

The Treatment of Urea Cycle Disorder

a report by

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A urea cycle disorder (UCD) is a genetic disease caused by a deficiency in one of six enzymes responsible for removing ammonia from the bloodstream; excess nitrogen (N_2) from protein metabolism causes a build-up of ammonia (NH_3). Children acquire the disorder through either X-linked or recessive genes. One of the disorders, ornithine transcarbamylase (OTC) deficiency, is inherited through an X-linked gene. This disorder is more prevalent in boys because if they inherit the defective X chromosome they will inherit the disease. Girls will inherit a milder form or be an asymptomatic carrier. Other forms of UCD are inherited through recessive genes. A child may receive two recessive genes and inherit the disorder, receive one gene and be asymptomatic, or may receive no recessive genes at all.¹ In a healthy person ammonia is converted into urea and excreted via urine, but in patients with a UCD it is not detected, and therefore not removed as a matter of course, but accumulates unchecked. This build-up will cause hyperammonemia, with which there is then a risk of irreversible brain damage and/or death.²

The six UCDs are: carbamyl phosphate synthetase (CPS), N-acetylglutamate synthetase (NAGS), OTC, argininosuccinic acid synthetase (citrullinemia) (AS), argininosuccinase acid lyase (AL/ASA) (argininosuccinic aciduria), arginase (AG) and all refer to the particular defective, or missing, enzyme. Not all UCDs present at birth and children with a milder form of disorder may present with symptoms later. This temporary asymptomatic state might be because of the rapid growth of their bodies, the ability to 'tolerate higher levels of protein without becoming ill'.³ This ability can diminish as the growth rate slows and so a UCD may present. Symptoms in an infant can include avoidance of high-protein foods, irritability, hyperactive behavior, and episodes of vomiting. In a newborn, they can include refusal to eat, listlessness, difficult to wake, hyperventilation, and eventually a coma. Those with a severe disorder will present with these 24–72 hours after birth. However, often physicians can mistake these symptoms for newborn sepsis and will treat with antibiotics.⁴ Currently, there is no cure for UCDs and treatment is a combination of gene therapy treatment, diet regulation, and supplementation. In addition, there is frequent

monitoring by blood tests throughout the patient's life. Treatment for acute hyperammonemia is hemodialysis and the administration of combined sodium phenylacetate and sodium benzoate (Ammonul®).

Hyperammonemia

Hyperammonemia can occur in patients already diagnosed with UCD, often triggered by viral infections, accidents, or even exhaustion. However, a hyperammonemic episode may be the first obvious signal of childhood- or late-onset UCD. A prompt diagnosis of a UCD is necessary to reduce the harm to the body, to treat absence of protein and to rid the body of the toxic NH_3 . George Diaz, Principal Investigator at the Mount Sinai School of Medicine and head of one of the Urea Cycle Disorder Consortium (UCDC) academic centers dedicated to urea cycle research and treatment, explains how common hyperammonemia is: "Typically it is the key presenting symptom, present in all patients." However, in patients already diagnosed and being treated for a UCD it is a little more complicated. He continues, "There are variables that include intrinsic factors, such as which specific disease the patient has (the more proximal disorders (OTC and CPS) are more difficult to manage than the more distal disorders, when some of the NH_3 has been detoxified), and the severity of the mutations (mild mutations should be easier than severe ones to control); and the extrinsic factors, such as how well a patient complies with diet and tolerates the medication and the exposure to catabolic stresses (intercurrent illness e.g. chicken pox, colds and flu)."

Treatment for a UCD

Day-to-day treatment for a UCD is a combination of a protein-monitored diet, additional supplementation and a course of medication. Protein monitoring, rather than prohibiting, is advised because disproportionate protein will trigger excessive NH_3 production, which is fatal, while insufficient protein will mean catabolism occurs and this too can cause production of excess NH_3 .⁵ A dietary balance needs to be identified for each patient, and needs to be

adjusted in accordance with the patient's growth. The diet will be heavily supplemented; with multivitamins and calcium, as well as specific formulas of amino acids (cyclinex, UCD I and II) developed for use in UCDs. These can be prescribed in order to provide up to 50% of the patient's daily protein allowance. In addition, some patients may require individual branched chain amino acid supplements. Patients will also have a metabolic nutritionist, to prescribe calorie modules (Prophree, Polycose and ModuCal) to be used in combination with the amino acid formulas. For OTC and CPS deficiencies, pharmaceutical grade L-citrulline (or L-arginine free base for ASA and cirrullinemia) will also be required. The medications, 'ammonia scavengers', sodium phenylbutyrate (Buphenyl®) used with sodium benzoate, provide an alternate pathway for excretion of NH_3 . These drugs are administered three to four times a day to insure continual removal of the toxic NH_3 .⁵

Treatment for Acute Hyperammonemia

Hyperammonemic episodes can be recognized quite quickly in patients already diagnosed with a UCD, as the patient's family are vigilant to the signs and symptoms. It can be difficult to recognize in an infant yet to be diagnosed, because the common symptoms (lethargy and reluctance to feed properly) can often be attributed to a 'difficult' baby and are not necessarily picked up "until the baby has progressed to the point of non-responsiveness", Dr Diaz informs. Hemodialysis is the first line of treatment, because it is the most efficient way to lower NH_3 , and should be initiated as soon as possible. Dr Diaz explains how the drugs perform the role: "In the absence of a functional urea cycle, phenylbutyrate metabolizes into phenylacetate, phenylacetate and benzoate conjugate with glycine and hippurate, respectively, and are excreted via the kidney to remove a net of three ammonia nitrogens. It will excrete more moles of nitrogen than just oral therapy alone. However, in cases of acute hyperammonemia (where the patient has signs of neurological compromise or is obtunded), speed is very much of the essence to detoxify the NH_3 , and so readily available medications proved effective at lowering the levels of NH_3 and can be administered while the dialysis is being prepared." Once hemodialysis is set up, ammonia scavengers can be administered as an adjunctive course.

The adjunctive therapy is administered as a loading dose with 250mg/kg each of sodium phenylacetate and benzoate and 600mg/kg of arginine hydrochloride 10% in solution, in 25–35ml/kg of 10% dextrose in water over 90 minutes. The same dose can be administered as a maintenance infusion over 24 hours. Up to 500mg/kg

sodium phenylacetate/benzoate (loading dose and the maintenance infusion) may be given during the first 24 hours. It is strongly recommended that management of the hyperammonemia be in conjunction with a specialist in metabolic diseases.⁶

The evidence for efficacy of the adjunctive therapy sodium phenylacetate/sodium benzoate was first reported by Brunsilow in 1984.⁷ However, there are no good published clinical trials because the number of patients is too few and clinical efficacy in practice makes using a placebo unethical. Ucylyd Pharma (manufacturers of Ammonul) gathered mortality data from numerous sites where the drug was used as an investigational agent, and in 2005 presented to the US Food and Drug Administration (FDA) to obtain approval. Long-term outcome data is currently being investigated (National Institutes of Health (NIH)-sponsored, multicenter longitudinal study by the UCDC of the Rare Diseases Clinical Research Network.⁸

Adverse side effects to the treatment include hypokalemia as well as nausea and vomiting, which can occur during the infusion. There are often neurological signs, with tingling in the extremities and sometimes confusion and changes in mental status. Loss of appetite, mood changes, and muscle pains or cramps are also side effects of the drug. As the loss of appetite can be dangerous for the patient—it poses a risk of excessive production of NH_3 from catabolism—children may benefit from receiving the medications via a gastrostomy (G) or nasogastric (NG) tube. Insertion of a tube can make a crucial difference in the patient's metabolic stability, which in turn can help avert a hyperammonemic crisis. Some centers report a 70% reduction in hospitalisation after the placement of G-tubes or when parents were trained to use an NG-tube.⁵

Detection

A newborn can be born with a UCD, and if it is not diagnosed and treated immediately there is a high risk of fatality. Measures are under way to try and reduce this, along with further treatment research into UCDs themselves. One option is screening, ideally to identify before the child is born whether they have a UCD and thus there would be treatment on hand immediately at birth. But this is difficult, as Dr Diaz explains: "In terms of screening it is difficult because it is new-onset mutations, or these are generally recessive disorders, and so two parents will be carriers and the only way to really know [prior to the birth] is to identify carrier parents to identify if pregnancies are at risk. *In utero* the babies are protected by the placental clearance of toxic compounds, and so they

are born healthy. It is difficult to screen while the infant is *in utero* unless you are looking for specific enzyme activity, and this is not really feasible for widespread screening. A few of the disorders will generate metabolites newborn screening may be able to pick up, via tandem mass spectrometry, and in fact a few infants have been detected with UCDS, but this is only relevant to the late-onset disorders. For the more proximal and serious disorders there are really no good markers and so newborn screening methods have not been helpful in this regard.”

The Future

Regarding the unmet needs for UCD treatment, Dr Diaz comments: “In my opinion, the major issue is to find a way to more effectively prevent neurological damage in infants presenting with acute hyperammonemia. Current treatment strategies have reduced mortality, but neurological morbidity remains significant. Even if long-term corrective treatments such as gene therapy can be made feasible, the benefits will not be as great as if we can provide more satisfactory neurological outcomes.” ■

References

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