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Case Report

Fatal consequences of limited health literacy in a patient with a rare metabolic disease☆

Markey C. McNutt *

McDermott Center for Human Growth and Development, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390, USA

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ABSTRACT

A Black young adult female diagnosed with argininosuccinate lyase deficiency at 6 months of age encountered significant barriers to care for the first 16 years of her life due to socioeconomic factors and parental neglect. Once in the care of her paternal grandmother, she received appropriate treatment with a nitrogen scavenger, amino acid supplementation, and a low-protein diet. However, due to repeated hyperammonemic crises early in her life, she was minimally communicative and unable to perform activities of daily living. During her final hyperammonemic crisis, she presented to a hospital unfamiliar with urea cycle disorders and without a metabolic service. As a result, she did not receive optimal care and died.

1. Introduction

Ammonia is produced in the colon and small intestine and transported to the liver, where it is broken down via the urea cycle (Fig. 1) [1]. A defect in any of the 6 enzymes or 2 transporters of the urea cycle, including argininosuccinate lyase (ASL), results in cycle function impairment and ammonia accumulation and is referred to as a urea cycle disorder (UCD) [2–5]. UCD subtypes are named based on the missing or defective enzyme in the urea cycle. Although defects may arise spontaneously, they are typically inherited; 5 of the 6 UCD subtypes are inherited in an autosomal recessive manner and 1 is inherited in an X-linked fashion [2]. Disease-causing variants in the *ASL* gene (OMIM 207900) are inherited in an autosomal recessive manner [2].

Individuals with ASL deficiency may develop hyperammonemia at any point in their life [3]. The symptoms of hyperammonemia are nonspecific and may include lethargy, irritability, vomiting, increased respiration, dehydration, lack of appetite, and coma [1,3]. Normal and inevitable life events, such as illness, changes in diet, and stress, are potential triggers of hyperammonemia [6,7].

Patients experiencing a hyperammonemic crisis are at risk of developing life-threatening complications such as cerebral edema and brain herniation. Treatment with intravenous nitrogen scavenger therapy and intravenous lipids and/or glucose should be started immediately in the acute care setting, with the option to progress to hemodialysis if ammonia levels do not normalize [1,4]. In patients with acute hyperammonemia who have been in a coma for more than 3 days or have significantly elevated intracranial pressure, the health care team may want to consider the prognosis before determining whether to continue treatment or begin palliative care [3]. Long-term management plans aim to control ammonia through low-protein diet, arginine supplementation, and nitrogen scavenger therapy. Close adherence to long-term management plans helps reduce the risk of crisis and cognitive decline [3,4,8]. Because of the nonspecific nature of hyperammonemia symptoms and the urgency to treat patients to prevent life-threatening complications, it is important for nonspecialty clinicians to be aware of ASL deficiency and other UCDs [1,9].

Despite the urgency to treat patients with ASL deficiency and the importance of continuous management, many are unable to receive appropriate care due to barriers posed by social determinants of health (SDOH). Studies show that not only does access to medical care and food impact patient well-being, but factors such as income level, education, housing safety, and social support also affect health outcomes [10,11]. Individuals with the least education and lower economic status tend to have the worst health [11]. This may in part be due to clinician perceptions and approaches to care. Studies indicate that individuals with low socioeconomic status are often perceived as less intelligent, less

Abbreviations: ASL, argininosuccinate lyase; CPS, child protective services; DME, durable medical equipment pharmacy; G-tube, gastrostomy tube; mEq, milliequivalents; NaBz, sodium benzoate; NaPA, sodium phenylacetate; NaPB, sodium phenylbutyrate; SDOH, social determinants of health; UCD, urea cycle disorder.

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* Corresponding author.
E-mail address: Markey.McNutt@UTSouthwestern.edu.

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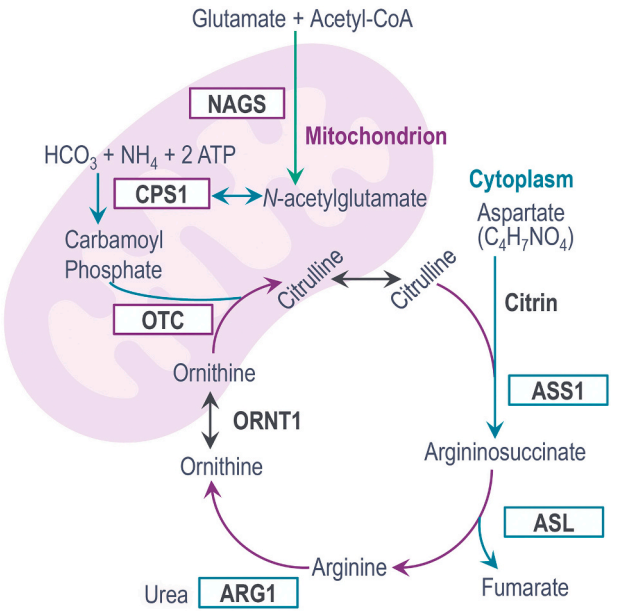

Fig. 1. The urea cycle.
ARG1, arginase 1; ASL, argininosuccinate lyase; ASS1, argininosuccinate synthetase; CPS1, carbamoyl phosphate synthetase 1; NAGS, *N*-acetylglutamate synthase; ORNT1, ornithine transporter mitochondrial 1; OTC, ornithine transcarbamylase.
The urea cycle is responsible for the conversion of ammonia to urea, a water-soluble compound that can be excreted via the kidneys. A deficiency in any of the 6 enzymes or 2 amino acid transporters results in a urea cycle disorder [1,2].

independent, and less responsible as well as less likely to comply with medical advice than patients of higher socioeconomic status [12–14]. Furthermore, management decisions are impacted by the patient's ability to access medications and tests [13,15].

When someone is diagnosed with a chronic illness such as a UCD, not only is their life impacted, but also the lives of their loved ones. Families of patients with a UCD report changes in employment, economic status, and relationships after diagnosis as well as increased emotional stress. This stress is typically attributed to fears for the patient's health, increased financial burden, and lack of freedom as patients must adhere to strict diets and schedules. Finances are often impacted by family members leaving jobs to provide adequate care for the affected individual and by the costs of medications and dietary supplements. Unsurprisingly, families of lower economic status find it more difficult to adapt to the burden of living with a chronic illness [16,17].

In this report, we present the case of a Black young adult female with ASL deficiency who received inadequate care due to socioeconomic factors and parental neglect for the first 16 years of her life. This patient experienced abuse as a result of her mother's drug addiction, with multiple child protective services (CPS) investigations and sexual assault examinations. Although the patient's care and management improved after her paternal grandmother gained full custody, transportation barriers, low socioeconomic status, and her grandmother's perceived lack of medical literacy continued to pose challenges.

2. Case presentation

2.1. Medical and social history

The patient was her father's first child and mother's second. The mother's first child was removed from her care by CPS prior to the patient's birth. From birth to age 2 years, the patient and her parents lived with her paternal grandmother. At age 6 months, the patient was taken to the hospital with lethargy and lack of urination. She had severe hyperammonemia, requiring dialysis, and was diagnosed with ASL deficiency. The patient had significant neurologic injury from this decompensation, causing her to be wheelchair bound and dependent upon a caretaker for all activities of daily living. No initial laboratory data are available from this hospital stay. During this hospitalization, the patient was given a G-tube for feeding and was prescribed appropriate metabolic formula, arginine, and a nitrogen scavenger; however exact dosages are unknown. She was discharged from the hospital after a 3 month stay.

The patient's mother and father separated when she was 2 years old, at which time she and her mother moved away. At age 5 years, the patient and her mother moved back to the paternal grandmother's home for support, and the patient entered public school in the special education program. The paternal grandmother was involved in the patient's care, attending metabolic clinic visits with the patient before the family again moved out 7 months later.

When the patient was around 9 years old, her grandmother was notified that the patient had missed her metabolic clinic appointments. The grandmother discovered that the patient's mother had started drinking and progressed to alcoholism. The mother entered an abusive relationship, and by the time the patient was 11 years old, her mother was using illicit drugs. During this time, the patient was missing about half of school days and was hospitalized for hyperammonemia about every 3 months. The grandmother stepped in to care for the patient but could only provide care part time as she worked full time. As a result, the patient bounced back and forth between her grandmother's and mother's homes.

When the patient was 15 years old, her grandmother moved away and attempted to take the patient with her. However, police returned the patient to her mother's custody. When the patient was between 15 and 16 years old, CPS performed multiple investigations, finding the patient and her mother living in a car and then later in a home with no bathroom. The patient was found by police on a dirty mattress on the floor, unattended, in only a shirt and dirty diaper. At this time, the patient was removed to the custody of a foster family; her grandmother was not alerted to the situation. None of the patient's medications, which included a nitrogen scavenger and arginine, were provided to the foster family, and the family was not appropriately educated on her treatment. Without medications, the patient had a severe hyperammonemic crisis accompanied by severe perineal skin breakdown. She had a prolonged hospital stay and was not expected to survive. During this hospitalization, her grandmother was notified of the situation and obtained full custody of the patient.

2.2. Presentation to clinic

The patient came to be in the care of our pediatric colleagues at the age of 16 years, when her grandmother obtained custody. She had significant neurologic injury, that primarily occurred during her first decompensation at 6 months, which further regressed in all domains after the decompensation at age 16 years. She remained wheelchair bound and had no expressive language at the time of presentation to our clinic and required a caretaker for all activities of daily living.

2.3. UCD management

With the change in custody at age 16 years, the patient moved to a different state and established care with the pediatric genetics team. At presentation to the pediatric genetics team, she had severe malnutrition (38.6 kg) and eczema and had been prescribed arginine (0.35 g/kg/day, 3.5 g via G-tube every 6 h), but her grandmother was only giving approximately 0.5 g every 6 h. She had also been prescribed a nitrogen scavenger (NaPB, 0.3 g/kg/day, approximately 3 g via G-tube every 6 h), but her grandmother was giving 2.5 g every 6 h. The discrepancy in prescribed and administered doses was attributed to poor

communication at hospital discharge. She was also on sodium citrate/citric acid (0.5 g every 6 h), citric acid (0.334 g every 6 h), and potassium chloride (20 mEq daily). Her prescribed diet was 20 g of natural protein by mouth and essential amino acid supplementation by G-tube, but she had never received the formula due to insurance issues. Additionally, her grandmother reported significant difficulties obtaining and refilling medications, supplements, and metabolic formulas because they came from different pharmacies and DMEs.

At her first visit with the pediatric genetics team, the patient was placed on Cyclinex®-2 (86 g, 4 times daily) and essential amino acids (5 g, 3 times daily) in addition to the 20 g of protein by mouth. She rapidly achieved a normal weight (68 kg), and her eczema resolved. Arginine was adjusted to 7 g, 4 times daily and NaPB to 5 g, 4 times daily as her weight increased. The metabolic team worked with her grandmother to obtain all medications and formula through Medicaid. Her grandmother received dietary and disease counseling at each visit. A metabolic dietitian and metabolic geneticist provided counseling while the patient was managed by the pediatric genetics team. Counseling was transitioned to a medical geneticist when the patient was transferred to adult genetics. A written emergency protocol letter was provided, and a plan for emergency management was discussed at each visit.

The patient's grandmother followed the low-protein diet regimen closely despite continued challenges obtaining low-protein foods. The patient also received speech, occupational, and physical therapy twice a week. Her communication improved as she was able to express several words and short sentences. However, she never attained independent mobility or the ability to complete activities of daily living unassisted.

Home health nursing was obtained through Medicaid at 16 years old (40 h weekly), allowing the grandmother to continue working full time. However, when the patient turned 19 years old, coverage for home health nursing was reduced to 20 h, forcing the grandmother to quit her job to provide full-time care. The patient was out of school from ages 15 to 19 years, but reentered the public school system at age 19 years through 21 years.

From ages 17 to 23 years, her management remained largely unchanged; her functional status plateaued and remained stable after the initial improvements with therapy. It was recommended that the patient visit the clinic every 6 months for follow-up assessments and laboratory testing (Table 1), but she was only able to attend appointments annually due to her distance from our clinic.

2.4. Outcomes

Although overall management improved after the patient moved to her grandmother's care, she was still hospitalized 2 to 3 times a year for hyperammonemia, typically triggered by intercurrent viral or bacterial illness. As far as could be determined, none of these hospitalizations were due to nonadherence to the treatment plan. During hyperammonemic episodes, the patient would present to the closest emergency department. In most cases, these were facilities without metabolic providers. The outpatient metabolic team was notified at all presentations, and management recommendations were given by phone. Treatment typically consisted of intravenous dextrose and continuation of home medications. NaPA/ NaBz was required during at least 1 hospitalization. The patient recovered to baseline after each hospitalization. Communication with her outpatient metabolic team was generally limited to presentation and verification that the patient was ready for discharge.

At the age of 23 years, the patient had another hyperammonemic episode and was taken to the nearest hospital. She had never been admitted to this hospital, which lacked a metabolic team. The hospital initially contacted the outpatient metabolic team, who recommended dextrose infusion and nitrogen scavengers as well as initiation of dialysis if ammonia levels did not improve after 6 h. Despite repeated requests from the patient's grandmother and clinical decline, no further attempts were made to contact the outpatient metabolic team nor was dialysis started. The inpatient team recommended palliative care as the patient's condition continued to decline. As a result, the patient remained hyperammonemic. Within 2 days, she developed seizures and died.

Table 1
Historical laboratory data.

UCD biomarkers μmol/L (reference range)	Age 17 years	Age 19 years	Age 23 years, before decompensation
Ammonia	25 (13–34)	NA	58 (11−32)
Glutamine	369 (410–700)	657 (371–957)	NA
ASA	570 (≤2)	418 (≤2)	–
Alanine	445 (150–570)	525 (200–579)	–
Citrulline	436 (10–60)	193 (17–46)	–

ASA, argininosuccinic acid; NA, not available; UCD, urea cycle disorder.
Biochemical laboratory test results available for the patient obtained during regular follow-up appointments with the metabolic clinic. No data are available from the time of her diagnosis through early adolescence.

2.5. Barriers to care

The grandmother adhered to the patient's management plan while continuing to navigate numerous barriers to care. As the sole provider for the household, the grandmother continued working at the large company where she had been employed for 25 years. This was only feasible with the availability of home health nursing for 40 h a week. When the patient was 19 years old, coverage for home health nursing was reduced to 20 h a week, forcing the grandmother to quit her job so she could better provide the full-time care the patient required.

When the patient was 18 years old, her grandmother became the full-time caregiver for 3 other grandchildren (first cousins to the patient) while their mother was in prison. The other children were in their early to mid-teens and provided tremendous assistance with caring for the patient until they returned to their mother's care 3 years later.

From ages 16 to 19 years, the patient and her grandmother lived over 365 miles, a 5 h drive, from the nearest metabolic clinic, making it difficult to perform laboratory testing and provide care every 6 months as recommended. Instead, the patient visited annually, utilizing Medicaid transport by airplane as her grandmother was not comfortable transporting the patient 5 h by car. During the COVID-19 pandemic, telehealth became available, allowing for clinical follow-ups every 6 months as recommended. These more frequent appointments helped the family become more comfortable with the metabolic team. However, laboratory follow-ups remained a challenge, and no significant changes were made to care.

Lack of access to inpatient metabolic providers during hyperammonemic crises contributed to the patient's worsening disease and, ultimately, death. During the patient's final hospital stay, the grandmother implored the treating team to contact our metabolic team but was repeatedly dismissed. Furthermore, communication between the treating team and grandmother was poor, as details of the patient's state were not clearly communicated to the grandmother. The grandmother's lack of medical literacy and perceived medical literacy by providers limited her ability to appropriately advocate for the patient with the treatment team.

Access to medications and low-protein foods is a common barrier for patients needing specialty medications, medical formula, and foods. Fortunately, Medicaid paid for the medications and supplements the patient needed. Medicaid did not cover low-protein foods; however, financial assistance was obtained from the National Organization for Rare Disorders to cover the expenses. The metabolic dietitian and social worker made the grandmother aware of this support and helped her gain access.

Although there were no issues with the patient's food security, the grandmother and her other grandchildren experienced severe food

insecurity once the grandmother quit her job to care for the patient full time. Unfortunately, formal custody of the 3 other children was not obtained, so they did not qualify for food stamps. While the metabolic team proactively inquired about the patient's food security, no one considered food security for the rest of the family.

3. Materials and methods

Medical records and clinical parameters were reviewed by the treating clinical team. Informed consent was obtained from our patient's next of kin/legal guardian for publication of this case.

4. Discussion

The circumstances under which people are born and live that impact health outcomes are referred to as SDOH (Fig. 2). As reinforced by this case, SDOH are complex, as are the interactions and feedback loops among them [10]. This case of a Black young adult female highlights the impacts of SDOH, such as racism, food insecurity, community support, home insecurity and safety, and access to care, on health outcomes.

For the first 16 years of the patient's life, her health was negatively impacted by housing insecurity, lack of a safe environment, her mother's substance abuse, and her family's low socioeconomic status. The patient was diagnosed with ASL deficiency during her first hyperammonemic crisis at the age of 6 months and was placed in the care of a metabolic clinic. However, her mother's eventual inability to adhere to the management plan due to her addiction caused the patient to experience numerous decompensations, rendering her unable to communicate or perform activities of daily living. Furthermore, the patient was repeatedly placed in unsafe living conditions while in her mother's care. CPS paid multiple visits to the mother and patient, but it wasn't until the patient was found only in a shirt and a dirty diaper at the age of 15 years that she was moved to foster care. The details of her UCD were not properly communicated to the foster family, nor were they given her necessary medications, causing yet another hospitalization.

Once the patient had secure and safe housing under the care of her grandmother, her care improved dramatically. Her treatment plan was adhered to closely, and she was able to receive therapies that helped her obtain some, albeit minimal, communication. Although her care improved, SDOH-related barriers to care continued to affect the care she received. The patient still lived far from the clinic, food insecurity and access to medications were a concern due to finances, and support services were needed so the grandmother could work outside the home. However, because the patient's grandmother actively pursued care for the patient, the metabolic team, including social workers and dietitians, was able to help the family navigate these barriers and get the patient access to the medications and care she needed through Medicaid and the National Organization for Rare Disorders.

Fig. 2. Social determinants of health underlying health inequality in patients with inborn errors of metabolism.
Conditions under which people are born, grow, live, work, and age that create social stratification and are responsible for health inequities in people with inborn errors of metabolism [10].

Patients with rare diseases and their caregivers are often forced to become experts on their disease and related therapies due to lack of awareness among non-specialist clinicians [18]. This case is no exception. However, because the non-specialists treating the patient did not perceive the grandmother as being medically literate, her attempts to advocate for her granddaughter were repeatedly ignored. While it is impossible to say with certainty the reasons for this, it is possible her socioeconomic status and race may have played a part [14].

Because the grandmother placed all of her resources and energy into caring for her granddaughter, she and the other grandchildren in her care often experienced food insecurity. The grandmother also eventually had to quit her job of more than 25 years in order to provide the around-the-clock care the patient needed when the hours of home health nursing provided by Medicaid were reduced by half. She has shared that since the death of her granddaughter, she has not been able to find employment and the funeral expenses have left her destitute. Caring for patients with a chronic illness impacts the entire family [16]. As such, it is important to consider SDOH impacting the entire family and resources that might help improve the family's life circumstances as well.

5. Conclusions

This case highlights the importance of considering SDOH, family circumstances, and the well-being of caregivers when caring for patients with UCDs. Limited access to care left this patient unable to complete activities of daily living and ultimately proved to be fatal. Furthermore, because of the sacrifices the grandmother made to provide appropriate care for the patient, her own well-being and the well-being of her other grandchildren suffered.

Consent for publication

Informed consent was obtained from the patient's legal guardian for this work.

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Author statement

I the undersigned declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere.

I confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. I further confirm that the order of authors listed in the manuscript has been approved by all involved.

I understand that the Corresponding Author is the sole contact for the Editorial process. He/she is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.

CRediT authorship contribution statement

Markey C. McNutt: Writing – review & editing, Writing – original draft.

Declaration of competing interest

Markey C. McNutt, MD, PhD, has participated in advisory boards and/or received honoraria from Amgen Inc. He has also received consulting fees/honoraria from BioMarin Pharmaceutical, Eton Pharmaceuticals, Acer Therapeutics, Ultragenyx, Applied Therapeutics, Jnana Therapeutics, Alexion, and Chiesi. He has been a site principal investigator for clinical trials sponsored by Aeglea Biotherapeutics, Reneo Pharmaceuticals, PTC Therapeutics, Homology Medicines, Amgen Inc., Arcturus Therapeutics, Jnana Therapeutics, Synlogic Therapeutics, and BioMarin Pharmaceutical.

Data availability

No data was used for the research described in the article.

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