avoid mortality

and reduce complications [17]. In the case of suspected IEMs, the management should be initiated before the birth [18]. A number of IEM-related conditions are detectable by current newborn screening (NBS) programs. NBS allows for the detection of an IEM during an asymptomatic period and the performance of medical treatments that change the disease's natural history. A few IEM can be treated, and as a result, many are incorporated in NBS services in different countries [19-21].

OVERVIEW OF UCDS

The urea cycle is the primary mechanism for removing nitrogen waste produced by the breakdown of proteins and other molecules containing nitrogen by converting the ammonia to urea. The urea cycle comprises five catalytic enzymes (CPS1, OTC, ASL, ARG1, and ASS1), two amino acid transporters which are Ornithine translocase and Citrin [22,23]. Besides this, it consists of N-acetyl glutamate synthetase (NAGS), a co-factor producing enzyme. UCDs are inborn metabolic errors caused by defects in the waste product's metabolism that is generated during the breakdown of protein and other nitrogenous substances [24]. UCDs are caused by deficiencies that are inherited in either of the urea cycle pathway's 6 enzymes or 2 transporters (CPS1, OTC, ASS1, ASL, ARG1, NAGS, ORNT1, or citrin). The abnormal protein's role in the pathway, as well as the seriousness of the defect, influences the severity of the UCD. As a consequence, urea excretion is compromised, resulting in the ammonia accumulation and other precursor metabolites [25].

The most common clinical manifestation of UCDs is hyperammonemia. Although the severity changes considerably due to the variations that cause this disease, it can also be related to defects in at least eight proteins of the urea cycle at various stages and may affect them accordingly. In newborns with these disorders, ammonia levels frequently reach 1000 mmol/L. UCDs are generally characterized by acute and chronic hyperammonemia, and medical treatment aims to reduce the concentrations of ammonia by limiting protein consumption and using alternative-pathway medications to increase nitrogen waste excretion [26,27]. A few studies have shown that among various UCDs, just two of the eight diseases, argininosuccinate synthetase deficiency (ASSD; or citrullinemia type 1) and lyase deficiency (ASLD) may be accurately identified and estimated using tandem mass spectroscopy-based NBS.

EPIDEMIOLOGY AND PATHOPHYSIOLOGICAL CLASSIFICATION

In the current developing world, where excellent amenities and services are accessible, the average record of the children with UCDs still remains unsatisfactory [28]. As hyperammonemia is caused by a variety of conditions, acquiring reliable data on its prevalence is challenging. The overall prevalence of UCDs is estimated to be 1 in every 8000 to 1 in 44,000 live births. In India, all types of UCDs can be observed, and the incidence of the disorder is approximately one in 10,000 births, also indicating a noticeable surge in case identification and diagnosis in the past few years.

The clinical classification of UCDs from a pathophysiological perspective is mainly based on deficiencies in the enzymes or the transporters [29,30].

Carbamoyl phosphate synthetase I deficiency

It is also known as CPS I deficiency (CPSID) which is an autosomal recessive UCD that develops due to deficiency of the carbamoyl phosphate synthetase I enzyme. CPSID results in an extreme nitrogen accumulation in the blood in the form of ammonia causing hyperammonemia. The overall incidence of CPSID is predicted to occur 1 in 150 to 1 in 200,000 live births. However, since UCDs such as CPSID are often not recognized, they are under-diagnosed, making it impossible to ascertain the true prevalence of UCDs [31,32].

Ornithine transcarbamylase (OTC) deficiency

The most common UCD in humans is OTC deficiency. The deficient enzyme in this condition is OTC, which is the final enzyme in the urea cycle proximal portion. It catalyses the conversion of carbamoyl phosphate and ornithine into citrulline. OTC deficiency is a hereditary condition that induces excess amounts of ammonia to accumulate in the blood [33]. The prevalence of OTC deficiency has been estimated to be 1 in 14,000 to 1 in 77,000 individuals. The degree of onset of OTC deficiency differs from one person to another, often within the family [34-38].

Argininosuccinate synthetase deficiency

This deficiency is also called as Citrullinemia. It is a UCD of autosomal recessive type. Citrullinemia leads to accumulation of toxic compounds and ammonia in the blood [39]. Argininosuccinate synthetase deficiency is of two types, that is, Type I citrullinemia (citrullinemia) and Type II citrullinemia. The reason for the deficiency is due to mutations in genes which differ for both the types and clinical manifestations are also different [40-42]. The most common type of Citrullinemia is Type I citrullinemia exhibiting overall incidence more than 1 in 57,000 of global population. Type II citrullinemia shows prevalence of one in 100,000 to 230,000 people and is found majorly in the population of Japan.

Argininosuccinic aciduria (ASA)

ASA is a genetic disorder that occurs due to the partial or complete deficiency of argininosuccinate lyase (ASL) enzyme and it is the second most common type of UCD. This deficiency leads to the argininosuccinic acid accumulation in the urine and blood. ASA can be observed probably 1 in 70,000 to 1 in 218,000 live births, and this disorder accounts for 16% of overall UCDs. Mostly, this disorder can be recognized through NBS after the birth of the child [43-45].

Arginase deficiency (Argininemia)

Arginase deficiency results in the gradual accumulation of ammonia and an amino acid called arginine in the blood, and it is a very rare heritable genetic disorder. The clinical manifestations include spasticity in the muscles, particularly in the legs, and the disorder can be identified by the age of three. The symptoms may be of low severity in some individuals and might not appear till a certain age. The overall prevalence of the disorder is one in every 300,000 to 1,000,000 [46-49].

NAGS deficiency

NAGS deficiency occurs due to defects in the enzyme NAGS which is the rarest type of UCD and was first identified in 1981. The clinical features of this deficiency are not evident usually till later stages of life in a few affected individuals, and the severity of the disorder is based on the partial or complete lack of the NAGS enzyme. The incidence of this disorder is reported to be less than one in 2,000,000 individuals [50-52].

Ornithine translocase deficiency

It is a genetically heritable disorder that leads to accumulation of ammonia and other toxic compounds in the blood of affected individuals. Ornithine translocase deficiency rarely occurs and is estimated to have an overall prevalence of about 100 affected people as mentioned in the scientific literature [53,54].

INHERITANCE AND GENETIC CAUSE

The inheritance of the UCDs is the following types [55-57].

X-linked

OTC deficiency is the most common type of UCD that is generally passed on from mother to child through the X-chromosome who is not affected mostly. When this gene is inherited by a male individual, will more likely exhibit symptoms, whereas in women the symptoms may be observed or do not exist. Hence, they are called carriers of the disorder.

Autosomal recessive

Apart from OTC, in all the other UCDs, the defective gene is carried by both the parents and passes on a copy of this gene. When an individual inherits two copies of the same gene, it leads to UCD and may exhibit related symptoms.

Random mutation
This is also termed as "*de novo*," a type of mutation which results in a defective gene development at the cell forming stage, consequently leading to UCD.

Different forms of UCDs are caused by various genes. There are eight distinct forms of UCDs, which are also referred to as "subtypes." The UCD genes encode the urea cycle enzymes as well as those needed for their effective functioning, and defects in these genes results in disorders [58]. The genes that are involved in UCDs are OTC encoding OTC, ASL encoding ASL, NAGS encoding NAGS, ASS1 encoding argininosuccinate synthetase, CPS1 encoding carbamoyl phosphate synthetase I, ARG1 encoding arginase 1, SLC25A13 encoding citrin, and SLC25A15 encoding the mitochondrial ornithine translocator.

CLINICAL PRESENTATION

The clinical manifestations of UCDs are induced by defects in the enzymes or products, accumulation of toxic compounds or sometimes both. The onset of the clinical symptoms will range from the newborn phase to adulthood, depending on the deficient enzyme's residual function. In UCDs, the clinical symptoms are generally nonspecific and are psychological, gastrointestinal, or neurological in nature. UCDs can appear as acute or chronic symptoms, and clinical signs and symptoms can occur at any age of 12–16 [59,60]. These are often caused by excess load of protein, catabolic activities, or due to some medications. In certain instances, it is impossible to identify a precipitating cause [61]. Most UCDs are distinguished by hyperammonemia, a nonspecific indicator of insufficient detoxification of nitrogen [62]. UCD is distinguished by the fact that ammonia toxicity is at a high range based on whether the blockage is in the initial or next level.

Hyperammonemia causes cerebral edema, hypothermia, neurologic posturing, lethargy, hyperventilation or hypoventilation, anorexia, fatigue, and coma which are the symptoms of this condition [63-65]. Hyperammonemic crisis may occur due to extended periods of fasting and mild illness with fever or low oral intake because of high proteolysis and catabolism. Similarly, consumption of excess protein leads to elevated ammonia production and, as a result, causes encephalopathy. In a few cases, impairment in the liver or administration of valproic acid also causes hyperammonemia. Hence, the patients should be tested for any of these disorders. Based on the proximity of defects in the enzyme, the severity of hyperammonemia can be estimated. Therefore, the UCD subtypes incidence is NAGS deficiency, carbamoyl phosphate synthetase I deficiency, OTC deficiency, argininosuccinate synthetase deficiency, ASA, and arginase deficiency in the descending order [66,67].

DIAGNOSTIC METHODS

The diagnosis of UCDs can be made by urinary orotic acid and plasma amino acid analysis [68]. In general, the metabolic abnormalities are considered to be inconsistent and vary accordingly. There are various diagnostic methods for the detection of UCDs and their subtypes.

NBS and Differential diagnosis
At present, NBS employs tandem mass spectrometry to detect the UCDs [69-71]. Moreover, the specificity and reliability for the UCDs using this screening technique varies [72]. Hyperammonemia can also be caused by a few other disorders that affect the liver and thus resemble the characteristics of UCD [73]. These include the use of some drugs such as valproic acid, cyclophosphamide, diseases of the biliary tract, and liver as well as other genetically related disorders. Various genetic disorders such as propionic acidemia, and isolated methylmalonic acidemia are taken into consideration for differential diagnosis of UCDs [74].

Prenatal testing
In many countries, prenatal testing is available that enables termination of pregnancy in case of abnormality in the fetus [75]. Prenatal analysis aid in perinatal management and can also indicate the presence of UCDs at the milder range. A counseling session by metabolic specialists and clinical geneticists is essential for the prenatal testing [76,77]. Mutation analysis is the tool of choice for reliable detection of UCDs, genetic counseling, and, in some cases, predicting prognosis. One of the examples for this testing is mutation analysis from CVS or AFC for CPS1D disorder using the DNA.

Molecular genetic testing
The diagnostic method which is primarily used for the accurate detection and confirmation of all the UCDs is molecular genetic testing. Molecular genetic testing is a preferential prenatal method for all the eight UCDs. The analysis of enzyme activity is supplanted by this method as a reliable diagnostic method. It includes consideration of the single and multi-gene testing; exome sequencing; and genome sequencing.

Enzyme activity assay
In case of uninformative molecular genetic testing, enzyme activity assay is a reliable method to detect UCDs. Enzyme activity can be helpful if the estimation based on DNA is not appropriate, and it can detect most of the disorders. If the molecular testing fails to detect particular UCD, enzyme activity assays involve the use of erythrocytes, intestinal mucosa, fibroblasts, and liver tissue for the detection [78].

PROGNOSIS

The prognosis for UCDs is mainly based on the primary condition that causes the increase in levels of ammonia. Patients of UCDs with early and late-onset of hyperammonemia were estimated to be 35% and 87%, respectively, in an 11-year survival rate. In individuals affected with serious hepatic encephalopathy, the probability of survival is recorded to be around 42% and 23% in individuals with 1 and 3 years of age [79].

MANAGEMENT OF UCDS

At present, there is no available treatment for UCDs. The type of urea cycle disease depends on the early or late diagnosis, acute manifestations, and implementation of the plan of diet and treatment. For the child to have positive outcomes, early intervention and care are required. Babies that are diagnosed within the 1st week of birth and immediately placed on a diet may improve the condition. Normal brain activity will be achieved by adhering to the diet. Thus, the nutrition therapy must be provided based on the severity of the disorder, despite the availability of various medications for the elimination of nitrogen. With the use of appropriate treatments methods, the survival rate can be prolonged in affected individuals [9,80-83].

Management of acute manifestations
In the earlier times, with respect to UCDs, the morbidity and mortality were in the highest range and severe neurological consequences have been experienced by the affected individuals. The prognosis and predicted neurodevelopmental outcome should be noticed when treating acute hyperammonemia since they would affect the clinical decision [84]. The management of acute hyperammonemic manifestations includes restriction of protein in diet, regulation of high concentration of plasma ammonia to normal levels [85], management of catabolic state, treating seizures, and preventing overload of fluids must be considered for reducing the risk of neurological damage. Alternative pathway therapy can be suggested for the elimination of excess nitrogen. This therapy utilizes the administration of sodium phenylbutyrate or sodium phenylacetate/benzoate for the nitrogen elimination in the form of hippuric acid and phenylacetylglutamine [86,87].

Long-term management
The main idea for long-term management of the UCDs is to attain normal growth and development and to prevent hyperammonemia condition. This type of management is based on supplementation of essential amino acids, vitamins and minerals, maintenance of low protein diet, and replacement of arginine and citrulline [88] based on the UCD subtype condition of the affected individual and also involves

pharmacological assistance for elimination of excess nitrogen like sodium benzoate [89].

Recently, commonly available Glycerol phenylbutyrate is used as a pharmacological treatment that ensures improved patient condition. In severe cases of the UCD affected children, liver transplantation is recommended [90,91]. A treatment plan including emergency instructions and information about contacting the local hospital or for metabolic assistance must be provided in advance to the caretakers or parents.

Liver transplantation

The sole treatment or cure for UCDs is liver transplantation, which allows for a transition to a normal diet and the cessation of pharmacological treatment. Transplantation of hepatocyte is being suggested as a bridging therapeutic procedure in affected patients with UCD [92]. At present, trials are being conducted to assess the procedure's safety and effectiveness. Management of the disorder which includes liver transplantation, for all UCDs except NAGSD and the HHH syndrome, is treatable in terms of enzyme deficiencies and helps with the low-protein diet and alternative pathway therapy discontinuation, although it does not reverse the existing neurological impact [93].

Transplanted patients need immunotherapy as well as long-term monitoring. Thus, in terms of quality of life, liver transplantation is a safer approach to conventional care for seriously affected UCD patients when compared with the medical treatment [94,95]. As the pre-existing neurological injury exists, it is critical to avoid hyperammonemia and endogenous catabolism before and throughout liver transplantation.

Gene replacement therapy

Recently, gene therapy has been known to be effective for treating various metabolic disorders including UCDs. Gene therapy can be used for delivering the therapeutic gene specifically to the liver, which can eventually result in normal ammonia levels. Based on information from the previous research, adeno-associated viral (AVV) vectors are considered as primary agents of the gene therapy for UCDs among various other multiple vector systems due to their efficiency. Liver-directed gene replacement therapy using AVV vectors for ARG1 deficiency, ASL deficiency, ASS1 deficiency, and OTC deficiency has been reported in a few animal models [96-99].

Patient monitoring

UCD patients acquiring medical treatment need lifetime supervision, which includes anthropometric results, metabolic testing, food and medication reviews, history of coexisting conditions, and the use of the emergency instructions. Person visit periods should be determined based on age, development, severity, physiological health, and adherence to diet and drug therapy. Younger and more seriously affected patients may need testing every 3 months, whereas older or less severely affected patients will only need yearly reviews. Assessment on the diet should be performed on a regular basis. The diet must be planned according to age and development. As low protein diets can raise the risk of osteoporosis, bone density screening may be necessary from time to time [100].

DETERRENCE AND PATIENT EDUCATION

The information regarding the clinical manifestations of UCDs must be familiarized to the affected patients. Knowledge and education concerning medical compliance are crucial. Each individual patient must be provided with a specific diet plan and information related to particular dietary supplements also to be given. The growth and development must be constantly monitored in children affected with UCD, and parents must be advised on the condition accordingly. As many of these conditions are treatable, patient education and knowledge about IEMs leads to early diagnosis and effective treatment that can be lifesaving [101-103].

CONCLUSION

Inborn metabolic errors belong to a heterogenous class of disorders that can occur due to inheritance or as a consequence of mutations of spontaneous type. UCD are a common type of IEMs that are caused by the defects in enzymes of the urea cycle pathway resulting in excessive accumulation of certain metabolites and mainly ammonia. In general, UCDs are genetic disorders, and all of these except OTC deficiency are autosomal recessive disorders. Whereas the OTC deficiency is an X-linked inherited disorder. UCDs exhibit common clinical signs of hyperammonemia which causes disruption of neurotransmitters, functioning of mitochondria in the brain, ion gradients and metabolites transportation, especially in newborns after a few periods of feeding. In most of the cases, prevention of severe neurological damage and death in UCDs mainly depend on early diagnosis and consideration of effective treatment methods. IEMs can be diagnosed accurately using NBS, which can detect these disorders at an asymptomatic stage and perform medical intercessions that positively change the disease's natural history. Even in the case of negative NBS results, the clinicians must still recognize the probability of the disorder. Early diagnosis and appropriate treatment ensure attaining the advantages of these recent developments in the affected individuals. In particular, the number of treatable IEMs is increasing over time, and care for the disorders that are not treatable is improving.

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