

Urea cycle disorders: clinical experiences compared. A series of cases from 14 Italian Centers

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INTRODUCTION

Protein and amino acids homeostasis depends on complex anabolic and catabolic-oxidative processes. In adults, the estimated daily protein turnover is 250-400 g, largely exceeding dietary protein intake (50-80 g/day).¹ The urea cycle is a fundamental metabolic pathway for detoxification of ammonia derived from protein catabolism. Localized exclusively in the liver, it is characterized by a series of successive mitochondrial and cytosolic reactions that lead to the production of urea (**Fig. 1**).¹

Within the complex context of inherited metabolic diseases, defects in the urea cycle represent an important cause of mortality and morbidity, with highly specialized clinical-diagnostic and therapeutic implications. In particular, patients affected by severe mitochondrial (and in some cases cytosolic) defects in the urea cycle present neonatal hyperammonemic coma, representing an absolute neonatal metabolic emergency.

Each enzymatic step of the urea cycle and each cytosolic-mitochondrial transporter can be the site of an inherited defect in the urea cycle. These inherited defects generally

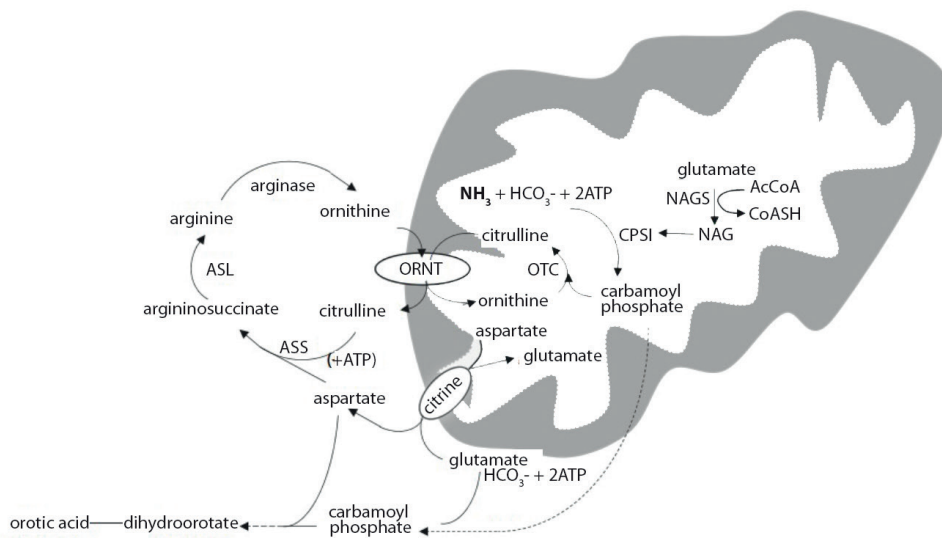


Fig. 1. The urea cycle. The reactions indicated allow detoxification of ammonia through the production of urea which is excreted in urine (graphic elaboration from¹). ASL: argininosuccinate lyase; ASS: argininosuccinate synthase; CPS1: carbamoylphosphate synthase; NAGS: N-acetylglutamate synthase; ORNT: mitochondrial ornithine transporter; OTC: ornithine transcarbamylase.

place affected patients at high risk of developing potentially fatal hyperammonemic crises, especially during catabolic episodes (e.g. physiological neonatal catabolism, febrile illnesses, peri-partum period) or in cases of excessive exogenous protein intake.² Urea cycle defects (UCDs) are pan-ethnic with an overall incidence, including late-onset forms, of approximately 1 in 35,000, although this may vary among different populations.² The most common deficiency is ornithine transcarbamylase deficiency (OTCD) (incidence 1 in 56,500), while the least common is arginase 1 deficiency (ARG1-D) (approximately between 1:350,000 and 1:1,000,000). With the exception of OTCD which is linked to the X chromosome, all UCDs are autosomal recessive.³ Moreover, some metabolic disorders can lead to secondary impairment of the urea cycle, including ornithine aminotransferase deficiency, pyrroline-5-carboxylate reductase deficiency, lysinuric protein intolerance, carbonic anhydrase deficiency and classical organic acidurias. **Table 1** reports typical examples of amino acid profiles in UCDs.¹

European guidelines for the diagnosis and management of UCDs represent a valid tool for the management of these complex conditions.⁴

In addition to hyperammonemic coma, some UCDs can

present specific clinical signs or symptoms. For example, both arginemia and HHH syndrome can present with spastic paraparesis as a peculiar sign. Moreover, UCDs can also manifest chronically, with gastroenterological symptoms (vomiting, hypertransaminasemia), neurological, or psychotic symptoms.¹

The mechanism of hyperammonemic neuropathology is only partially understood. Ammonia, glutamate, and glutamine are implicated differently in neurotoxic pathogenesis. Glutamate is a major excitatory neurotransmitter and its prolonged accumulation may be responsible for neuronal degeneration in a variety of neurological disorders. Both hyperammonemia and the resulting excess of glutamine cause cellular and cerebral edema and increased permeability of the blood-brain barrier with consequent alterations in the homeostasis of neurotransmitters and neuronal amino acids.³

The mechanisms involved in hepatic encephalopathy remain to be defined, although it is widely recognized that ammonia is an important factor in its pathogenesis and that astrocytes represent a major target of its CNS toxicity. *In vivo* and *in vitro* studies have shown that ammonia induces oxidative/nitrosative stress, mitochondrial abnormalities (mitochondrial permeability transition, MPT), and

Table 1. Summary of UCDs main clinical, biochemical, and molecular characteristics (graphical elaboration from¹). ARG1-D, arginase 1 deficiency; ASLD, argininosuccinic acid lyase deficiency; ASSD, argininosuccinic acid synthase deficiency; CPS1D, carbamoylphosphate synthase deficiency; NAGSD, N-acetylglutamate synthase deficiency; OTCD, ornithine transcarbamylase deficiency.

Disease	Clinical feature	Specific change of aminoacids		Urinary orotic acid	Inheritance	Gene symbol	Gene locus
		Plasma	Urine				
CPS1D	Hyperammonemia	Citrulline ↓		–	AR	<i>CPS1</i>	2q34
OTCD	Hyperammonemia	Citrulline ↓		2+	X-linked	<i>OTC</i>	Xp21.1
ASSD	Hyperammonemia	Citrulline ↑	Citrulline ↑	2+	AR	<i>ASS1</i>	9q34.11
ASLD	Hyperammonemia	Argininosuccinic acid ↑	Argininosuccinic acid ↑	+	AR	<i>ASL</i>	7q11.21
	Hepatomegaly	Citrulline ↑					
	Hair abnormality						
ARG1-D	Hyperammonemia	Arginine ↑↑	Arginine ↑	2+	AR	<i>ARG1</i>	6q23.2
	Retardation			±			
	Spastic paraplegia						
NAGSD	Hyperammonemia			–	AR	<i>NAGS</i>	17q21.31
Ornithine aminotransferase deficiency	Gyrate atrophy of choroid and retina, hyperammonemia	Ornithine ↑		+ ~±	AR	<i>OAT</i>	10q26
Citrin deficiency	Liver dysfunction	Citrulline ↑		±	AR	<i>SLC25A13</i>	7q21.3
	Neonatal cholestasis						
	Hyperammonemia						
HHH syndrome (ornithine transporter)	Hyperammonemia	Ornithine ↑	Homocitrulline ↑	+	AR	<i>ORNT1</i>	13q14.1
Lysinuric protein intolerance (basolateral membrane)	Hyperammonemia		Lysine ↑↑	+ ~±	AR	<i>SLC7A7</i>	14q11.2
	Hepatosplenomegaly		Ornithine ↑				
	Osteoporosis		Arginine ↑				
	Pneumopathy						

swelling of astrocytes, which is a major component of cerebral edema associated with fulminant liver failure.⁵

Ammonia-induced oxidative stress appears to trigger a cascade of events that result in the induction of MPT (an additional source of free radicals) as well as the activation of intracellular signaling kinases. This cascade of events culminates in the inability of the astrocyte to adequately regulate its intracellular volume, leading to cellular swelling, presumably by affecting the integrity of mitochondria, plasma membrane, and/or ion channels and transporters within the plasma membrane.⁶

How ammonia causes these changes in astrocytes is not well

understood. It has long been accepted that the conversion of glutamate to glutamine, catalyzed by glutamine synthase, a cytoplasmic enzyme widely present in astrocytes in the brain, is a major means of ammonia detoxification. However, the “benign” aspect of glutamine synthesis has been questioned. At high levels, glutamine is indeed a noxious agent. One proposed mechanism by which glutamine exerts its toxic effects in astrocytes is the “Trojan horse” hypothesis (**Fig. 2**). Much of the newly synthesized glutamine is subsequently metabolized in the mitochondria by phosphate-activated glutaminase to produce glutamate and ammonia. In this way, glutamine (the Trojan horse) is transported in excess

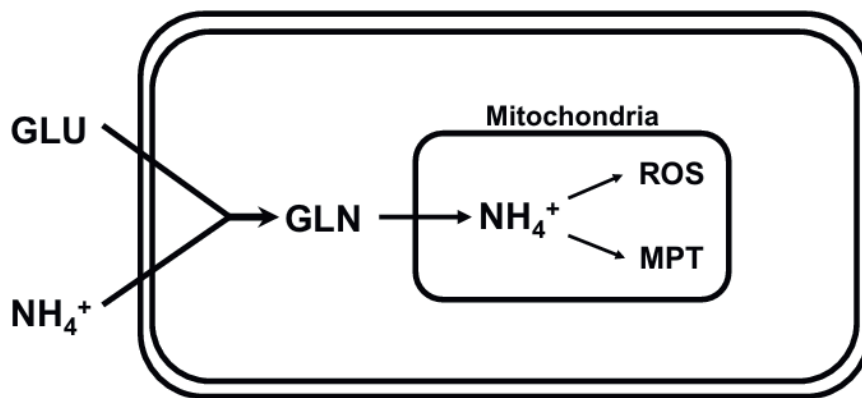


Fig. 2. The “Trojan horse” hypothesis. Ammonia is conjugated with glutamate (GLU) to form glutamine (GLN) within the smooth endoplasmic reticulum via the action of glutamine synthetase. Glutamine then enters the mitochondria where it is hydrolyzed by phosphate-activated glutamine to produce ammonia. This means that most of the ammonia entering the astrocyte will be concentrated in the mitochondria resulting in the generation of reactive oxygen species (ROS) and the phenomenon of mitochondrial permeability transition (MPT) (graphic elaboration from⁵).

from the cytoplasm to the mitochondria, acting as a transporter of ammonia. It has been hypothesized that the ammonia derived from glutamine within the mitochondria interferes with mitochondrial function, giving rise to excessive production of reactive oxygen species (ROS) and the induction of MPT; both these phenomena are known to cause dysfunction of astrocytes, including cell swelling.⁵

Clinically, any encephalopathy should raise suspicion of UCDs, making measurement of ammonia in blood mandatory.⁴

Normal ammonia levels according to the Association of Biochemical Chemistry are:¹

- Premature neonates, <150 μmol/L (255 μg/dL)
- Full-term newborns, <100 μmol/L (170 μg/dL)
- Infants and children, <40 μmol/L (68 μg/dL)
- Adolescents and adults, 11-32 μmol/L (19-54 μg/dL).

The levels of ammonia are measured in μg/dL (conventional unit) and μmol/L (SI unit): μg/dL × 0.587 = μmol/L.⁷

In parallel, evaluation of the amino acid profile and orotic acid excretion are essential for the etiological clinical definition of the defect (subsequently confirmed at molecular level).

Obviously, emergency management of patients in acute decompensation is immediate and often occurs before the

complete results of biochemical and molecular tests are available.⁸ From a therapeutic emergency point of view, hemodialysis represents the treatment of choice for hyperammonemia.⁹ Metabolic medical management must be performed in parallel to concur to rapid reduction in ammonia levels. In addition to the suspension of protein intake and interruption of catabolism through high-dose infusion of glucose, the use of intravenous [sodium phenylacetate (NaPa)] or [sodium benzoate (NaBz) and/or sodium phenylbutyrate (NaPBA)] ammonia scavengers and L-arginine hydrochloride are also indicated. Oral carnitine, is also indicated to ensure the activity of carbamoylphosphate synthase (CPS1) and is fully effective in the case of N-acetylglutamate synthase (NAGS) deficiency.

In chronic management, low protein diet, prevention of a catabolic states, specific amino acids supplementations, and oral nitrogen scavengers are the cornerstones for reducing the risk of acute metabolic decompensations and chronic UCD manifestations. This management is essential throughout life, unless liver transplantation is performed.¹

Since both European⁴ and US¹⁰ recommendations are based mainly on the opinions of experts, a constant discussion among healthcare professionals is of fundamental importance to evaluate current practice and therapeutic perspectives in real-world settings.

In this view, this article aims to provide a summary of two recent meetings involving Italian experts in UCDs practicing at 14 Centers for the treatment of inherited metabolic diseases. Real clinical cases are presented, divided into different topics of discussion, with the aim of drafting a consensus document to support clinical practice of both first and second level. This project represents a preliminary step for the development of more advanced recommendations for the long-term management of UCDs.

METHODS

In June 2024, two meetings were held in Milan and Rome, called *UCD Experience Exchange Day* which involved the participation of 16 pediatricians skilled in treating inborn errors of metabolism. The panel, with additional skills in genetics, neonatology, and pediatric neurology, met with the aim of reaching consensus on the importance of outcomes and key issues in the management of UCDs. Specific thematic areas of discussion were identified:

1. *UCD diagnosis: from neonatal screening or clinical suspicion to diagnosis*
2. *Early treatment of mild UCD patients*
3. *Management of naïve patients*
4. *Therapeutic switches in UCD patients*
5. *Eligibility for liver transplantation*
6. *The transition from pediatric to adult care*

For each area, real clinical cases were presented to outline the clinical decision-making process at different Centers. Summary of the clinical cases are described below.

CASE REPORTS

1. UCD DIAGNOSIS: FROM NEONATAL SCREENING OR CLINICAL SUSPICION TO DIAGNOSIS

Case 1

In 1998, a girl of 8.5 years of age was referred to the Emergency Department in a “state of somnolence”. The parents reported frequent vomiting in previous months and poor reactivity

in the last days. Symptomatic antiemetic therapy was administered (metoclopramide and domperidone). At physical examination, the child appeared pale, asthenic, somnolent, and uncooperative, with confused speech. Vital signs were normal. Ataxic gait was observed and Mingazzini 1 and finger-nose tests were positive. Lumbar puncture was negative. Despite treatment based on the initial suspicion of encephalitis, further deterioration of the clinical condition was observed with the need of orotracheal intubation. Worsening hyperammonemia was then revealed (from 260 to 456 $\mu\text{mol/L}$) until intervention of the metabolic team.

Protein-free nutrition and pharmacological therapy with sodium benzoate (NaBz) (250 mg/kg bolus then 24 hours) and arginine hydrochloride (250 mg/kg bolus then every 24 hours) were administered. Subsequent biochemical findings oriented the diagnosis towards OTCD: urinary orotic acid was 378 $\mu\text{mol/L}$ (n.v. 0.05-3.54 $\mu\text{mol/L}$) and glutamine 860 $\mu\text{mol/L}$ (n.v. 457-662 $\mu\text{mol/L}$). Anamnestic data revealed pre-existing food selectivity with repeated refusal of foods with a high protein content. Upon discharge, treatment with sodium phenylbutyrate (NaPBA), citrulline and arginine was established. At present, the patient has almost completed the transition to adult care after the switch from NaPBA to glycerol phenylbutyrate (GPB), given its commercial availability from late 2018, progressively increasing the dose as indicated (10 mL/m²/day for a BSA > 1.3 m²).

Case 2

This patient, the first child of non-consanguineous parents, was born at term from uneventful pregnancy (birth weight 3840 g, Apgar score 9/10). During the first day of life, the mother noticed weak sucking of breastmilk, with subsequent episodes of vomiting and tremors. Routine tests were negative for infections but hyperammonemia was present (310 $\mu\text{mol/L}$). The baby was promptly transferred to the neonatal Intensive Care Unit (ICU) in a deteriorated clinical condition with respiratory distress, reduced left ventricular function, and tonic-clonic seizures. At this point, raised hyperammonemia (664 $\mu\text{mol/L}$) was accompanied by hyperlactacidemia (9.27 mmol/L) and slight metabolic acidosis.

Protein intake was immediately stopped, parenteral glucose, lipids and NaBz (250 mg/kg/day) were initiated beside hemodiafiltration. As a definitive diagnosis was not yet available, intravenous (iv) arginine (250 mg/kg/day), carnitine (100 mg/kg), hydroxocobalamin (1 mg), and oral biotin (10 mg) and N-carbamylglutamate (100 mg/kg/day) were administered. The patient also received resuscitation support. Specific metabolic tests documented increased glutamine (1.279 $\mu\text{mol/L}$, n.v. 335-727) with concomitant reduction of citrulline (3 $\mu\text{mol/L}$, n.v. 6-33) and normal orotic acid, consistent with carbamoylphosphate synthase deficiency (CPS1D) or N-acetylglutamate synthase deficiency (NAGSD). Molecular analysis confirmed CPS1 deficiency. In consideration of the reduction of ammonia, hemodiafiltration was interrupted after 24 hours, and iv therapy with NaBz

(250 mg/kg/day) in association with arginine (250 mg/kg/day) and NaPBA (250 mg/kg/day) were administered. From the fourth day, parenteral protein intake was reintroduced, switching to nasogastric tube nutrition on the seventh day. Therapy was changed on the tenth day to oral GPB (with change of therapy as indicated in the Summary of Product Characteristics for patients already treated with NaPBA) and citrulline (200 mg/kg/day).

By this management, the patient achieved satisfactory metabolic control. At the age of 23 months the child had no acute metabolic decompensations, showing normal ammonia (47-72 $\mu\text{mol/L}$) and glutamine (341-765 $\mu\text{mol/L}$) levels. A slight delay in psychomotor development remained and brain MRI was compatible with neonatal hyperammonemia. Liver transplant has been scheduled at the achievement of 10 kg of body weight.

Evidence	Real-life
<ul style="list-style-type: none"> • For Whom: Ammonia levels should be immediately assessed in any acutely-ill neonate, child, adolescent, and adult with unexplained neurological symptoms. • When: Neonatal hyperammonemia resembles sepsis (“sepsis-like” presentation), with temperature instability, respiratory distress, and hyperventilation. • Why: In patients with UCD, brain damage correlates with the duration and severity of acute hyperammonemia,¹¹⁻¹³ especially in younger patients probably due to an increased susceptibility of the brain to the deleterious effects of ammonia.¹⁴ To improve survival rate and quality of life, patients with UCD should be treated as early as possible (hemofiltration).¹⁵ 	<ul style="list-style-type: none"> • In case of positive neonatal screening (citrullinemia, argininosuccinic aciduria), the newborn is referred in emergency to the nearest specialized clinical Center for the treatment of metabolic diseases. • In the acute phase, besides measurement of ammonia, plasma amino acids, organic acids, and orotic acid can confirm the biochemical diagnosis and address adequate treatment. • Blood gas analysis and levels and urinary organic acids are useful for differential diagnosis (organic acidemias). • The emergency protocol in patients with acute hyperammonemia should include: stop of protein intake, inhibition of catabolism (iv glucose), iv scavengers (bolus + continuous), iv arginine (bolus + continuous), oral carglumic acid (100 mg/kg/day), iv vitamin B12 (methylmalonic acid test - MMA), oral biotin (PA), im thiamine (maple syrup urine disease - MSUD), and iv carnitine.

2. EARLY TREATMENT OF PATIENTS WITH MILD UCD

Case 3

This newborn (female) was recalled for abnormal newborn screening for increased citrulline (31.96 $\mu\text{mol/L}$) (cut off: <28.1 μM) and argininosuccinic acid (2.47 μM) (cut off: <1 μM). In the suspect of argininosuccinic aciduria,

the newborn was admitted to the neonatal ICU where therapy was started with low-protein diet, iv glucose, and arginine. Metabolic tests (at 5 days of life) showed slight increase of glutamine (897 $\mu\text{mol/L}$) and citrulline (36 $\mu\text{mol/L}$) and reduced arginine (36 $\mu\text{mol/L}$), and presence of argininosuccinic acid, confirming the biochemical suspect of argininosuccinic aciduria (ASA). Ammonia was normal. Molecular analysis of the *ASL* gene identified

two variants (one pathogenetic and one of uncertain significance).

At longitudinal follow-up, the child showed normal psychomotor development. The child is currently attending elementary school with excellent results, following a specific diet (protein 1.1 g/kg/day), and integration with oral arginine. Normal metabolic control (ammonia and glutamine), normal brain by MRI and an IQ of 120 characterize the picture. Further protein restriction was recommended in case of intercurrent febrile illnesses in addition to immediate access to the Emergency Department.

Case 4

This girl was born to first-degree cousins with a family history of Brugada Syndrome. At Extended Neonatal Screening, the level of argininosuccinic acid was 1.3 μmol (cut-off: $<0.5 \mu\text{mol}$) along with citrulline 58 $\mu\text{mol/L}$, compatible with the suspect of argininosuccinic acidemia. Upon arrival in the neonatal ICU on the 5th day of life, slightly increased ammonia was detected while on breastfeeding (120 $\mu\text{mol/L}$). At physical examination, she appeared moderately hypotonic but reactive. Dietary

protein intake was suspended and glucosaline solution and iv arginine hydrochloride administered, with rapid normalization of ammonia. Brain ultrasound was normal. Metabolic tests showed slightly increased glutamine levels (969 $\mu\text{mol/L}$) and molecular testing confirmed the biochemical suspicion of argininosuccinic acidemia (homozygous pathogenic variants). Parents were found to be carriers of the detected variants; the mother also harbored a mutation in the *ASS1* gene.

Breastfeeding was continued and oral arginine was administered and close clinical and biochemical follow-up was maintained. At the age of 2 months, axial hypotonia emerged (prevalent of the upper limb girdle) with a tendency to deviate the head to the left. Given the neurological involvement, scavenging therapy with GPB was started with rapid normalization of glutamine and acquisition of normal stages (sitting at 6.5 months independently). At 11 months, the child has normal development (autonomous crawling, good manipulation, walking with manual support, and bisyllabic speech), growth (8.9 kg). After therapy, ammonia and glutamine were normal, as well as follow-up brain MRI.

Evidence	Real-life
<ul style="list-style-type: none"> • For Whom: Patients diagnosed with mild UCD deficiency. Symptomatic patients with suspected UCD should be identified by measuring ammonia (and related metabolites) and treated immediately. Early interventions include suspension of protein intake, 10% glucose (with electrolytes) iv, ammonium scavengers and L-arginine iv; collection of samples for plasma amino acids and urinary orotic acid is essential but should not delay initiation of treatment.⁸ • Mild and very mild forms of type I citrullinemia can be distinguished by serum citrulline levels.⁸ However, caution should be exercised in classifying mild forms, that may be insidious in their course, as the so-called late-onset forms. The two terms do not necessarily coincide. • When and Why: Current guidelines state that early diagnosis and treatment of mild UCD can improve survival and prevent metabolic decompensations and neurocognitive deterioration.⁸ 	<ul style="list-style-type: none"> • Careful evaluation of biochemical parameters and close clinical monitoring. • Avoid under- and over-treatment. • Maintenance of breastfeeding according to the clinical and metabolic evaluations and consider the use of scavengers. • The likely severity of the metabolic phenotype (i.e. the severity of the enzyme defect) is estimable through family history, biochemical parameters, and genotype. These presumptive assessments can clinical management and eventual treatment in the pre-symptomatic period. • Close neurocognitive evaluation is necessary.

3. MANAGEMENT OF THE NAÏVE PATIENT

Case 5

Born from uneventful pregnancy (birth weight 3480 g), this male newborn presented recurrent hypoglycemic crises and poor reactivity. In the neonatal ICU, the finding of high levels of insulin suggesting hyperinsulinism addressed the start of treatment with oral diazoxide. While collecting family history, it emerged that the mother had gestational diabetes. Despite correction of hypoglycemia, feeding difficulties persisted with a tendency to hypotonia and episodic vomit. Hyperammonemia (290 $\mu\text{mol/L}$) was detected at 9 days of life, in the absence of metabolic acidosis. Treatment

with NaBz, arginine, carnitine, and vitamin B12 was followed by ammonia normalization within 24 hours.

At 30 days of life, the patient was switched to oral GPB with improved metabolic control (significant reduction of plasma glutamine from 2283 $\mu\text{mol/L}$ to 202 $\mu\text{mol/L}$). Ureagenesis functional test showed 54.9% activity (n.v. 79-121). Genetic analysis revealed a pathogenic variant in the *OTC* gene (c.594C>A, p. Asn198Lys). In addition, a heterozygous in the *HNF4A* gene (associated with hyperinsulinism) variant was concomitant and also present in the mother.

Subsequently, additional episodes of drowsiness with high ammonia levels occurred, with the need of detoxification therapy. Alternative treatment options are currently being considered, including liver transplantation or gene therapy.

Evidence	Real-life
<ul style="list-style-type: none"> • Ammonia levels must be assessed early in all pathological newborns, as early intervention is essential to avoid irreversible neurological damage. • Newborns with hyperammonemia present similarly to those affected by sepsis with a “sepsis-like” picture. • Always keep in mind the possibility of coexistence of different genetic variants involving different metabolic pathways. • Extended Neonatal Screening in Italy does not include proximal UCDs, so that clinical suspicion remains crucial. 	<ul style="list-style-type: none"> • Neonatal Intensive Care Units should be aware of the potential need of early treatment with detoxifying drugs to reduce ammonia levels in UCDs. • Besides ammonia levels, other metabolic tests (plasma amino acids, organic acids, orotic acid, and acylcarnitines) are useful to address the diagnosis. • Molecular testing can include extended panels that could also identify additional genetic disorders. • Clinical management is in accordance with the specialists of the Reference Centers for Inherited Metabolic Diseases.

Case 6

Extended newborn screening revealed increased citrulline [387 $\mu\text{mol/L}$ (n.v. 7.2-25.9 $\mu\text{mol/L}$)] with normal argininosuccinic acid [0.43 $\mu\text{mol/L}$ (n.v. <0.65 $\mu\text{mol/L}$)] and arginine (19 $\mu\text{mol/L}$ (n.v. 8-37 $\mu\text{mol/L}$)). Besides normal clinical examination, hypercitrullinemia [456 $\mu\text{mol/L}$ (n.v. 10-37 $\mu\text{mol/L}$)] was confirmed with concomitant normal ammonia concentration.

Planned follow-up during the first 6 months of life confirmed the stability of the above-described parameters while on exclusive breastfeeding.

At weaning the mother reported refusal to meat-based homogenized foods.

Molecular testing was not consistent with citrullinemia. However, after high-protein meal (homogenized vegetables, parmesan cheese, and rabbit) the infant showed lethargy and vomiting accompanied by significant hyperammonemia (280 $\mu\text{mol/L}$).

Emergency treatment with iv glucose and arginine hydrochloride was immediately effective. Successive good metabolic control was achieved simply by a low-protein diet and treatment with GPB since 18 months of age. Deeper molecular testing revealed homozygous variation for a pathogenic intronic mutations confirming the biochemical suspect of citrullinemia type I.

Evidence	Real-life
<ul style="list-style-type: none"> • For Whom: Patients with UCD naïve to treatment. • When and Why: The goals of long-term management are to achieve normal development and prevent hyperammonemia, while ensuring a good quality of life and avoiding side effects and complications. Management is based on low-protein diet specific amino acid supplementations, and nitrogen scavengers. Special care and emergency treatment during intercurrent illness is needed. Liver transplantation can be an option for selected patients. An emergency regimen card should be provided to the parents/guardians (and to the child's nursery or school) including instructions on when and how to contact the metabolic team or local hospital.⁴ 	<ul style="list-style-type: none"> • In case of acute neonatal onset, metabolic emergency management is best complemented by hemodialysis (according to guidelines). • After the correction and stabilization of the acute metabolic picture, oral GPB is a valuable option even since the first month of life. • A low-protein diet supplemented with specific amino acids (citrulline and/or arginine as appropriate) and associated with GPB can allow lasting metabolic control and normal growth. • An emergency card is essential for the management of intercurrent catabolic emergencies. • Both the adolescence and transition phase are at high metabolic risk. • Liver transplant (and its most appropriate timing) can be an option in some patients with UCDs.

4. THERAPEUTIC SWITCH IN "EXPERIENCED PATIENTS"

Case 7

A female patient was diagnosed with OTCD (c.469A>C, p.Ile157Leu) in 1989. Until 1993, the patient showed recurrent episodes of hyperammonemia and he was referred in the USA.

Since in 1997, she was followed at a specialist Center in Italy. Treatment included a low-protein diet, oral L-citrulline (118 mg/kg/day), and NaBz (120 mg/kg/day). However, metabolic control was unsatisfactory, and the dose of both drugs was increased to 150 mg/kg/day. In February 2003, a switch was made from NaBz to NaPBA in tablets (500 mg) due to poor compliance with the granular formulation.

During a day-hospital visit in 2005, the patient was moderately torpid with alterations in mood. Blood tests had revealed a pathological level of ammonia 2 hours after a meal and, above all, increased glutamine (1396 µmol/L). Poor compliance with NaPBA before meals was identified as the cause, and citrulline powder (8 g/day) and NaPBA tablets (500 mg, 4 tablets 3 times a day before main meals, for a total of 6 g/day) were prescribed.

During a subsequent check-up in October 2016, a further increase in citrulline was considered (from 8 g/day to 10 g/day) maintaining the treatment with NaPBA in tablets. Starting in

2018, following transfer and the start of an independent life, the patient self-managed her diet and pharmacological therapy maintaining fair compliance with L-citrulline and NaPBA in tablets.

In July 2019, hyperammonemic decompensation occurred after a period of prolonged fasting from solids and liquids with recurrent vomiting during which the patient suspended drug therapy. This episode was likely due to excessive protein intake in preceding days.

In September 2019 a new episode of hyperammonemic decompensation occurred. Given this recurrence a switch from NaPBA to GPB [8.25 g/day (5.4 g/m²/day)] was made, which was more acceptable to the patient and allowed for adequate compliance.

At subsequent follow-up in March 2023, the patient showed unsatisfactory metabolic control (glutamine 1423 µmol/L and reduced levels of nutritional amino acids) and weight loss of 5 kg in 6 months due to reduced caloric intake. The therapy was then reassessed with an increase in the dose of GPB [9.9 g/day (6.2 g/m²/day)], low-protein diet, citrulline 12 g/day (4 g 3 times a day) and essential amino acids in micro-tablets (PE 20 g/day). After further tailoring of therapy, the patient underwent two six-month follow-ups and presented with fair clinical stability and no further episodes of metabolic decompensation.

Case 8

A 15-month-old girl was referred because of vomit and lethargy. Blood tests (not including ammonia levels) were negative. The patient was treated with intravenous hydration therapy. Persistence of symptoms addressed the repeat of metabolic tests, revealing an increase of ammonia (289 µmol/L).

The patient came to the attention of the clinicians with the sole support of glucose solution. Family history documented a twin brother in apparent good health with refusal to protein-containing foods and recurrent episodes of vomiting. Successive evaluations revealed reduced ammonia levels (141 µmol/L) but significant alteration of liver function (GOT of 2525 IU/L, a prothrombin time of 21%, and an INR of 3,6).

Therapy was initiated consisting of cessation of protein intake, iv glucose (7 mg/kg/min), iv NaBz (250 mg/kg in 2 hours), and arginine (250 mg/kg in 2 hours). This was followed by maintenance therapy (NaBz 250 mg/kg in 24 hours and arginine hydrochloride 250 mg/kg in 24 hours, both iv).

Subsequent tests showed normal ammonia (81 µmol/L), citrulline, arginine, and glutamine levels; increase in orotic acid oriented towards a diagnosis of OTCD. After initial fluctuations, ammonia levels rapidly stabilized, while

hepatic transaminases, after the peak detected during the first 24 hours, took much longer to decrease.

The child was discharged with a low-protein diet and oral NaBz (250 mg/kg in 3 administrations/day), arginine (175 mg/kg in 3 administrations/day), and citrulline (175 mg/kg in 3 administrations/day). During the first month of treatment, compensation was not satisfactory, and NaPBA in powder (175 mg/kg/day) was added to the therapy.

At follow-up at 14 months, due to the persistence of significant fluctuations in glutamine and orotic acid, the doses of medications were changed along with a reduction in dietary protein intake. In conjunction with the subsequent hospitalization due to the child's refusal to take oral therapy, and in light of the clinical situation a progressive switch to GPB was made.

After additional 10 months of follow-up, following two hospitalizations for mild hyperammonemic decompensation, recurrent orotic aciduria and borderline/high levels of glutamine, the dosage of GPB was increased with satisfactory metabolic control, elimination of hospital admissions and no adverse effects.

In the following years, the patient showed significant improvement in her metabolic profile.

Evidence	Real-life
<ul style="list-style-type: none"> • For Whom: For patients who are reluctant to take NaPBA or who are currently treated with oral NaBz (not approved in UCDs). • When: After previous treatments that do not provide optimal control of the disease. • Why: The switch from NaBz to GPB can reduce the mean levels of ammonia and glutamine without adverse reactions, resulting in a preference for GPB due to its lower volume and greater palatability, maintaining good metabolic control and facilitating clinical management.¹⁶ 	<ul style="list-style-type: none"> • A switch to GPB can be considered for: 1) patients with poor compliance with NaPBA, such as younger children who have difficulty taking the powder formulation due to volume, taste and consistency (considerable amount of product to dissolve); 2) adolescent/adult patients with poor compliance to NaPBA due to inconveniences in daily life; 3) patients who require scavenger therapy and who prefer a liquid formulation; 4) patients with severe forms of UCD who require scavenger administration at every meal and for whom a more manageable formulation may be advantageous; 5) patients who use a gastrostomy route (exclusive or not) to take drugs and food. • Consider the switch to GPB in patients who are already treated with traditional scavengers and who have unsatisfactory metabolic control, in order to obtain better metabolic control in terms of clinical and biochemical stability. • Use GPB to improve adherence given the easy administration at all ages, but especially in younger ages.

5. ELIGIBILITY FOR LIVER TRANSPLANTATION

Case 9

A full-term baby girl was subjected to prenatal screening because of family history of a brother died due to neonatal hyperammonemia due to ASL deficiency. Prenatal molecular analysis confirmed a diagnosis of ASA. The child was admitted to the neonatal ICU and an umbilical venous catheter inserted, from which a medium-flow glucose solution was infused. Breastmilk feeding was introduced following oral treatment in the first 6 hours of life with NaBz and arginine. Clinical-instrumental monitoring and blood levels of ammonium, glucose and electrolytes were always within normal limits.

Following discussion, the patient was placed on the waiting list for a liver transplant. Pre-transplant tests showed minimal patency of the foramen ovale with left-to-right

shunt on echocardiography, absence of significant cerebral morphological alterations with a normal myelination pattern on brain MRI, and a slight delay in acquisitions mainly on motor function during a neurological visit (April 2022). Pre-transplant therapy included oral arginine (1.66 g/20 mL), NaBz i (5.6 mL, 4 times a day, eq 250 mg/kg/day), iron supplementation (10 drops/day, 10 mg) and a low-protein diet.

The patient underwent successful liver transplantation in March 2023 at the age of 2.5 years. At the 3-month follow-up (June 2023), the child started a free diet remaining on therapy with tacrolimus (3 mg in the morning and 3 mg in the evening, which was subsequently reduced), mycophenolate mofetil (100 mg, 0.5 mL 2 times a day, corresponding to 10 mg/kg 2 times a day), acetylsalicylic acid (50 mg once a day), esomeprazole (10 mg once a day), iron supplementation (15 drops 2 times a day, 7.5 mg iron), folic acid 7.5 mg (½ tablet 3 times a week), bicarbonates (5 mmEq 4 times a day), magnesium pidolate (1 sachet per day), and allopurinol (10 mg/day).

Evidence	Real-life
<ul style="list-style-type: none"> • For Whom: Liver transplantation might be considered in patients with severe UCDs. • When: Transplantation can be postponed until 3 months of age and/or 5 kg of body weight to minimize complications and increase survival. It should be performed before 1 year of age to achieve the preventive effects, especially in CPS1D, in males with OTCD, and ASS1 deficiency. Moreover, it can be considered also in patients with recurrent metabolic decompensations despite treatment, or when compliance with treatment is poor. Females with OTCD presenting with recurrent decompensations in the first 2 years of life have a second peak of lethality between 12 and 15 years of age and can be considered for liver transplantation. • Why: The only curative treatment for UCD is liver transplantation.⁴ 	<ul style="list-style-type: none"> • Strengthen the network between the main diagnostic and transplant centers. • Establish shared guidelines to decide when to refer a patient for transplant, including stability/instability of clinical conditions, discussion with family members, at least fair neurological conditions, body weight around 8 kg, consultation and approval of the transplant team, ability of the family to manage UCD, and number of metabolic decompensations.

6. TRANSITION FROM PEDIATRIC TO ADULT SETTINGS

Case 10

This is the case of a female patient, born in 1986, who showed early marked aversion to protein-containing foods

along with poor growth and states of agitation/irritability. At the age of 3 years, she was admitted to the infectious diseases department for liver failure, during which hyperammonemia was detected and later associated with OTCD. The patient was adequately stabilized and received maintenance therapy consisting of citrulline, NaBz,

Na-phenylbutyrate, and an appropriate diet. However, during subsequent years she experienced recurrent episodes of hyperammonemia.

Since 2011, the patient reported episodes of vomiting for which she underwent esophagogastroduodenoscopy that documented the presence of chronic active gastritis. In 2021, at the age of 35 years, she was admitted to the Metabolic Diseases Department for an episode of hyperammonemia (186 $\mu\text{mol/L}$). She underwent intravenous detoxification and was switched from NaPB to GPB.

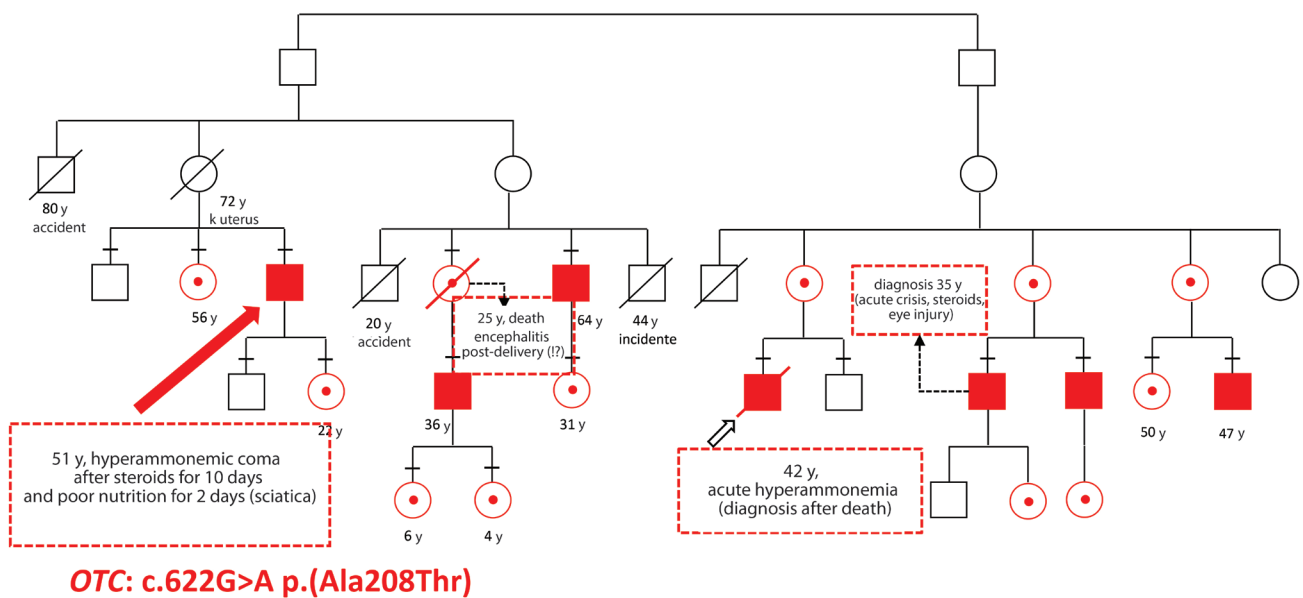
In 2022, the woman, due to the persistence of gastroenterological symptoms, scheduled a series of control visits at the Adult Center even if she remained under care of pediatric Center given the high risk of decompensation and the accelerated pathway for emergency management of hyperammonemic crises. Maintenance therapy was confirmed and based on GPB, NaBz (3.5 g 3 times a day), citrulline (3 g 3 times a day) and natural proteins (41 g/day, 0.74 g/kg/day).

Case 11

In May 2019, this male patient, born in 1968, presented with sciatica that had been treated with steroid therapy for 10 days. The patient had painful symptoms, poor nutrition and showed altered speech, aggression, and drowsiness that degenerated into coma (Glasgow Coma Scale 8). The patient was admitted to the ICU which contacted the Reference metabolic team after finding very high ammonia levels (832 $\mu\text{g/dL}$), for which intravenous glucose, arginine, and NaBZ were administered, along with hemodialysis. A positive family history for OTCD emerged, even if the subject had never been evaluated. The diagnosis of OTCD was confirmed by genetic testing and several other at-risk subjects were examined in the family who were given genetic counseling and appropriate clinical-therapeutic management (Fig. 3).

The patient has been on maintenance therapy since 2019, consisting of citrulline (4 g 3 times a day) and correct nutritional intake (total protein 0.79 g/kg). He has satisfactory control of the disease without further episodes of metabolic decompensation.

Family tree of 2 males and 3 females referred to an Adult Center



From: Von Diggelen et al. 1996, Clin Genet 50(5):310-6; Cavicchi et al. 2014, Orphanet J Rare Dis 9:105; Bijvoet et al. 2016, Neth J Med 74(1):36-9; Daijo et al. 2017, Clin J Gastroenterol 10(4):383-7

Fig. 3. The network of national collaboration Hospitals - Specialized Laboratory - Primary Healthcare is essential.

Evidence	Real-life
<ul style="list-style-type: none"> • For Whom: Patients with UCD who reach adolescence/adulthood as carriers of “mild” deficits and/or due to good adherence to therapy. • When and Why: Survival of children with UCD has improved significantly over the years, and the need for transitional care into adulthood has emerged. Routine monitoring of symptoms, adherence to a low-protein diet, and lifelong specialized medical care are necessary for individuals with UCD to maintain good health. Treatments for UCD are individualized based on the specific type of UCD, prior decompensation, and protein tolerance. Continuity of care is essential for individuals with UCD to maintain stable metabolic control and minimize chronic complications, but patients and families may encounter barriers to adherence to diet and medications.¹⁷ 	<ul style="list-style-type: none"> • Identification of an Adult Center, production of regional documents for collaboration between Pediatric and Adult Centers, with shared paths. • Implementation of training programs for adult medicine in metabolic pathologies and specifically UCD; knowledge in chronic and acute management (hyperammonemia); prevention of hyperammonemia in case of need for fasting for interventions or procedures; pregnancy and delivery. • Establish a predefined path for urgent patient access (in the ER or Emergency/Urgency Department), providing specific training for physicians and triage staff. • Organize clinics or day hospitals dedicated to adult medicine. • Dedicated metabolic dietitian in adult medicine. • Dedicated intensive/sub-intensive department in which a multidisciplinary team operates. • Promote close collaboration between the adult service and the metabolic laboratory, even in other centers/hospitals. • Provide all adult patients with a metabolic card for emergency situations. • Resolve critical issues related to access to the ER and management of emergencies. • Ensure personalization of the patient’s transition based on the defect, the clinical state and the different organization of the adult team with different timing of follow-ups.

DISCUSSION

Evidence on the natural history, treatment, and clinical outcomes of patients with UCD is still limited. Biochemical parameters derived from neonatal screening may help to initiate therapy based on the levels of individual amino acids (e.g., glutamine, citrulline, argininosuccinic acid, and arginine) suggesting specific disorders. However, it is not always easy to interpret the clinical phenotype and discriminate which forms can be defined as “mild” or “late-onset” so that clinicians should often manage presymptomatic subjects. The subsequent diagnostic process, including genetic testing, can identify the phenotype as more or less severe, and will guide the decision to start dietary and/or pharmacological therapy.

In recent years, some scientific societies and consortia such as the American Urea Cycle Disorders Consortium

(UCDC)¹⁸ and the European Registry and Network for Intoxication Type Metabolic Diseases (E-IMD)¹⁹ aimed to improve knowledge on the natural history, treatment, and clinical outcomes of individuals with UCD. These research groups focused on the understanding of the pathophysiology, early prediction of clinical severity, safety and efficacy of dietary treatment, pharmacological therapy and liver transplantation, developing evidence-based consensus recommendations for care, and empowerment of patients and their families.²⁰

These goals will be achieved over the next years. Thus, in the current situation, the shared opinion of a group of experts can help clinicians in their practice and in the development of future perspectives. The experts who participated in the two meetings presented herein agreed on the benefits of the traditional use of neonatal screening in Italy, which has shown

that UCD cannot be considered only in its acute forms and that late-onset cases can represent a relevant proportion of patients if adequate diagnostic processes are available.

In the absence of large-scale clinical trials, however, the treatment and management of UCD is currently based on protocols in the acute setting, and modifications are limited. At the same time, the experts are confident that early diagnosis of late-onset cases can prevent adverse outcomes. The discussion between experts can provide a useful framework for the management of UCD and a basis for the design of specific clinical trials, until additional evidence is available. A first finding from the comparison of the experts' experiences is that strategies to implement newborn screening along with clinical observation and enzymatic assessments are fundamental to reach a general consensus on the management of UCD. The considerable experience of clinicians in newborn screening and management of metabolic disorders is a strength of the present document.

Regarding the diagnostic approach for UCDs, increasing knowledge of the pathology in recent years allowed to carry out metabolic tests in parallel with tests for neonatal sepsis. Severe forms with neonatal onset cannot be intercepted by newborn screening, since clinical presentation can occur before the test is available. This highlights the importance of alerting neonatologists in case of nonspecific symptoms in the newborn. Furthermore, it should be emphasized that the most frequent UCD – OTCD – is not included in the Italian newborn screening panel and therefore the warning must receive maximum consideration regardless of screening execution.

Another important aspect is that metabolic tests (e.g. ammonia) should be repeated in case of diagnostic suspicion and inconclusive initial findings. Even in the presence of borderline laboratory values, the expert clinician has a crucial role.

The metabolic experts agreed on the importance of optimizing the timing for genetic analysis, especially in pathologies whose management greatly depends on a prompt diagnosis, for example through “fast-track” paths.

At present, there are difficulties in the management of specific situations, including women affected by OTCD in

which accurate family history (previous deaths in neonatal age, vague symptoms in the maternal component etc.) is of particular importance; in the case of type I citrullinemia, it is mandatory to identify parameters that can allow for early diagnosis or screening (such as detection of increased citrulline) and, secondly, to correctly differentiate it from other conditions such as citrin deficiency.

From a diagnostic point of view, it is also important to consider late-onset conditions as can lead to later metabolic decompensations and warrant robust therapeutic approaches.

Patients with mild UCD can represent a diagnostic challenge due to the chronic and nuanced symptoms mainly represented by poor appetite, recurrent vomiting, lethargy, and deficits in growth and neurological development that worsen over time. It is very difficult to distinguish between the “mild” and “late-onset” forms: “mild” implies a mild enzymatic defect (potentially at risk of clinical symptoms); “late-onset” implies the occurrence of later symptoms of the underlying disease. In the latter, patients can remain asymptomatic even until the elderly. In the latest version of the dedicated guidelines on UCD,⁴ there are no precise indications for the management of mild/late-onset forms. It would thus be desirable to prevent the onset of any form of imbalance through rapid diagnosis and initiating appropriate therapy from the first days of life. At the same time, it is necessary to carefully monitor evolution of the disease, especially in light of the risk of providing under- or over-treatment and under- or over-medicalization of these patients. It is therefore necessary to develop treatment schemes, based on precision medicine, that allow therapy to be adapted according to the clinical situation.

In mild forms, it is important that nutritional counseling and adequate instructions on weaning are provided on a regular basis during the first year of life, with simultaneous growth assessment. Establishing a management plan from the beginning in order to create stable contact with the family and provide the necessary support after diagnosis allows the patient to be followed even without starting any treatment, leaving the switch from “wait-and-see” to an “active” approach. A alteration of metabolic parameters coupled

to genetic profiles associated with severe UCD in relatives should address the decision to start treatment. The choice between treatment methods – dietary and pharmacological – should take into account, in addition to the characteristics of the patient, those of the family and socio-economic level.

Dietary treatment can be the first approach, especially because of the absence of adverse effects and low costs. However, starting dietary treatment after following a free diet could represent a challenge for both the patient and family, potentially resulting in inadequate compliance and/or arbitrary suspension of the dietary regimen prescribed. Breastfeeding remains an option given the low protein content of human milk. With this regard, it is possible to consider continuing breastfeeding without corrections, except in the most complex forms where this is alternated with protein-free formulations. In the context of weaning, similarly, the aim is to try to maintain usual diets by reducing the natural protein intake.

In the mild forms, it is important to underline the importance of careful evaluation of biochemical parameters with close monitoring, especially in the first months of life and at weaning, considering the use of scavengers when clinically indicated. The clinician must therefore acquire experience in detecting the early signs without underestimating alterations at the encephalic level. This is because the term “mild” includes a series of extremely different phenotypes: according to the experts, this definition can be associated with a particular biochemical phenotype where “mild” indicates an enzymatic activity other than zero.

To date, there is no univocal guidance for the management of a patient with mild forms, but the most reasonable approach may include a normal/mildly restricted protein intake in association with pharmacotherapy. This should also be accompanied by the recognition that these are apparently stable subjects who, in the case of even modest stressful events, can develop severe metabolic disorders, thus making it essential to consider medical therapy. The experts thus reiterated the need for reliable tests to distinguish “mild” forms that can guide the choice of therapy. At present, the lack of potentially predictive markers was confirmed, including the recently introduced ureogenesis test which is

considered poorly specific/sensitive, showing inconclusive results in clinical trials even if the real causes for this remain largely unknown. Some experience with the test has been reported in male patients with late-onset pathology, although the test results were always within normal values.

Another topic of interest is the switch from a traditional scavenger to GPB, which is possible following previous treatments that were ineffective to ensure optimal control of the disease, in order to optimize the overall metabolic profile and level of compliance. It was agreed that the introduction of GPB is associated with significant improvement in adherence and compliance due to the characteristics of the formulation and quantity of the drug administered. This improved adherence is followed by improved metabolic stability (including episodes of acute metabolic decompensation and chronic nutritional problems), as well as easier management of febrile episodes and metabolic stress conditions. In presented cases, after the switch to GPB, ammonia and glutamine levels were controlled and liver function was always normal.

GPB was developed to address difficulties in long-term chronic compliance with traditional scavengers, such as salt content, flavor, and dosing volume. It is a liquid formulation consisting of three phenylbutyrate (PBA) molecules attached to a glycerol backbone. It is nearly tasteless and odorless liquid, contains no sugar or sodium, and is administered in low-volume doses. GPB is currently approved for the chronic management of adult and pediatric patients with UCD, who cannot be managed with dietary protein restriction and/or amino acid supplementation alone.^{21,22} The safety and efficacy of GPB was demonstrated in numerous patient cohorts during its clinical trial program. It was first approved for patients 2 years of age and older in 2013, 2 months of age and older in 2017, and finally for neonates and older in 2018.²³⁻²⁶

In a recent open-label study by Longo et al.²⁷ in patients with UCD aged 0 to 2 months, consisting of an initiation/transition period (1-4 days) to GPB, followed by a safety extension period (6 months to 2 years), infants were safely transitioned from NaPBA to GPB while maintaining control of ammonia and glutamine. The study demonstrated that

GPB undergoes intestinal hydrolysis without accumulation of phenylacetic acid (PAA) in patients with UCD younger than 2 months, while patients aged 0 to 2 months are able to switch/initiate GPB and maintain control of ammonia levels in the long term. These results support the use of GPB in patients with UCD aged 0 to 2 months who cannot be managed with dietary protein restriction and/or amino acid supplementation alone.

A potential issue related to switching is that the Summary of Product Characteristics is not very comprehensive regarding the switch from oral NaBz to GPB. In this regard, it is interesting to report the results of a retrospective study conducted in the United Kingdom, that used data obtained from electronic medical records of 20 subjects with various types of UCD collected for a period of up to 3 years before a patient started GPB, in January 2019, and for the subsequent duration of treatment until July 2022.¹⁶ Patients were started on GPB to allow discontinuation of one or more intravenous or oral sodium scavengers. The initial approach for the first three patients involved a gradual transition in phases over 1 to 2 weeks, after which the scavenger was directly substituted, stopping NaBz and introducing GPB on the same day. Overall, it was observed that the mean levels of ammonia and glutamine decreased significantly once patients started GPB. In addition, the introduction of GPB led to a 78% reduction in the number of patients exposed to sodium above the recommended daily limits during treatment with NaBz. Patients who started or switched to GPB also reported a significant reduction in hyperammonemic episodes (1.9/year vs. 0.2/year, $p=0.02$) and hospital admissions (2.2/year vs. 0.5/year, $p=0.01$).

Another advantage of GPB is linked to its stabilizing action on glutamine, which can be used as a marker of response in patients who do not fall within the classic UCD phenotype and therefore symptomatically “silent”. In this category of patients, GPB can also be useful in monitoring the most appropriate dosage.

Liver transplantation has emerged as a cure of some severe UCDs due to its ability to overcome the metabolic deficiency and eliminate the risk of hyperammonemia. However, it is a complicated surgical procedure, which

carries a risk of mortality and morbidity and requires a lifelong regimen of immunosuppression. Although post-transplant survival rates are high in patients with metabolic disorders, as shown in US and European registries, the risk-benefit ratio of liver transplantation is particularly difficult to determine in patients with mild-to-moderate forms, and such ambiguity can make treatment decisions very difficult for families.²⁸

There is a discrepancy in current clinical practice between European medical opinion, which does not consider liver transplantation a valid therapeutic option for UCDs, and the opinion of Italian experts. According to the experts, at least four pathologies, namely ornithine transcarbamylase deficiency (OTCD), carbamoyl phosphate synthase deficiency (CPS1D), neonatal citrullinemia and argininosuccinic aciduria (ASA), represent a first-line indication for liver transplantation. Experiences²⁹ on the impact of liver transplantation in patients with neonatal-onset argininosuccinate lyase deficiency (ASLD) showed that, after transplantation, all showed sustained metabolic stability, without recurrence of hyperammonemia despite withdrawal of nitrogen scavengers and arginine and the transition to unlimited dietary protein intake. In addition, other disease-related complications, such as growth retardation, hypokalemia and dyslipidemia improved and/or resolved. Regarding neurological complications commonly reported with ASLD, no patient developed epilepsy at long-term follow-up, EEG changes remained stable, and movement disorder resolved soon after transplantation in one of two patients. Based on these considerations, early liver transplantation represents a new potential treatment in the severe of ASLD.

In this regard, there was undisputed agreement among the experts in reiterating the high level of expertise in Italy in liver transplantation and management of UCDs, also thanks to the availability of neonatal screening, which is not practiced in all European Centers. The board agreed on the need to obtain satisfactory stabilization of the patient before planning a transplant procedure, since this can be significantly influenced by the severity of residual symptoms and the number of crises that occurred prior to the transplant. However, it was emphasized that

the indication for transplantation must be evaluated considering the severity of the disease, the evolution of the patient's clinical situation which may, if necessary, lead to considering extended timing in the event of satisfactory stabilization, a reduction in the number of crises and other parameters. The history of treatment of UCDs has recent new developments and data on individual cases from the major Reference Centers still needs to be consolidated, especially considering the forthcoming comparison that will take place between liver transplantation and new upcoming advanced therapies.

Regarding the transition from pediatric to adult settings, it is first of all appropriate to establish which patients should be transitioned, but in most cases it involves those affected by "late-onset" forms with variable risk of decompensation. These are commonly male individuals affected by "late-onset" OTCD and who had a first event in a pediatric age or in adulthood, but who have remained in the care of the Pediatric Center. However, patients with "early-onset" forms who received a timely diagnosis, and therefore adequate treatment, could also be included in this category. Other possible categories are female OTC patients with severe onset in pediatric age, oligosymptomatic OTC females with episodes of hypertransaminasemia, and asymptomatic adults with a positive family history for OTCD and/or with altered biochemical parameters.

The transition of these patients from childhood-adolescence to adulthood care is often critical, since they go from a phase of life where parental/caregiver supervision predominates to one with a strong need for self-management, with significant repercussions on adherence and compliance to dietary and pharmacological therapy.

During the transition in care, the issue of long-term management arises and whether it is more appropriate for these patients to remain in the care of Pediatric Departments that are specialized in metabolic diseases or to transition to Adult Medicine. Currently, there is no real preference in this regard; therefore, it becomes essential to transfer adequate knowledge of low-protein diet therapy to Adult Centers through specific and innovative training of metabolic dieticians. The second step consists in better understanding

of dietary-metabolic therapy with single amino acids through citrulline and arginine supplementation and then introducing the team caring for adult patients to the concept of "life-saving" amino acid therapy. In the training of the latter, it is also necessary to introduce the concept of prevention associated with GPB therapy, moving from a symptomatic to a preventive pharmacological approach and, finally, increase the diagnostic ability of "late-onset" forms.

The transition must be a structured and shared process between various specialists with appropriate training: all this must occur by identifying clinicians in adult care that can be part of a multidisciplinary team, with regional collaboration and creation of shared pathways. In the setting of the adult patient, in fact, additional problems relating to the emotional and working spheres must be taken into consideration.

The experts also agreed on the need for pediatricians who are experts in metabolism that can become a core feature of the transition process of patients with UCDs and be available to colleagues who practice in the adult setting by providing training and actively guiding the transition. This last aspect obviously requires the appropriate training of emergency physicians, internists, gastroenterologists and psychiatrists in order to enhance the capacity for emergency management of these pathologies.

CONCLUSIONS

Treatment for patients with UCD must be personalized to achieve an optimal metabolic balance, as demonstrated by the clinical cases presented herein. At the same time, timely and personalized management of patients with UCD, based on a precise diagnosis and continuous tailoring of therapy, is essential to improve long-term prognosis. From the point of view of the physician-patient relationship, it is also essential to regularly provide nutritional counseling and instructions for weaning to the families of patients with UCD to ensure effective dietary management from the first days of life.

Another fundamental aspect is represented by the careful monitoring of patients with "mild" or "late-onset" forms to avoid under- and over-treatment and adapt management to

the clinical situation. In the case of patients scheduled for transplant, collaboration between Diagnostic/Treatment and transplant Centers is crucial. The transition of patients from the pediatric to the adult setting requires structured paths to ensure continuous and consistent management. The latter can be achieved by focusing on training and collaboration between pediatric and adult specialists, to ensure that patients have an effective and adequate transition to their new needs (life and work).

In this context, personalization of treatment, including

nutritional management and the use of specific therapies such as GPB, is essential to improve the quality of life of patients. GPB is effective and well tolerated in the metabolic control of patients with UCD, significantly improving adherence to treatment.

As demonstrated by the experience gathered by the various Authors of this paper, the collection of clinical data and the continuous and shared comparison of experiences are essential to refine therapeutic strategies to improve the long-term outcomes of UCDs.

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