Challenges in diagnosing and managing adult patients with urea cycle disorders

Karolina M Stepien[1,*], Tarekegn Geberhiwot[2], Christian J. Hendriksz[3], Eileen P. Treacy[4,5]

[1]Mark Holland Metabolic Unit, Adult Inherited Metabolic Diseases Department, Salford Royal NHS Foundation Trust, Salford, M6 8HD, United Kingdom
[2]Centre for Endocrinology, Diabetes and Metabolism, Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, B15 2TH, United Kingdom
[3]University of Pretoria, Department of Paediatrics, Steve Biko Academic Hospital, Pretoria, South Africa
[4]National Centre for Inherited Metabolic Diseases, The Mater Misericordiae University Hospital, Dublin 7, Ireland
[5]Department of Paediatrics, Trinity College, Dublin, Ireland

*Correspondence: Karolina M. Stepien, Mark Holland Metabolic Unit, Adult Inherited Metabolic Diseases Department, Salford Royal NHS Foundation Trust, Salford M6 8HD, UK. Email: kstepien@doctors.org.uk

Abstract

Urea cycle disorders (UCD) are a group of rare inherited metabolic conditions of amino acid catabolism caused by an enzyme deficiency within the hepatic ammonia detoxification pathway. The presentation of these disorders ranges from life-threatening intoxication in the neonate to asymptomatic status in adults. Late-onset UCDs can present for the first time in adulthood and may mimic other causes of acute confusion or psychiatric diseases, and are often associated with neurological symptoms. Late-onset UCDs may become apparent during periods of metabolic stress such as rapid weight loss, gastric bypass surgery, chronic starvation or the postpartum period. Early diagnosis is critical for effective treatment and to prevent long-term complications of hyperammonemia. The challenges of management of adults include for example: (a) poor compliance to dietary and medical treatment which can result in recurrent hospital admissions; (b) severe neurological dysfunction; (c) the management of pregnancy and the postpartum period; and (d) access to multidisciplinary care perioperatively. In this review, we highlight a number of challenges in the diagnosis and management of adult patient with late-onset UCDs and suggest a systematic management approach.

1 INTRODUCTION

The clinical manifestations of urea cycle disorders (UCD) in adults are variable. The presentation ranges from life-threatening intoxication in the neonate to asymptomatic status in adults. Late-onset presentations of UCD associated with partial enzyme deficiencies may occur at any age, with up to 10% of UCD, mainly ornithine transcarbamylase deficiency (OTCD, OMIM 311250), rarely argininosuccinic acid lyase deficiency (ASLD, OMIM 207900), being diagnosed after the age of 16 years.[1-5]

The age and severity of presentation depends on the causative mutation, the residual enzyme activity and physiological and environmental influences.[6-9] It is recognized that there may be differences in the severity of presentation in affected families.

OTCD, an X-linked disorder, is the commonest UCD with a worldwide estimated prevalence of (1/63 000).[1] There may be significant phenotypic variability of OTCD heterozygous

females.[10] Individuals with less severe diseases causing mutations can have clinically silent disease until encountering metabolic stressors that initiates a catabolic state and unmasks the disease process.[11] Males are usually severely affected, with 15%-20% of females ultimately developing symptoms.[12]

Late-onset UCD is associated with diverse symptoms and are associated with a high mortality rate of 11%.[1] Mortality rate (neonatal plus late-onset) is greatest in carbamoyl phosphate synthetase 1 deficiency (CPS1D, OMIM 608307) (42%), followed by OTCD (11%), argininosuccinic acid synthetase deficiency (ASSD, OMIM 215700) (7%), and ASLD (6%).[1] Therefore, it is essential that symptoms are recognized early to ensure prompt diagnosis and treatment,[5, 13] otherwise the prognosis may be poor.[14]

Prompt recognition is critical to reduce mortality and prevent irreversible neurological damage. This review outlines precipitating factors, clinical manifestations, and challenges in managing UCDs in adult patients.

2 DIAGNOSTIC CHALLENGE

2.1 Clinical manifestations

An increased awareness of relevant signs and symptoms could facilitate an early diagnosis of late-onset UCDs. A detailed history of clinical symptoms and signs, that may be nonspecific, is key in diagnosing a UCD in an adult patient.[15] Unexplained neurological disorder or confusion, protein aversion or the family history of neonatal death are diagnostic clues. These should prompt ordering a plasma ammonia concentration to search for a UCD (Table 1).

TABLE 1 Recommendations regarding diagnosis and management of UCDs in adults

1. Consider measuring ammonia levels in the acute confused patient without obvious cause
2. Consider measuring ammonia in the patient presenting with psychiatric manifestations especially if there is an associated history of protein aversion or cyclical vomiting
3. Consider measuring ammonia in the acute confused postpartum patient
4. Hyperammonemia is a medical emergency and expert advice should be sought urgently in all patients with ammonia concentration greater than 100 μmol/L
5. The initial management of hyperammonemia in the adult consists of resuscitation, stopping all dietary protein, use of high calorie IV infusions or oral high calorie emergency fluids and the use of ammonia scavengers if available
6. Early recognition and aggressive management will limit neurological sequelae
7. Hyperammonemia without an obvious cause due to underlying hepatic disease should prompt investigation for an underlying metabolic disorder

Abbreviations: IV, intravenous; UCD, urea cycle disorder.

2.2 Neurological and psychiatric manifestations

Related acute neurological features include altered level of consciousness, seizures, loss of appetite, sleep disorders, metabolic stroke, and transient visual loss.[14-18] Chronic presentation includes different degrees of cognitive impairment, confusion, lethargy, dizziness, headache, cyclical vomiting, ataxia, dysarthia, asterixis, tremor, and learning disabilities.[15] Undiagnosed UCD may mimic encephalitis or drug intoxication.[18] The neurological outcome of UCDs is linked to the extent and to the duration of hyperam-monemia,[18, 19] therefore the earlier the diagnosis the better the outcome[17] (Table 2).

Late-onset UCD may mimic psychiatric diseases such as mania, paranoia, hallucinations in acute presentation [15] or acute schizophrenia,[30-32] which may be associated with neurological symptoms.[17] The chronic psychiatric symptoms may be nonspecific, but usually include stereotypic behavior, behavioral disinhibition, automatism, emotional, or personality changes. Nonspecific psychiatric problems are the most common symptoms[14, 17, 18] and often are the only symptoms in adult patient.[33]

Progressive spastic paraplegia is a feature of arginase deficiency (ARG1D; OMIM 207800) and often occurs between 2 and 4 years of life.[15] The condition may however remain misdiagnosed since hyperammonemia occurs rarely during acute illness. Three of adult siblings had a clinical diagnosis of familial spasticity syndrome until they were confirmed to be affected with ARG1D following NGS (personal observation).

2.3 Gastrointestinal manifestations

Gastrointestinal symptoms may accompany the nervous system phenomena and include nausea, cyclic vomiting, progressively poor appetite, and protein avoidance.[18] Aversion to foods containing high protein density, such as animal-derived proteins is the most striking. Other reported habits included increased frequency of meals and overeating of low-protein foods, and high consumption of low nutrient-dense foods.[14, 34] A misdiagnosis of anorexia nervosa may occur in individuals who restrict protein intake and present with recurrent vomiting episodes.[17, 35]

2.4 Risk factors

Nutritional changes are common risk factors that may precipitate metabolic decompensation and presentation of UCDs. Alterations in nitrogen turnover and load can be triggered by poor nutritional intake and rapid weight loss, for example, during gastric bypass surgery, chronic starvation (anorexia or bulimia). A sudden increase (parenteral nutrition) or decrease in protein intake may also contribute to nitrogen imbalance and precipitate decompensation and deterioration.[5, 20, 25, 34]

Reports of unmasked OTCD are becoming increasingly prevalent in females after bariatric surgery presenting with hyperammonemia. Although this should prompt investigation for an underlying metabolic disorder, not all patients have a defined metabolic defect after careful investigation. Sudden weight loss post bariatric surgeries and concomitant nutritional deficiencies were previously recognized as a precipitating factor of UCD.[14, 36] In general, low serum concentrations of micronutrients, including vitamins and trace elements, are common in critically ill patients. Low zinc (cofactor for ornithine transcarbamylase [OTC]) and arginine concentrations were demonstrated to decrease OTC activity.[37]

TABLE 2 Late-onset UCDs and recommendations on their diagnosis and management

Case	References	Genetic defect/Diagnosis	Clinical manifestation	Management	Recommendations
1	Alameri et al[16]	119G variant, in exon 2 *OTC* gene	17-year-old man, nausea and vomiting for 1 week, followed by a witnessed new-onset prolonged generalized tonic-clonic seizure, and a rapidly deepening coma over a 3-day period. Ammonia 787 μmol/L	L-Arginine supplementation, SB, with intermittent CVVHD	**Awareness of UCDs** • To consider UCD diagnosis for any adult presenting with unexplained hyperammonemic coma or unexplained change in mental status • To raise awareness of emergency department staff in considering OTCD in the differential diagnosis of sudden neurological and behavioral disorders associated with hyperammonemia at any age and in both genders • To recognize promptly this rare and complex condition and to rapidly initiate adequate metabolic therapy to prevent irreversible neurological sequelae and to avoid LT **Triggering factors** • To consider protein loading due to the Atkins diet as an environmental factor that triggers a hyperammonemic crisis • To consider menses, cortisone, sodium glutamate in diet, hormonal fertility treatment as precipitants for acute hyperammonemia in UCD • To screen for micronutrient deficiencies in a malnourished patient • To consider a trigger of acute hyperammonaemic crisis such as illness, gastrointestinal bleeding, medications, high protein load, or surgery **Screening for UCDs** • To screen at risk family members after an inborn error of metabolism is diagnosed • To be aware that the same genetic defect can have varying degrees of presentation within the same family, further highlighting the unpredictability of the disease process • To establish UCD genotype, as it can help clinicians make earlier decisions on the need for invasive therapy (eg, liver transplantation) or conservative therapy (diet and medications)
2	Ben-Ari et al[20]	p.Ile159Met (c.477T>G) mutation in exon 5 *OTC* gene	47-year-old man, hyperammonemic encephalopathy after a high-protein diet. Ammonia 541 μmol/L	CVVHD combined with the administration of L-arginine and PBA and an intravenous hypercaloric regimen of 20% glucose and 20% intralipid preparation. Low-protein diet	
3	Cavicchi et al[2]		Acute encephalopathy and coma in cases:		
		p.Arg40Leu (c.119G>T)	45-year-old male, cortisone therapy for joint pain, ammonia 153-422 μmol/L	TPN, BCAA infusion, lactulose	
		p.Gly105Glu (c.314G>A)	44-year-old male, diet change, poor feeding, weight loss after dental surgery, ammonia 339-845 μmol/L	Ammonia scavengers, protein restricted diet, L-arginine, CVVHD	
		p.Arg40His (c.119G>A)	21-year-old male, diet change, a meal of fish in a Chinese restaurant, ammonia 156-377 μmol/L	TPN, BCAA infusion, ammonia scavengers	
		p.Ala208Thr (c.622G>A)	66-year-old male, chemotherapy, ammonia 251-1145 μmol/L	TPN, ammonia scavengers, CVVHD	
		p.Arg277Trp (c.829C>T) in *OTC* gene	34-year-old female, infertility hormone therapy, ammonia 362-901 μmol/L	TPN, BCAA infusion, ammonia scavengers, protein restricted diet, HD	
4	Daijo et al[21]	p.Ala208Thr (c.622G>A) in *OTC* gene	69-year-old man, 3-day loss of appetite, early morning vomiting, and state of confusion. Ammonia 293 μmol/L	Long-term CVVHD, administration of L-arginine and lactulose	
5	Lee et al[22]	p.Arg40His (c.119G>A) mutation in *OTC* gene	27-year-old man, confused and ataxic after 30 km marathon. His liver was donated to two patients who became symptomatic. The ammonia result of 91 μmol/L in the context of normal liver function was undervalued	Patient died, no metabolic investigations were performed in time	

TABLE 2 (Continued)

Case	References	Genetic defect/Diagnosis	Clinical manifestation	Management	Recommendations
6	Ramanathan et al[23]	p.Arg92Gly (c.274C>G) in *OTC* gene	63-year-old man had liver transplanted from a donor affected with OCTD. Ammonia 1234 μmol/L	PBA and SB, CVVHD, died from brain edema	• In the absence of positive provocative biochemical testing and a positive clinical examination, to acquire an extensive family history in addition to molecular testing in OTCD **General recommendations** • To consider UCDs as a cause of an acute encephalopathy • To establish a definitive diagnosis in a donor prior to consideration for organ donation • To include OTCD among the causes of ALF in adults and to suspect it in cases of nonjaundiced ALF associated with severe hyperammonemia, regardless of the serum aminotransferase activity • In the case of potential donors with brain death of unclear origin, maximum efforts are required to establish the diagnosis, for which blood ammonia determinations should be performed • In all patients with coma of unknown origin, an acute metabolic disease has to be considered and plasma ammonia must be determined • To consider plasma amino acids and urine organic acid in behavioral changes and hyperammonemia that cannot be explained by hepatic failure or medications • To consider a metabolic disorder in a patient suffering from postpartum psychosis • To perform plasma amino acids and urine organic acids in addition to ammonia measurements in all patients with acute neurological symptoms during the postpartum period • To consider UCDs (OTCD, ASSD) in adult patients with liver failure of an unknown etiology • To consider UCDs as a possible diagnosis in any patient with unexplained neurologic disorders, even in adulthood, especially when associated with altered
7	Rohininath et al[3]	p.Val337Leu mutation in *OTC* gene	62-year-old man, 4-day history of encephalopathy, disorientation, fluctuating somnolence, dysarthia. Ammonia 1285 μmol/L	CVVHD, L-arginine, SB, PBA, a hypercaloric iv regime and withdrawal of all protein. Died from neurological complications	
8	Weiss et al[24]	p.Lys307Glu (c.919 A>G) in exon 9 of *OTC* gene	28-year-old females, at 7 week in gestation, acute liver injury as a presentation of OTC. Ammonia 281 μmol/L	The removal of protein intake, intravenous SB and CVVHD	
9	Plochl et al[12]	p.Arg40His in exon 2 Liver biopsy: OTC activity was about 10% of the normal	26-year-old man, nausea, vomiting, ataxia, coma and death	Donated liver resulted in ammonia of 3793 μmol/L and death in a 65-year-old female. CVVHD and mechanical ventilation	
10	Wells et al[25]	Nutritional deficiencies unmasked UCD	60-year-old woman, chronic alcoholism, malnutrition and sudden weight loss of 22 kg, sudden onset change in mental status, ammonia 256 μmol/L, failure to thrive, GCS 7/15, died.	L-carnitine 500 mg intravenously (IV) every 4 h, L-arginine 200 mg/kg daily via continuous infusion, and SB/PBA 175 mg/kg daily via continuous infusion with 10% dextrose. Solution at 40 mL/h. Ascorbic acid 500 mg per nasogastric tube twice daily and thiamine 100 mg IV daily. TPN. CVVHD	
11	Häberle et al[26]	p.A118T homozygous	27-year-old female, 2 days postpartum irritability and difficulties in speech, movement disorder, progressed to coma, died 7 days later. Ammonia 285 μmol/L	CVVHD	
		c.773+49C>T homozygous	31-year-old female, 4 days postpartum headache, dizziness, disorientation, progressed to generalized tonic-clinic seizures, progression to coma. Full recovery after 6 months. Ammonia 800 μmol/L	CVVHD	
		p.R363Q heterozygous /? in *ASS1* gene	37-year-old female, 4 days postpartum disorientation and drowsiness, rapid progression to coma, well on treatment. Ammonia 363 μmol/L	CVVHD	

TABLE 2 (Continued)

Case	References	Genetic defect/Diagnosis	Clinical manifestation	Management	Recommendations
12	Reid et al[27]	p.Val178Met (c.532 G>A) mutation and a 13-base-pair deletion, c.1045_1057delGTCATCTCTACGC in *ASAL* gene	34-year-old female, known to have ASSD, 6-week pregnant, uneventful pregnancy	Protein restricted diet, L-arginine	level of consciousness, behavioral changes, vomiting, anorexia, or a self-imposed protein-restricted diet • To include a thorough history of the food intake, that is, protein avoidance
13	Salek et al[28]	Compound-heterozygous for p. Ala118Thr(c.352G>A) in exon 5 and for p.Gly390Arg (c.1168G>A) in exon 15 *CTLN1* gene	25-year-old female, 18-week pregnant, acute liver failure, ammonia 150 μmol/L	iv dextrose (10%) and intralipid (20%) to prevent further catabolism, and her diet was adjusted to limit her protein intake to 0.5 g/kg/day. L-Arginine (1 g by mouth twice daily) and PBA (1 g by mouth twice daily)	
14	Eather et al. 2006[60]	Liver biopsy: CPS activity 20% of the lower limit of normal	41-year-old female, 17-week pregnant, severe episodes of confusion, headache, drowsiness, ataxia, slurred speech.	SB, L-arginine intravenously. Positive neurological outcome in mother. Fetus born at 22-week of gestation died	
15	Van de Logt et al[29]	p.Lys201Asn (c.603G>C) in exon 2, in *NAGS* gene	59-year-old female, hyperammonemia after surgery, intellectual disability. Ammonia 280 μmol/L	Natural protein restriction, administration of L-arginine/citrulline and SB	
16	Summar et al[14]	Liver biopsy: enzyme activity and DNA sequence analysis, the patient had partial *N*-acetylglutamate synthetase (NAGS) deficiency and was unable to make cofactor for the CPS enzyme	A 30-year-old man, head injury after a car accident. Seizures, ammonia 553 μmol/L	CVVHD, PBA, SB, and L-arginine, iv dextrose, mechanical ventilation. Died	
		Liver biopsy: OTC deficiency activity reduced	58-year-old female, recurrent asthma attacks treated with intravenous steroids, ammonia 280 μmol/L, cerebral edema on CT scan, no seizures	CVVHD, PBA, SB, and L-arginine, iv dextrose, mechanical ventilation, survived the episode with no neurological deficits	
		Liver biopsy: CPS1 enzyme activity reduced	34-year-old female, weigh loss of 78 kg over 8 months, after bariatric surgery, hyperammonemia (442 μmol/L), weakness and status epilepticus. Died on day 6	CVVHD, PBA, SB, and citrulline	

Abbreviations: ALF, acute liver failure; ASSD, argininosuccinic acid synthetase deficiency; BCAA, branched-chain amino acids; CPS1, carbamoyl phosphate synthetase 1; CT, computed tomography; CVVHD, continuous veno-venous hemofiltration; GCS, Glasgow Coma Scale; iv, intravenous; HD, hemodialysis; LT, liver transplantation; OTCD, ornithine transcarbamylase deficiency; PBA, phenylbutyrate; SB, sodium benzoate TPN, total parenteral nutrition; UCD, urea cycle defect.

Donor-derived UCDs, with OTC deficiency being the most common, should be included in the differential diagnosis of post-transplantation hyperammonemia in addition to impaired liver function and dysfunction of the allograft.[23] Education among transplant teams remains the best method of avoiding such complication in patients undergoing liver donation.[23] Importantly, recipients of kidney, heart, and lung from the OTCD donor had a successful outcome, as OTC is expressed in the liver[22] (Table 2).

Several cases of late-onset OTCD masqueraded by chronic liver disease were described in the literature[3, 21, 23] with a case from our clinical practice involving a 70-year-old man who had a grandson affected with OTCD. Importantly, elderly patients with or without comorbidities may remain asymptomatic or develop atypical symptoms over a period of time. In some patients who manage to survive to adulthood before reaching a hyperammonemic threshold, there are several physiologic mechanisms that can tip the nitrogen balance[14] (Table 3).

Other risk factors include infections, fever, decreased energy (fasting prior to surgery, major weight loss), catabolism, prolonged, or intense physical exercise, unusual protein load (parenteral nutrition, excessive exercising)[5, 14, 18] (Table 2).

Recommendations regarding diagnostic clues have been summarized in Tables 1 and 2.

2.5 Investigations

A high ammonia concentration, a hallmark of UCDs, may present with variable clinical patterns with the main manifestations affecting the central nervous system in the absence of hepatocellular dysfunction.[38] Importantly, when the patient is asymptomatic, ammonia concentrations may be within normal limits. A high index of suspicion, and further biochemical and genetic work-up, are required to make the diagnosis in these situations when ammonia concentrations are normal. Other recommended blood tests include lactate, glucose, electrolytes, and arterial blood gases.[10] Low blood urea concentrations, because of ureagenesis inhibition or low protein intake, are important diagnostic parameters. Normal glucose and electrolyte concentrations with a high ammonia concentration and respiratory alkalosis (ammonia ≥100 μmol/L), electrolyte or acid-base disturbance are previously observed in adult UCD patients. Quantitative plasma amino acids, urine orotic acid analysis, and liver biopsy can help to distinguish between the different types of UCD.[18] Liver biopsy, however, is recommended only if genetic testing fails or if there is a clinical need for confirmation of the diagnosis before the result of genetic testing is available.[15] Plasma acylcarnitine profile may help exclude other metabolic disorders causing secondary hyperammonemia[15] (Table 3).

Although the allopurinol test is a noninvasive way of distinguishing between OTC heterozygotes and noncarriers,[39] it is not routinely used because of its limited sensitivity (91%) and specificity (70%). The protein loading test may also be used in OTCD females, but as it is dangerous, it should be avoided.[15]

Mutation analysis of a candidate gene or the application of NGS gene panels is the method of choice for the definitive diagnosis. In the majority of patients with OTCD, the mutation appears de novo (mother not carrier) and in approximately 25% of cases of OTCD patients the mutation is not identified.[18, 40]

TABLE 3 Secondary causes of hyperammonemia in adult patients. Adapted from Summar et al[14]

Causes and mechanisms
Urea cycle defects triggers from nitrogen turnover and load
• Rapid weight loss and poor nutritional intake -gastric bypass surgery
• Internal bleeding or damage -fracture/trauma -surgical damage -gastrointestinal bleeding
• Viral illness or other generalized stress
• Postpartum period
• Seizures
• Bone marrow transplantation
• Multiple myeloma
• Dramatic increase/decrease in habitual protein intake -High protein diet strategies (Atkins diet, total parenteral nutrition) -Change in food access or preparation -Malabsorption conditions (starvation, severe exercise)
• Medications affecting protein catabolism -Intravenous or high-dose glucocorticoids -Chemotherapy (asparaginase or pegaspargase)
Genetic predisposing conditions affecting capacity of the urea cycle
• Genetic defects in enzyme/transporter function of the UC components or decreased function polymorphisms
• Distal renal tubular acidosis
• Comorbid metabolic conditions -Organic acidemias (MMA, PA, HMG CoA lyase deficiency, IVA) -Fatty acid oxidation defects -Primary hepatic (hepato-cerebral) mitochondrial disorders
Pharmacological or toxic effect
• Chemical or toxic effect on enzyme function
• Transurethral prostate resection syndrome (caused by glycine solution used during the procedure)
• 5-pentanoic acid (Jamaican vomiting sickness)
• Valproic acid/carbamazepine
• Chemotherapeutic agents (cyclophosphamide)

MMA-methylmalonic acidemia; PA- propionic acidemia; HMG CoA-3-hydroxy-3-methylglutaryl-CoA; UC- urea cycle; IVA- isovaleric acidemia.

Magnetic resonance imaging (MRI) in patients with late-onset UCD may show white matter lesions and diffuse cerebral edema.[18, 41] Importantly, not all patients with UCD will show these changes and MRI can be normal, with changes only appearing during an episode of acute hyperammonemia.[15, 41] Magnetic resonance spectroscopy can reveal elevated brain glutamine levels helpful to detect subtle changes in OTC females.[44] Modern neuroimaging techniques have a significant role in clinical monitoring and acute treatment.[15, 43]

3 MANAGEMENT CHALLENGE

The key principles of managing UCDs in adults are outlined in guidelines by Häberle et al[18] and in the revised UCD guidelines.[15] The British Inherited Metabolic Diseases Group

(www.bimdg.org.uk) also published recommendations on the application of ammonia scavengers in a single or multiple therapies in adult patients.

3.1 Acute

Patients in hyperammonemic crisis require urgent treatment, with the initial medical management often applied at the local hospital, before the transfer to a specialist center for the definitive diagnostic workup would be performed.[18] The principles of the management of adults in acute hyperammonemic crisis include physical removal of the ammonia by hemodialysis or continuous veno-venous hemofiltration (CVVH), reversal of the catabolic state through caloric supplementation and pharmacologic scavenging of excess nitrogen.14 In adult-onset UCDs, CVVH is considered as a first line treatment in acute decompensations when ammonia exceeds 200 μmol/L.[15] It does not however apply to all patients with ammonia concentration >200 μmol/L. In some adult cases, which are poorly compliant with their ammonia scavenger therapy, ammonia concentration may vary between 200 and 500 μmol/L but patients are still fully conscious and lead their day-to-day life.

3.2 Long-term management

Treatment is individualized according to the severity of the illness, previous decompensation, and protein tolerance. Some adults with mild UCD may only require preventive measures during acute illness or surgery, instead of a life-long protein-restricted diet and ammonia scavenging agents. Symptoms and signs may only reappear during times of extreme stress like severe illness and the managing team should be aware of this in a patient who does not take chronic medications.

3.2.1 Dietary

Late-onset UCD patients who are on a self-selected low-protein diet generally require vitamin and mineral supplements as they are likely to be deficient in cobalamin, iron, and calcium. In adult patients who require low-protein diet, regular dietary assessments and monitoring of their compliance to therapy remains a challenge. In particular, women postpartum may develop protein aversion suggestive of an UCD. In such cases the dietary regimen must be highly individualized with a gradual introduction of natural protein.[15]

3.2.2 Medical

The majority of patients treated in the United States receive the medications sodium or glycerol phenylbutyrate (PBA) alone, whereas in Europe sodium benzoate is considered as the first line medication.[15] Limited palatability, volume and frequency of the drug administration are causes of poor adherence. PBA may deplete branch-chain amino acids by activation of branched-chain keto acid dehydrogenase, and increase the risk of endogenous protein catabolism.[44] This is effectively managed with supplementation of natural protein and protein synthetic analogues.

Importantly, in adult ASLD patients with concomitant chronic liver disease, managing acute, and chronic manifestations of UCD may be particularly difficult as ammonia scavengers do not optimally conjugate the toxic metabolites if the liver function is compromised (personal observation).

Arginine is an essential amino acid in all UCDs (except ARG1D). The rationale for its supplementation in symptomatic patients, apart from avoiding plasma arginine deficiency, is to reduce the frequency of hyperammonemia episodes.[15] It may however not be required in mild phenotypes.

3.2.3 Liver transplantation

Liver transplantation may be considered in late-onset UCD patients who suffer from recurrent metabolic decompensations, resulting in prolonged hospitalizations, despite medical therapy, and who have limited access to tertiary care. Criteria for transplantation are associated with neurologic status, duration of coma, and availability of livers.[14] It has been reported in acute encephalopathy and/or acute liver failure but these are high risk situations and they require case by case discussions if patient's situation allows.[15] Liver transplantation has been reported in late-onset CPS1D case with a good outcome[46] (Table 2). This has been shown to improve poor compliance and to eradicate the need for medications and dietary restrictions.[15]

3.2.4 Surgery

The peri-operative care of adult patients with UCD requires multidisciplinary team (MDT) input including adult metabolic physician, dieticians, nurses, anesthetist, surgeon, intensivist (if CVVHD is required), and clinical psychologist. In such settings, the main point is to avoid a catabolic state by considering total parenteral nutrition if enteral feeding is not possible for a prolonged time. For treatment of acute hyperammonemia, it is prudent to establish and maintain anabolism by providing high-dose glucose +/− insulin (plus lipids). It is recommended to maintain protein-free nutrition for up to 24 hours.[15] Preoperative ammonia and plasma amino acids should be within normal ranges[15] and ammonia scavengers administered intravenously.

Most anesthetic agents have been shown to be safe in UCD (midazolam, s-ketamine, fentanyl, isoflurane, and ropivacaine).[15, 18]

3.2.5 Mild learning difficulty

A proportion of individuals with OTCD have a wide spectrum of neuropsychological complications including developmental delay, intellectual disability, attention deficit, hyperactivity disorder, and executive function deficits.[47] Most adult-onset patients remain asymptomatic, until they present with rapid decline in mental status and subsequently chronic encephalopathy.[5, 18, 48] Fluctuating hyperammonemia may cause delirium, confusion, and incoherent speech. In addition, subsequent regression, lack of attention leads to unemployment and introverted behavior.[49] Waisbren et al[50] demonstrated that nearly all asymptomatic 156 women with OTCD attained a full scale Intelligence Quotient (IQ) of 102 ± 16. Among 25 men, the full scale IQ noted was 101 ± 21. No differences were noted between verbal and performance scores. In addition, in 27% of females and 33% of males, deficit in working memory was observed.[50]

The ammonia concentration and its duration appear to be key determinants of the long-term outcome.[38] One study found average IQ values in 33%, 40% or 66% cases of ASSD, ASLD, and OTCD studied, respectively51 with 25% of late-onset patients presenting moderate to severe intellectual disability.[52]

This emphasizes the need for early diagnosis to avoid neurological complications. In one study 75% were affected by cognitive impairment if the delay was >1 year, compared to 46% if the delay was ≤1 year.[53]

It is recommended that symptomatic adults with UCD diagnosed in adulthood are followed up by a psychologist to monitor their emotional, behavioral, and psychological parameters. The need for a clinical psychologist should be decided on an individual basis. Psychologists should be involved in patient care early after diagnosis to cope with initial anxiety and with later-developing psychological problems and also to assess the cognitive level and neuropsychological functions of the patient.[18, 54] Longitudinal studies are required to determine the long-term neurocognitive outcome for adult patients with UCD.[50]

3.2.6 Pregnancy

The diagnosis of OCTD may become apparent during periods of metabolic stress such as during pregnancy or the postpartum period.[5] Pregnancy favors both prolonged fasting due to hyperemesis gravidarum and/or increased energy demands during the puerperium and therefore can reveal UCD.[24]

Hyperemesis gravidarum, a risk factor for metabolic decompensation due to caloric deficit, may be both a cause, and consequence, of hyperammonemia. Complications of hyperammonemia in pregnancy can masquerade as more common problems. Nausea, vomiting, headaches, and mood disturbance may falsely be attributed to hormonal changes. Liver failure initially attributed to fatty liver of pregnancy, was considered unusual presenting in early pregnancy with hyperemesis, weight loss, and prominent depression of synthetic function.[24, 28, 55] Acute liver failure, described in 40% of confirmed OTC symptomatic adult females, is caused by ammonia-induced suppression of hepatic protein synthesis, mitochondrial dysfunction, damage, and cell death.[56] In addition, the use of glucocorticoids recommended for hyperemesis gravidarum,[57] an intercurrent condition[55] or anticipated preterm delivery, may aggravate a catabolic state.

During prolonged catabolic situations, such as delivery and postpartum periods, vomiting, disorientation, seizure activity, or coma may occur due to hyperammonemia in females with OTCD[47, 58, 59] and other UCDs: citrullinemia type 1,[55] ASLD,[27] CPS1D.[60] Undefined agitation and alterations in consciousness in postpartum women may be diagnosed as postpartum psychosis.[61]

While the antenatal period as an anabolic state usually remains uncomplicated, with the exception of hyperemesis gravidarum which induces a catabolic state, commonly metabolic decompensation occurs in the catabolic postpartum period. Day 3-8 is a particularly high risk because of collagen and smooth muscle breakdown as the uterus involutes.[47] Previously asymptomatic and undiagnosed women have developed severe hyperammonemic encephalopathy following a normal pregnancy.[62] It has been observed in CPS1D, OTCD, and ASSD.[26] Additional catabolic stress may result from caesarean section, birth trauma, infection, for example, wound infection, mastitis, and blood transfusion may represent an added protein load.

Therefore, ammonia concentration should be measured in undiagnosed postpartum encephalopathic patients as early diagnosis and treatment of UCD are life-saving.

Despite anecdotal evidence of successful pregnancies of women taking PBA,[63] sodium benzoate is recommended to be potentially a safer choice during pregnancy.[18] PBA has been shown to cause menstrual dysfunction/amenorrhea in 25% of postpubertal females[63] and can decrease appetite, disturb taste, and cause disagreeable body odor.[18]

Pregnancy and lactation in UCD patients requires addressing special nutritional needs and close monitoring of metabolic status and protein consumption, particularly during and 5 days postdelivery to ensure prompt recognition and treatment of hyperammonemia.[18]

Prenatal testing may enable pregnancy termination of affected fetuses[18] or prepare for perinatal management[64] which may include hepatocyte transfer followed by early transplantation in some centers.[65] Chorionic villus samples, amniotic fluid cells, or cultures to track mutation or disease allele[51] is the method of choice since it gives rapid and clear-cut results relatively early on, with little fatal risk. Amniotic fluid ASSD and ASLD determinations are also suitable for respective ASSD and ASLD prenatal diagnosis.[66]

4 NEW DEVELOPMENTS

Treatment of adults with UCDs is still very challenging and there have been few new developments in pharmacological therapy in recent years. The formulation of glycerol PBA may have improved palatability and pharmacological properties (avoids sodium intake and is a tasteless liquid). The clinical trials on this product have shown equal effectiveness with sodium phenylbutyrate[67] with no significant difference in adherence to either of two preparations. In terms of cost, glycerol PBA is still more expensive. A number of clinical trials for this product are still ongoing.

Carglumic acid, which activates CPS1 as the first step of ammonia conversion to urea, can be useful for genetic defects or biochemical inhibition of the *N* -acetylglutamate synthase (NAGS)[68] is licensed in Europe and United States.[15] Adult patients diagnosed with NAGS deficiency (OMIM 237310) can be effectively treated with *N* -carbamylglutamate.[29] Together with low protein diet, the therapy optimized ammonia concentration and it returned to normal reference ranges.

Arginase is an enzyme replacement therapy for ARG1D that is being currently investigated.[15]

Among new emerging therapies, gene therapy for late-onset UCD is becoming an available therapeutic option[15, 69] and hepatocyte transplantation is proposed as a bridging therapeutic measure in compromised patients awaiting liver transplantation,[15, 65, 70] stem cell therapies,[15, 71] or therapeutic hypothermia.[15, 68] Nitric oxide supplementation for patients affected by ASLD and potential neuroprotective agents will still need to be determined in clinical trials.[68]

New therapeutic strategies offer an improvement of palatability, pharmacological properties but also include neuroprotection. Limitations include small number of UCD patients who may be recruited for studies on new therapies.

5 CONCLUSION

UCDs are a rare but important cause of acute encephalopathy and can present for the first time in adulthood. A persistently raised plasma ammonia level >100 μmol/L in a patient without end-stage renal or hepatic dysfunction should raise suspicion of the presence of a UCD. An extensive family history is required in addition to molecular analysis in OTCD. The management requires MDT care. The condition is treatable, but can be fatal if undiagnosed or untreated. More research is needed especially in the adult population where these conditions may be diagnosed late.

CONFLICT OF INTEREST

Authors have no conflict of interest for this article.

AUTHOR CONTRIBUTIONS

K.M.S.: conception and design, drafting the chapter, revising the chapter critically for important intellectual content.

T.H., C.J.H., E.T.: revising the chapter critically for important intellectual content.

All authors read and approved the manuscript before submission.

Guarantor: E.P.T.

REFERENCES

[1]Batshaw ML, Tuchman M, Summar M, Seminara J, Members of the Urea Cycle Disorders Consortium. A longitudinal study of urea cycle disorders. *Mol Genet Metab*. 2014; 113(1-2): 127- 130.

[2]Cavicchi C, Donati M, Parini R, et al. Sudden unexpected fatal encephalopathy in adults with OTC gene mutations-clues for early diagnosis and timely treatment. *Orphanet J Rare Dis*. 2014; 9: 105.

[3]Rohininath T, Costello DJ, Lynch T, Monavari A, Tuchman M, Treacy EP. Fatal presentation of ornithine transcarbamylase deficiency in a 62-year-old man and family studies. *J Inherit Metab Dis*. 2004; 27: 285- 288.

[4]Saudubray JM, Mochel F. The phenotype of adult versus pediatric patients with inborn errors of metabolism. *J Inherit Metab Dis* (ahead of print. 2018; 41: 753- 756. https://doi.org/10.1007/s10545-018-0209-9.

[5]Summar ML, Dobbelaere D, Brusilow S, Lee B. Diagnosis, symptoms, frequency and mortality of 260 patients with urea cycle disorders from a 21-year, multicentre study of acute hyperammonaemic episodes. *Acta Paediatr*. 2008; 97: 1420- 1425.

[6]Caldovic L, Morizono H, Panglao MG, et al. Late onset *N* -acetylglutamate synthase deficiency caused by hypomorphic alleles. *Hum Genet*. 2005; 25: 293- 298.

[7]Ficicioglu C, Mandell R, Shih VE. Argininosuccinate lyase deficiency longterm outcome of 13 patients detected by newborn screening. *Mol Genet Metab*. 2009; 98: 273- 277.

[8]Häberle J, Pauli S, Schmidt E, Schulze-Eilfing B, Berning C, Koch HG. Mild citrullinaemia in Caucasians is an allelic variant of argininosuccinate synthetase deficiency (citrullinaemia type 1). *Mol Genet Metab*. 2003; 80: 302- 306.

[9]Kurokawa K, Yorifuji T, Kawai M, et al. Molecular and clinical analyses of Japanese patients with carbamoylphosphate synthetase 1 (CPS1) deficiency. *J Hum Genet*. 2007; 52: 349- 354.

[10]Enns GM. Neurologic damage and neurocognitive dysfunction in urea cycle disorder. *Semin Pediatr Neurol*. 2008; 15: 132- 139.

[11]McCullough BA, Yudkoff M, Batshaw ML, Wilson JM, Raper SE, Tuchman M. Genotype spectrum of ornithine transcarbamylase deficiency: correlation with the clinical and biochemical phenotype. *Am J Med Genet*. 2000; 93(4): 313- 319.

[12]Plochl W, Plochl E, Pokorny H, et al. Multiorgan donation from a donor with unrecognized ornithine transcarbamylase deficiency. *Transpl Int*. 2001; 14: 196- 201.

[13]Enns GM, Berry SA, Berry GT, Rhead WJ, Brusilow SW, Hamosh A. Survival after treatment with phenylacetate and benzoate for urea-cycle disorders. *N Engl J Med*. 2007; 356: 2282- 2292.

[14]Summar ML, Barr F, Dawling S, et al. Unmasked adult-onset urea cycle disorders in the critical care setting. *Crit Care Clin*. 2005; 21: S1- S8.

[15] AWMF (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V., AWMF) online. Revision UCD Guideline (2018). https://www.awmf.org/uploads/tx_szleitlinien/027-006l_S3_Diagnostik-Therapie-Harnstoffzyklusstoerungen_2018-06.pdf. Date January 1, 2019.

[16]Alameri M, Shakra M, Alsaadi T. Fatal coma in a young adult due to late-onset urea cycle deficiency presenting with a prolonged seizure: a case report. *Austin J Clin Neurol*. 2015; 2(8): 1- 3.

[17]Bigot A, Brunault P, Lavigne C, et al. Psychiatric adult-onset of urea cycle disorders: a case-series. *Mol Genet Metab Rep*. 2017; 12: 103- 109.

[18]Häberle J, Boddaert N, Burlina A, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders. *Orphanet J Rare Dis*. 2012; 7: 32.

[19]Sloas HA 3rd, Ence TC, Mendez DR, Cruz AT. At the intersection of toxicology, psychiatry and genetics: a diagnosis of ornithine transcarbamylase deficiency. *Am J Emerg Med*. 2013; 31: 1420e5- 1420e6.

[20]Ben-Ari Z, Dalal A, Morry A, et al. Adult onset ornithine transcarbamylase (OTC) deficiency unmasked by the Atkins diet. *J Hepatol*. 2010; 52: 292- 295.

[21]Daijo K, Kawaoka T, Nakahara T, et al. Late-onset ornithine transcabamylase deficiency associated with hyperammonaemia. *Clin J Gastroenterol*. 2017; 10(4): 383- 387.

[22]Lee CH, Ellaway C, Shun A, et al. Split-graft liver transplantation from an adult donor with an unrecognized UCD to a pediatric and adult recipient. *Pediatr Transplant*. 2017; 22: e13073.

[23]Ramanathan M, Uppalapu S, Patel NM. Hiding in plain sight: a case of ornithine transcarbamylase deficiency unmasked post-liver transplantation. *Am J Transplant*. 2017; 17: 1405- 1408.

[24]Weiss N, Mochel F, Rudler M, et al. Peak hyperammonaemia and atypical acute liver failure: the eruption of an urea cycle disorder during hyperemesis gravidarum. *J Hepatol*. 2018; 68: 185- 192.

[25]Wells DL, Thomas JB, Sacks GS, Zouhary LA. Late-onset urea cycle disorder in adulthood unmasked by severe malnutrition. *Nutrition*. 2014; 30: 943- 947.

[26]Häberle J, Vilaseca MA, Meli C, et al. First manifestation of citrullinaemia type I as differential diagnosis to postpartum psychosis in the puerperal period. *Eur J Obstet Gynecol Reprod Biol*. 2010; 149: 228- 229.

[27]Reid L, Perreault E, Lafrance G, Clarke JT. Experience with the treatment of argininosuccinic aciduria during pregnancy. *J Inherit Metab Dis*. 2009; 32(Suppl 1): S191- S195.

[28]Salek J, Byrne J, Box T, Longo N, Sussman N. Recurrent liver failure in a 25-year-old female. *Liver Transpl*. 2010; 16(9): 1049- 1053.

[29]Van de Logt AE, Kluijtmans LAJ, Huiden MACDG, Hanssen MCH. Hyperammonaemia due to adult-onset *N* -acetylglutamate synthase deficiency. *JIMD Rep*. 2017; 31: 95- 99.

[30]Bonnot O, Herrera PM, Tordjman S, Walterfang M. Secondary psychosis induced by metabolic disorders. *Front Neurosci*. 2015; 9: 177.

[31]Demily C, Sedel F. Psychiatric manifestations of treatable hereditary metabolic disorders in adults. *Ann Gen Psychiatry*. 2014; 13: 27.

[32]Walterfang M, Bonnot O, Mocellin R, Velakoulis D. The neuropsychiatry of inborn errors of metabolism. *J Inherit Metab Dis*. 2013; 36: 687- 702.

[33]Sedel F, Baumann N, Turpin JC, Lyon-Caen O, Saudubray JM, Cohen D. Psychiatric manifestations revealing inborn errors of metabolism in adolescents and adults. *J Inherit Metab Dis*. 2007; 30: 631- 641.

[34]Yamamoto N, Tsutsui K, Yamamoto M, Arakaki H, Kurumaji A, Nishikawa T. Sliding doors (but not with beans or tofu). *Lancet*. 2008; 372: 1782.

[35]Gropman AL, Batshaw ML. Cognitive outcome in urea cycle disorders. *Mol Genet Metab*. 2004; 81(Suppl 1): S58- S62.

[36]Limketkai BN, Zucker SD. Hyperammonaemic encephalopathy caused by carnitine deficiency. *J Gen Intern Med*. 2007; 23: 210- 213.

[37]Sakusic A, Sabov M, McCambridge AJ. Features of adult hyperammonaemia not due to liver failure in the ICU. *Crit Care Med*. 2018; 46(9): e897- e903.

[38]Gropman AL, Summar M, Leonard JV. Neurological implications of urea cycle disorders. *J Inherit Metab Dis*. 2007; 30: 865- 879.

[39]Grünewald S, Fairbanks L, Genet S, et al. How reliable is the allopurinol load in detecting carriers for ornithine transcarbamylase deficiency? *J Inherit Metab Dis*. 2004; 27: 179- 186.

[40]Yamaguchi S, Brailey LL, Morizono H, Bale AE, Tuchman M. Mutations and polymorphisms in the human ornithine transcarbamylase (OTC) gene. *Hum Mutat*. 2006; 27(7): 626- 632.

[41]Gropman A. Brain imaging in urea cycle disorders. *Mol Genet Metab*. 2010; 100(Suppl 1): S20- S30.

[42]Gropman AL, Gertz B, Shattuck K, et al. Diffusion tensor imaging detects areas of abnormal white matter microstructure in patients with partial ornithine transcarbamylase deficiency. *Am J Neuroradiol*. 2010; 31: 1719- 1723.

[43]Gropman AL, Prust M, Breeden A, Fricke S, VanMeter J. Urea cycle defects and hyperammonemia: effects on functional imaging. *Metab Brain Dis*. 2013; 28: 269- 275.

[44]Gropman AL, Seltzer RR, Yudkoff M, et al. 1H MRS allows brain phenotype differentiation in sister with late onset ornithine transcarbamylase deficiency (OTCD) and discordant clinical presentations. *Mol Genet Metab*. 2008; 94: 52- 60.

[45]Scaglia F, Carter S, O'Brien WE, Lee B. Effect of alternative pathway therapy on branched chain amino acid metabolism in urea cycle disorder patients. *Mol Genet Metab*. 2004; 81(Suppl 1): S79- S85.

[46]Bates TR, Lewis BD, Burnett JR, et al. Late-onset carbamoyl phosphate synthetase 1 deficiency in an adult cured by liver transplantation. *Liver Transpl*. 2011; 17: 1481- 1484.

[47]Lichter-Konecki U, Caldovic L, Morizono H, Simpson K. Ornithine transcarbamylase deficiency. In: RA Paragon, MP Adam, HH Ardinger, et al., eds. GeneReviews. Seattle, WA: University of Washington, Seattle; 2013: 1993- 2015.

[48]Nassogne MC, Heron B, Touati G, Rabier D, Saudubray JM. Urea cycle defects: management and outcome. *J Inherit Metab Dis*. 2005; 28: 407- 414.

[49]Mahmood T, Nugent K. Nonhepatic hyperammonaemic encephalopathy due to undiagnosed urea cycle disorder. *Proc (Bayl Univ Med Cent)*. 2015; 28(3): 375- 377.

[50]Waisbren S, Gropman A, Members of the UCDCM, Batshaw ML. Improving long term outcomes in urea cycle disorders—report from the urea cycle disorders consortium. *J Inherit Metab Dis*. 2016; 39(4): 573- 584.

[51]Häberle J, Koch HG. Genetic approach to prenatal diagnosis in urea cycle defects. *Prenat Diagn*. 2004; 24: 378- 383.

[52]Krivitzky L, Babikian T, Lee HS, Thomas NH, Burk-Paull KL, Batshaw ML. Intellectual, adaptive, and behavioral functioning in children with urea cycle disorders. *Pediatr Res*. 2009; 66: 96- 101.

[53]Rüegger CM, Lindner M, Ballhausen D, et al. Cross-sectional observational study of 208 patients with non-classical urea cycle disorders. *J Inherit Metab Dis*. 2014; 37: 21- 30.

[54]Feillet F, MacDonald A, Hartung Perron D, Burton B. Outcomes beyond phenylalanine: an international perspective. *Mol Genet Metab*. 2010; 99(Suppl 1): S79- S85.

[55]Sinclair M, Ket S, Testro A, Gow PJ, Angus PW. Acute hepatic decompensation precipitated by pregnancy-related catabolic stress: a rare mimic of acute liver failure. *Obstet Gynecol*. 2014; 123(2 Pt 2 Suppl 2): 480- 483.

[56]Laemmle A, Gallagher RC, Keogh A, et al. Frequency and pathophysiology of acute liver failure in ornithine Transcarbamylase deficiency (OTCD). *PLoS One*. 2016; 11(4): e0153358.

[57]London V, Grube S, Sherer DM, Abulafia O. Hyperemesis gravidarum: a review of recent literature. *Pharmacology*. 2017; 100(3–4): 161- 171.

[58]Bailly P, Noury JB, Timsit S, Ben SD. Teaching NeuroImages: ornithine transcarbamylase deficiency revealed by a coma in a pregnant woman. *Neurology*. 2015; 85(20): e146- e147.

[59]Crosbie DC, Sugumar H, Simpson MA, Walker SP, Dewey HM, Reade MC. Late-onset ornithine transcarbamylase deficiency: a potentially fatal yet treatable cause of coma. *Crit Care Resusc*. 2009; 11(3): 222- 227.

[60]Eather G, Coman D, Lander C, McGill J. Carbamyl phosphate synthase deficiency: diagnosed during pregnancy in a 41-yearold. *J Clin Neurosci*. 2006; 13(6): 702- 706.

[61]Frassier T, Guffon N, Acquaviva C, D'Amato T, Durand DV, Domenech P. Misdiagnosed postpartum psychosis revealing a late-onset urea cycle disorder. *Am J Psychiatry*. 2011; 168: 576- 580.

[62]Brusilow SW, Horwich AL. Urea cycle enzymes. In: CR Scriver, D Beaudet, D Valle, WS Sly, eds. The Metabolic & Molecular Bases of Inherited Disease. 8th ed. New York, NY: McGraw-Hill; 2001: 1909- 1961.

[63]Batshaw ML, MacArthur RB, Tuchman M. Alternative pathway therapy for urea cycle disorders: twenty years later. *J Pediatr*. 2001; 138: S46- S54.

[64]Leonard JV, Ward Platt MP, Morris AA. Hypothesis: proposals for the management of a neonate at risk of hyperammonaemia due to a urea cycle disorder. *Eur J Pediatr*. 2008; 167: 305- 309.

[65]Meyburg J, Hoffman GF. Liver, liver cell and stem cell transplantation for the treatment of urea cycle defects. *Mol Genet Metab*. 2010; 100(Suppl 1): S77- S83.

[66]Chadefaux-Vekemans B, Rabier D, Chabli A, et al. Improving the prenatal diagnosis of citrullinemia using citrulline/ornithine+arginine ratio in amniotic fluid. *Prenat Diagn*. 2002; 22: 456- 458.

[67]Mokhtarani M, Diaz GA, Rhead W, et al. Elevated phenylacetic acid levels do not correlate with adverse events in patients with urea cycle disorders or hepatic encephalopathy and can be predicted based on the plasma PA to PAGN ratio. *Mol Genet Metab*. 2013; 110(4): 446- 453.

[68]Häberle J, McCandless SE. Orphan drugs in development for urea cycle disorders: current perspectives. *Orphan Drugs: Res Rev*. 2014; 4: 63- 70.

[69]Viecelli HM, Thöny B. Challenges of experimental gene therapy for urea cycle disorders. *J Pediatr Biochem*. 2014; 4: 65- 73.

[70]Lee AL, Sinha S, Fitzpatrick E, Dhawan A. Hepatocyte transplantation and advancements in alternative cell sources for liver-based regenerative medicine. *J Mol Med*. 2018; 96: 469- 481.

[71]Sokal EM. Treating inborn errors of liver metabolism with stem cells: current clinical development. *J Inherit Metab Dis*. 2014; 37(4): 535- 539.