

Early Clinical Manifestations and Eating Patterns in Patients with Urea Cycle Disorders

Thatjana Gardeitchik, MD^{1,2}, Maureen Humphrey, APD^{1,3}, Judy Nation, APD^{1,3}, and Avihu Boneh, MD, PhD^{1,4}

Objectives To characterize dietary habits and eating patterns in patients with a urea cycle disorder (UCD), and to identify dietary habits that may serve as clues to lead to earlier diagnosis of these disorders.

Study design This was a retrospective study of clinical and dietary data from hospital records of all patients with UCD (n = 90) attending the Royal Children's Hospital in Melbourne between 1972 and 2010.

Results Protein aversion, food refusal, frequent vomiting, poor appetite, and adverse reaction to high-protein-containing foods were documented in the majority of patients with available detailed dietary protein intake data. Fourteen of the 90 admissions for metabolic deterioration in which information regarding the precipitating factor(s) were available were directly related to protein intake (5 higher and 9 lower than prescribed).

Conclusion Protein aversion is a common feature of UCD and may serve as a diagnostic clue in patients presenting with food refusal, recurrent vomiting, behavioral problems, mental retardation, and "unexplained" episodes of altered consciousness. Dietary history should be included in the investigation of these symptoms, which might lead to earlier diagnosis. Metabolic decompensation is more frequently related to low energy/protein intake than to high protein intake in these patients. Special attention should be given to protein aversion, which often leads to eating patterns that make it difficult for a patient to achieve the prescribed daily protein requirement. (*J Pediatr* 2012;161:328-32).

Urea cycle disorders (UCD) comprise a group of inherited metabolic disorders with an estimated overall prevalence of 1:30 000.¹ Each of these disorders results from a deficiency of a particular enzyme along the hepatic ammonia detoxification pathway. The 6 urea cycle enzymes are carbamoyl phosphate synthetase 1 (CPS1) and its allosteric activator N-acetylglutamate synthetase, ornithine transcarbamylase (OTC), argininosuccinic acid synthetase (ASS), argininosuccinic acid lyase (ASL), and arginase. The clinical manifestations of these disorders are variable, and UCD phenotypes range from neonates dying from complications of hyperammonemia in the first week of life to apparently asymptomatic adults.

Neonatal symptoms of UCD usually present after the first 24-48 hours of life in infants born at term after a normal pregnancy and delivery. Common presenting symptoms are poor feeding, vomiting, lethargy, hypotonia, respiratory distress, irritability, and seizures. Without treatment, patients may deteriorate rapidly, possibly to coma and death.^{2,3} Symptomatology in late-onset forms of UCD is less marked, and patients may have less obvious features, which might lead to diagnostic delays.^{1,4-7} Reported symptoms include episodes of altered consciousness, behavioral changes, irritability, abnormal motor function, seizures, cyclic vomiting, loss of appetite, protein avoidance, poor growth, hypothermia, and developmental delay.^{1,4-7} The diagnosis may become apparent during periods of metabolic stress (eg, infection, during pregnancy or the postpartum period).^{6,7} Dietary changes (eg, high protein intake, persistent protein deficiency) also have been reported to precipitate presentation and deterioration.^{5,6,8-10} Several patients have been reported in whom a detailed history obtained after presentation with severe neurologic symptoms revealed severe, previously unrecognized protein aversion.^{9,11,12} The actual prevalence of this manifestation has not been reported, however.

The objective of the present study was to identify dietary habits and eating patterns in patients with UCD before and after diagnosis. We endeavored to find dietary clues that might lead to an earlier diagnosis of these disorders, which could potentially prevent presentations with severe (ie, irreversible) neurologic symptoms. We wished to identify dietary habits that might influence disease presentation and frequency of episodes of metabolic deterioration, and also to identify problems that might require specific attention to the specialized care for these patients.

ASL	Argininosuccinic acid lyase
ASS	Argininosuccinic acid synthetase
CPS1	Carbamoyl phosphate synthetase 1
OTC	Ornithine transcarbamylase
UCD	Urea cycle disorder

From the ¹Department of Metabolic Genetics, Murdoch Children's Research Institute and Royal Children's Hospital, Melbourne, Australia; ²Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands; ³Department of Nutrition and Food Services, Royal Children's Hospital; and ⁴Department of Pediatrics, University of Melbourne, Melbourne, Australia

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Methods

This study was part of a Metabolic Databank, which had been approved by the Institutional Ethics Committee (HREC 30066A). Data for all patients attending the metabolic clinic at the Royal Children's Hospital, Melbourne, with a confirmed diagnosis of UCD between 1972 and 2010 were included in this study. This clinic is a centralized service managing all known patients with inborn errors of metabolism in Victoria, Australia (current population of ~5.5 million). Diagnosis of UCD was considered confirmed if a pathogenic mutation was identified, liver enzymology showed reduced enzyme activity, a protein-loading test on cascade screening was positive, or the patient presented with an episode of hyperammonemia and amino acid and orotic acid analyses revealed characteristic abnormalities consistent with a diagnosis of UCD. Patients were stratified into a neonatal onset group, presenting during the first 28 days of life, and a postneonatal onset group. In addition, patients were divided according to mode of diagnosis: patients who presented clinically, those detected by cascade screening, and those detected through newborn screening.

Data were extracted from clinical patient charts, dietary records, and family genetic files, and were reviewed and coded by one person. For each patient, along with data on the clinical manifestations before or at the time of diagnosis, detailed dietary information was collected, including protein aversion, dietary changes before presentation, reported reactions to protein-rich food, presence of food refusal, details on the prescribed dietary regimen and general compliance, and self-reported eating patterns before and after diagnosis.

Results

Data from all 90 patients with confirmed UCD were included in the analysis. Eight patients (5 males; 3 females) had CPS1 deficiency, 64 (24 males; 40 females) had OTC deficiency, 11 (4 males; 7 females) had ASS deficiency, and 7 (1 male; 6 females) had ASL deficiency. In 44 patients (including 4 identified on cascade screening), diagnosis was made after a symptomatic presentation. Forty-one patients were identified by cascade screening after a family member had been diagnosed with UCD. Newborn screening identified 5 patients. In 1 patient, genetic screening for other medical reasons revealed a deletion of the OTC gene. One female patient with OTC deficiency was reportedly identified through routine screening for phenylketonuria. In 2 female OTC-deficient patients, information on the mode of diagnosis was unavailable for review. It should be noted that the retrospective nature of this study dictated that the quality of data depended on the quality of the records, and thus the extent of symptoms reported here might be underestimated or, at times, overinterpreted.

Neonatal Presentation

Twenty-six patients presented with symptoms in the first 28 days of life, including 24 patients presenting in the first week.

This group comprised 14 patients with OTC deficiency (all males), 4 with CPS1 deficiency, 6 with ASS deficiency, and 2 with ASL deficiency. Four neonates in this group (3 with OTC deficiency; 1 with CPS1 deficiency) presented during careful observation instituted because of a positive family history for UCD. The most common symptoms at presentation were respiratory distress, poor feeding, lethargy, and altered consciousness ([Table I](#)).

Postneonatal Presentation

Eighteen patients presented in the postneonatal period, with only 2 diagnosed after their 18th birthday. (The exact date of diagnosis was unavailable in 1 patient.) The median age at diagnosis was 1.62 years (range, 0.11-43.14 years). The most common symptoms at presentation were vomiting, lethargy, and altered consciousness ([Table I](#)). A detailed health history, including dietary history, was available in 17 patients and revealed unrecognized symptoms that could have been suggestive of UCD before the actual presentation that led to diagnosis. These included recurrent vomiting, protein aversion, episodes of altered consciousness, drowsiness, confusion, behavioral problems, and less specific manifestations, including developmental delay, lethargy when unwell, failure to thrive, cerebral palsy, and hypotonia ([Table II](#)). None of these 17 patients reported changes in diet immediately before clinical presentation. The most common dietary characteristics before diagnosis were protein aversion, food refusal, and adverse reactions to high-protein foods. Adverse reactions were reported in 9 patients and included vomiting (7 patients) and irritability after feeds in infancy (2 patients).

Cascade Screening

Forty-one patients were identified by cascade screening, and subsequently diagnosed by a protein-loading test, mutation analysis (including prenatal), or careful clinical and biochemical observation of patients at risk during the newborn

Table I. Symptoms at presentation in patients with neonatal onset and postneonatal onset

Neonatal onset (n = 26), symptom (number of patients)	Postneonatal onset (n = 18), symptom (number of patients)
Respiratory distress (15)	Vomiting (7)
Poor feeding (13)	Lethargy (7)
Lethargy (10)	Altered consciousness (6)
Altered consciousness (10)	Hypotonia (4)
Convulsions (8)	Food refusal (4)
Vomiting (7)	Irritability (4)
Irritability (7)	Ataxia (3)
Hypotonia (4)	Developmental delay (3)
Hypothermia (4)	Poor growth (2)
Jitteriness (4)	Convulsions (2)
Apnea (3)	Confusion (2)
Tremors (2)	Inappropriate behavior (1)
Hypertonia (1)	Hypothermia (1)
Weight loss >10% (1)	Incontinence (1)
	Paresis (1)
	Hypertonia (1)
	Weight loss (1)

Table II. Symptoms suggestive of UCD before the event leading to diagnosis in patients with postneonatal onset disease (n = 18) or before identification by cascade screening (n = 25)

Postneonatal clinical onset (n = 18), symptom (number of patients)	Cascade screening (n = 25), symptom (number of patients)
Adverse reactions to high-protein foods* (9)	Protein aversion (11)
Protein aversion (7)	Recurrent vomiting (4)
Developmental delay (4)	Nausea (1)
Lethargy when unwell (4)	Convulsions (1)
Episodes of altered consciousness (2)	Episodes of lethargy (2)
Drowsiness (2)	Developmental delay (1)
Failure to thrive (2)	Jitteriness in infancy (1)
Behavioral problems (1)	
Episode(s) of confusion (1)	
Cerebral palsy (1)	
Hypotonia (1)	

*Including vomiting (7) and irritability after feeds (2).

period. Of the 9 patients in the latter group (5 with OTC deficiency, 3 with CPS1 deficiency, 1 with ASS deficiency), 4 patients became symptomatic during the neonatal period (data included in the neonatal presentation group) and 3 presented with symptoms in the postneonatal period. Two of the 4 patients diagnosed by prenatal mutation analysis (all females and OTC-deficient) became symptomatic. So far, the other 2 patients have not exhibited UCD-related symptoms. In the postneonatal cascade screening group, 28 patients (25 females; 3 males) were diagnosed with OTC deficiency. The median age at diagnosis was 25.85 years (range, 2-73 years) in this group.

A detailed medical history was available in 25 of the 41 patients. Eight of these patients reported apparent UCD-related symptoms that went unrecognized at the time, including recurrent vomiting and nausea, convulsions, episodic lethargy, developmental delay, and jitteriness in infancy (Table II). A dietary history was available in 21 of the 41 patients but was incomplete in some, because of the retrospective data retrieval. Eleven patients reported protein aversion, and 4 patients reported "feeling unwell" after eating protein-rich foods.

Newborn Screening

Since 2002, when the extended newborn screening program using tandem mass spectrometry was initiated in Victoria, 5 newborns have been identified with UCD (3 with ASS deficiency, 2 with ASL deficiency), ranging in age from 3.5 to 7 years. Three patients were completely asymptomatic without any form of treatment. One patient with ASL deficiency was diagnosed with central nervous system periventricular nodular heterotopia, most likely accounting for her developmental delay and epilepsy. She experienced no episodes of metabolic decompensation. One patient with ASL deficiency (now ~4 years old) presented with transient drowsiness and poor feeding during a viral illness, but has had no other symptomatology or recurrence and is on an unrestricted normal diet.

Eating Patterns before and after Diagnosis

Sufficient information for calculating protein intake before diagnosis was available in only 16 patients (6 in the cascade screening group and 10 in the postneonatal presentation group). These patients consumed 50%-60% of the median protein content of a typical Australian child's diet.¹³ Information on dietary habits and eating patterns after diagnosis was available in 67 patients and is summarized in Table III according to specific diagnoses. Protein aversion was the most striking reported feeding behavior, in particular aversion to foods containing high protein density and protein of high biological value, such as animal protein and animal-derived proteins (eg, milk, eggs). Other reported habits included increased feeding frequency, overeating of low-protein foods, delay in self-feeding, food tantrums, delayed introduction of solids, and high consumption of low nutrient-dense foods. The number of patients was too small to allow identification of differences in eating habits in specific UCD diagnoses.

Hospital Admissions and Precipitating Factors

In 34 patients, the total number of admissions for metabolic deterioration with hyperammonemia (neonatal deaths excluded) was 224 out of a total of 290 patient-years. Almost all admissions of patients with UCD were at our center. A precipitating factor was recorded in only 90 admissions, with infection leading to 76 admissions, apparent inadequate protein intake leading to 9 admissions, and apparent excessive protein intake leading to 5 admissions. For all other admissions, precipitating factors were not recorded or, more typically, not known.

Discussion

This study aimed to identify early clinical manifestations and eating patterns in patients with UCD, which could aid early diagnosis of UCD. Although not all data of interest were available for every patient, given the study's retrospective nature, considering the prevalence of UCD, our cohort of patients was sufficiently large to be informative regarding clinical manifestations and dietary habits in patients with these diseases. However, the number of patients with specific diagnoses or genetic mutations was too small to allow us to draw conclusions about differences in clinical parameters and dietary habits among the various diseases.

Table III. Eating behavior after UCD diagnosis stratified by diagnosis

Diagnosis (number of patients)	Protein aversion	Poor appetite	Food refusal	Poor variety	Frequent vomiting
CPS1 deficiency (8*)	4 (4 [†])	3 (5)	5 (8)	2 (5)	4 (6)
OTC deficiency (47)	25 (39)	18 (29)	14 (34)	9 (28)	14 (37)
ASS deficiency (8)	2 (3)	2 (6)	7 (8)	4 (4)	5 (7)
ASL deficiency (4)	2 (4)	1 (4)	1 (3)	1 (4)	4 (6)
Total (67)	32 (50)	24 (44)	27 (53)	16 (41)	27 (56)

*Number of patients for whom information was available.

†Number of patients for whom information on the particular dietary habit was available.

The variety of presenting symptoms in our population was similar to that reported by others.^{1,3-6,14} The 3 most frequent symptoms at presentation in the newborn period were respiratory distress, poor feeding, and lethargy. In contrast, the most common presenting manifestations in the postneonatal onset group were episodes of vomiting, lethargy, and altered consciousness (Table I).

Diagnostic delay is relatively common in UCD.^{1,4-6} The number of patients diagnosed through cascade screening who became symptomatic after a biochemical or genetic diagnosis underscores the importance of cascade screening in the extended family when a new patient is diagnosed. Furthermore, the finding of a history of unrecognized UCD symptoms and protein aversion in almost half of the patients in our cohort highlights the importance of meticulous history-taking, including specific questions on dietary protein intake. This may lead to the suspicion of UCD in a child referred for investigation of food refusal, repeated vomiting, behavioral problems (eg, hyperactivity, agitation), mental retardation, and unexplained altered consciousness. Food refusal, poor appetite, and fussiness about eating are not specific manifestations of UCD. Many children experience a period of fussy eating behavior during the first few years of life. Children with UCD present with protein aversion and are especially fussy about meat, eggs, and dairy products but do like fruit and vegetables, in contrast to most "normal" fussy children, who tend to have more problems with vegetables. Patients and parents are not likely to volunteer this information themselves, because these dietary habits may seem normal and have been observed since early childhood.

The mainstay of successful nutritional management of patients with UCD is maintaining nitrogen balance. Protein must be sufficiently limited to minimize nitrogen overload yet sufficiently abundant to maintain cellular function and linear growth.^{7,15,16} Protein quality is just as important as protein quantity in maintaining adequate metabolic control and nutritional status, and must be considered when prescribing a low-protein diet.

Complying with the prescribed protein and energy intake may prove to be a major problem, and the literature is scanty on eating behavior and compliance with dietary management in patients with UCD and the influence on growth, general well being, and frequency of metabolic deterioration. A study of 1045 metabolic deteriorations requiring hospitalization ascribed 15% of these deteriorations to noncompliance with the prescribed diet; the authors did not distinguish between higher or lower intake than prescribed, however.⁶ It has been suggested that patients might eat more protein than recommended because of a reluctance to give up favorite foods, poor acceptance by their families, or severe peer pressure.^{7,16} Indeed, high protein intake has been reported as a precipitating factor for metabolic decompensation in UCD.^{5,6,9,12,17} Those reports contrast with the findings of protein aversion in our patients before diagnosis and failure to meet the prescribed daily protein requirement after diagnosis. Indeed, there have been reports of low protein intake in patients with UCD due to pathological eating behavior and severe

protein self-restriction.^{16,18,19} In our cohort, 9 admissions were due to ascertained low protein intake, which is probably an underestimate. It is likely that 76 admissions were precipitated by an "intercurrent infection," with reduced calorie and protein intake in most of them. However, it is difficult to distinguish between poor intake as the cause or the result of decompensation, especially when reviewed retrospectively. The most likely scenario would be a reduced protein and energy intake, leading to exacerbation of the metabolic derangement. Further research should be carried out to quantify these data and to analyze the effects on the number of metabolic deteriorations, biochemical parameters, growth, and general well being to eventually draw conclusions.

Finally, it should be noted that the eating patterns in children with UCD can cause stress in families related to the medical need to cope with a specific diet. In addition to the actual calculation of dietary limits, attention should be paid to the effects of the child's diet and behavior on the family. Counseling on the best way to handle possible problems should be provided.

In conclusion, we recommend cascade screening of at-risk patients after the diagnosis of a patient with UCD. A dietary history, including questions about protein aversion, reaction to protein-rich foods, and food refusal and fussiness, should be included in the investigation of all patients presenting with recurrent vomiting, behavioral issues, or unexplained altered consciousness. This may lead to earlier diagnosis of UCD and institution of treatment. ■

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Reprint requests: Avihu Boneh, MD, PhD, FRACP, Metabolic Genetics, Genetic Health Services Victoria, Murdoch Children's Research Institute, Royal Children's Hospital, Flemington Road, Parkville, Victoria 3052, Australia. E-mail: avihu.boneh@ghsv.org.au

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