Cystathionine Beta Synthase Deficient – Homocystinuria (HCU) –
Patient-led Listening Session
Executive Summary

June 26, 2020

Overview of Homocystinuria

Cystathionine Beta Synthase, better known as classical Homocystinuria (HCU), is an inborn error of metabolism caused by a defect in the Cystathionine beta synthase enzyme that metabolizes homocysteine, which can cause high methionine levels and a dangerous buildup of homocysteine. Homocystinuria affects approximately 1 in 200,000 in the US (estimated number of diagnosed approximately 1,650), but the incidence rate is likely even higher as the newborn screening test misses up to 50% of cases. Extended periods of high homocysteine levels result in cognitive and developmental delays, osteoporosis, lens dislocation, thrombosis and strokes.

Current treatment for HCU breaks down into two categories: Pyridoxine responsive and non-pyridoxine responsive. Patients who are pyridoxine responsive often only need B6 supplements, but those deemed non-pyridoxine responsive require strict low protein diet along with amino acid supplements, and often betaine, folic acid and B12. Compliance with the diet is often poor, and lessens with age, particularly in adolescents. The goals of treatment also depend on what type of classical HCU a patient has. For patients with B6 responsive HCU, the goal of total homocysteine (HCY) is 50 uM, where for B6 non-responsive patients the target total HCY of 100 uM (given that it is much harder for non-responsive patients to achieve lower levels, and the protein restriction that would be required can cause low BMD). At the 2019 SSIEM Conference, an abstract was presented on the Natural History Study (NHS) for

Classical HCU that is currently underway. The abstract showed poor control and prevalence of clinical issues for many treated patients. Some key facts from the current study include:

- Even in the high-quality medical centers participating in the NHS, 45 % of pediatric patients and 77% of adults had HCY levels greater than the goal of 100 uM at enrollment in the study
- 69% of enrolled patients had ocular deficits, primarily myopia (63%) and ectopic lenses (15%). HCY levels were negatively correlated with overall cognition (total cognition composite at 20th percentile), especially fluid cognition and executive function
- Low BMD is believed to be associated with low protein diet, as a positive correlation was shown between BMD and total protein dietary intake

On June 26, 2020 a group of four HCU patients and caregivers, along with HCU Network America's President (who lost 2 sisters to HCU), and a metabolic geneticist (lead author on the Guidelines for Diagnosis and Management of Cystathionine Beta-Synthase Deficiency) addressed the Food and Drug Administration (FDA). The group provided personal and emotional first-hand testimony of what it is like living and caring for someone with this rare and sometimes fatal disease.

The main topics discussed during the listening session were:

- Communicate struggles patients face with current treatments
- Share how HCU directly affects our health and daily lives
- Convey how important a new therapy is that can reduce dietary restrictions

HCU Meeting Participants:

- Margie McGlynn – President of HCU Network America, two late sisters with HCU

- Kim Chapman – MD, Children's National, Washington DC, treats patients with HCU and other genetic disorders

- Danae' Bartke – Executive Director of HCU Network America, HCU patient

- Justin Skeens – Father of 13 year old son with HCU

- Gabbi Lewis – 18 year old HCU patient

- Mark Lewis – Vice President of HCU Network America, father of two classical HCU patients – ages 29 and 18 (Gabbi).

FDA Divisions Represented

- Office of the Commissioner (OC)
    - Patient Affairs Staff
    - Office of Orphan Products Development
    - Office of Pediatric Therapeutics
- Center for Drug Evaluation & Research (CDER)
    - Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine; Division of Rare Diseases and Medical Genetics
- Center for Biologics Evaluation & Research (CBER)
    - Office of the Center Director
- Center for Devices & Radiological Health (CDRH)
    - Office of Ophthalmic, Anesthesia, Respiratory, ENT and Dental Devices, Office of Product Evaluation and Quality,
    - Office of Cardiovascular Devices
- Center for Food Safety and Nutrition (CFSAN)

Non-FDA Attendees:

- Reagan-Udall Foundation for the FDA
- NIH/NCATS

Summary of topics discussed

1. **Daily Life with HCU**

   Daily life with Homocystinuria involves the highly restrictive, tedious and time consuming management of protein intake.

   - The only available means of controlling HCY levels in a pyridoxine nonresponsive HCU patient is by a highly restrictive low protein diet along with a medical formula. The typical diet for a person with HCU limits the overall protein intake to an average of 5-15 grams of whole protein a day. (This will limit the intake of methionine, which is converted to homocysteine so must be restricted to lower homocysteine.) The diet excludes foods that contain moderate to high amounts of protein. As such, the diet does not allow for meat or dairy (with the exception of butter) and allows for limited amounts of grains in some cases, but even fruits and vegetables have to be carefully weighed and considered. As an example, one serving of Greek yogurt (approx. 20 g. of protein per serving) would exceed a full day's allowance of protein for the typical HCU patient. For those with HCU, there are no free passes with the low protein diet.
   - Patients prescribed a low protein diet also need to balance it with the intake of a medical formula. Medical formula is a prescribed essential amino acids blend (less methionine). These formulas come from a short list of companies in a variety of packaging forms including sachets of powder, cans of powder, coolers, juice boxes, gels and pills. Unfortunately, regardless of preparation or presentation, the taste of these products is unpalatable.
   - Because the diet is so restrictive, HCU patients also need to take a plethora of supplements to make sure they are getting appropriate micronutrients. Many patients also take B6, B12, Folic acid, Calcium, and Vitamin D. Many patients also take Cystadane (generic is Betaine Anhydrous), which helps convert HCY back to methionine, and a blood thinner to prevent clotting.

   During the FDA listening session, HCU patients spoke directly about their individual challenges with the diet, including how they often don't want to take their formula because it leaves them too full to eat the actual food they enjoy.

   > "I would like a formula that doesn't taste like licking the bottom of an old gym shoe" – Anonymous

   - Patients admit to skipping their medical formula 1-3 times a week. The primary reason for struggling and skipping is because of the off-putting taste, followed by inconvenience of having the formula when needed, and the significant volume they are required to ingest throughout a given day. Unfortunately, when a HCU patient reduces or even skips their medical formula, their bodies are essentially starved for protein and then start to break down muscle, which can further dangerously elevate homocysteine levels.

   - The low protein diet, formula and supplements can make regular occurrences such as birthday parties and family gatherings extremely challenging. In a typical day, HCU patients attempt to spread their daily protein, medical formula and supplements evenly

throughout the day with the goal to sustain a consistent HCY level. However, when an HCU patient is confronted with an atypical food event such as a social gathering where food is involved or an unplanned food event, this can easily upset this delicate balance. In order to offset these events, some HCU patients will resort to eating in advance to avoid the need to eat at said gathering, others will bring a few dishes they know they can eat safely. A more common option for many HCU patients is to adjust their protein intake around on the given day, e.g. by significantly reducing (or eliminating) protein intake prior to the event. This approach allows the patient to have the majority of their daily protein intake to be consumed during the said event. This means that they would take their formula and Cystadane without food or with very low protein content food (which most dietitians would advise against). Even in this case HCU patients inevitably exceed their daily protein goal. An example of this an HCU patient shared was the situation of a birthday party where cake and pizza was served. In preparation, the patient will only have the medical formula for breakfast and lunch. At the party the HCU patient would consume 2 slices of pizza (with the cheese removed) and a small corner slice of cake (mostly frosting). On a typical day, this patient's allowance is 9 g of protein, but at the party with just those 2 slices of cheese-less pizza and small birthday cake, they have consumed 13.2 g of protein.

2. **Overall Health**

Homocystinuria patients and caregivers have a wide variety of worries and concerns outside of the detrimental impact associated with the disease**.**

- When children are diagnosed, parents quickly start to think about the "typical" things their children may never get to experience – for example, will HCU impact my child's ability to have a family of their own.

- Parents and caregivers worry about the long term affects the low protein diet, formula and medications may have on their child or themselves. Additionally, many of the concerns center on long-term challenges of the diet and medical formula as the diet is impractical, time consuming, and does not lend itself to flexibility.

- Even when patients are committed to be adherent to diet, cost can be an obstacle. Low protein foods on average are 2-5 times more expensive than their grocery store counterparts and often are not covered by insurance companies. The meeting participants shared a number of examples including a 17.5 oz bag of low protein pasta that costs $11.49, while a 16 oz. box of supermarket pasta cost about $1.18. A loaf of low protein bread can cost $13.99, where as a typical supermarket loaf of bread costs about $1.68.

- In addition, the HCU patients also shared that they don't know their HCY levels during any given day (typically only measured once every few months), leaving the HCU patients unaware of their levels as they navigate compliance to the diet (including food and medical formula intake).

- The future also holds many concerns for HCU patients and caregivers. Parents and patients, once diagnosed with HCU and determined to be pyridoxine responsive or unresponsive, are

then given instructions on their treatment plan and how to maintain the low protein diet and administer formula if needed. This introduces many complications into their lives.

- Lastly, after we process how the diet may affect our long-term health, many patients and parents are also concerned about the unknown long-term health implications of HCU. One participant shared the story of how she lost 2 sisters to HCU, one at the age of 14 due to a stroke, and one at age 9 due to a pulmonary embolism. Recently, an 8-year-old boy with HCU who was missed by newborn screening but diagnosed later due to clinical issues died on how way home from a baseball game of a blood clot. Now because of improved newborn screening, professional awareness and patient education and improved dietary management, HCU patients who are diagnosed early are living longer, but there is little data on HCU at an older age as patients used to have a significantly shortened life span. Therefore, whether you are a parent of a newborn, or an older adult with Homocystinuria, patients and parents have many concerns.

3. Impact on family, relationships, school and work

The impact of HCU on family, relationships, school and work has affected each patient and caregiver differently, but one theme that echoed across all stories is how isolating the diagnosis makes the patient and their family feel. Homocystinuria is isolating because most people have not heard of it nor do they comprehend the metabolic complexities of the disease. Rarely do others take the time to understand the disease and what it takes to manage it. Homocystinuria is also isolating because the strict dietary restrictions often leave patients feeling left out and unwelcome, or like a burden. Many patients with poor control of HCU also suffer from cognitive defects or behavioral issues caused by HCU, which can also impact their ability to be successful in school or with jobs and can impact personal relationships.

The HCU patients also shared the sacrifices and challenges faced when a child within a family is diagnosed with HCU. This involves a significant change in the routines and lifestyle for the entire family. Parents of a HCU child devote themselves to giving their child the most “normal” life they could possibly have. This means administering care, and often making two meals – one for the child, one for the rest of the family. It means no longer going to your favorite restaurant because there isn’t anything for their child or loved one to eat. For some, the challenges of life with HCU means having to quit a job or take extended time away from work or school to attend to routine lab work, doctor appointments, surgeries and hospitalizations. The amount of sacrifice also compounds the isolation, because it’s hard finding others who can relate to the complexities associated with the disease (including in the healthcare community).

4. What would a new therapy mean for you?

A new therapy would mean a better quality of life, one with less worry and complications in daily life due to the treatment plan. As noted earlier, HCU takes careful planning – and even that doesn’t eliminate the many obstacles with the current therapy. Being able to eliminate or lessen the restrictiveness of the diet would mean patients can do “normal” things, like go out to eat

and attend social gatherings that center around food without worry. Avoiding the restriction may enable patients to not have to take the unpalatable and inconvenient medical formula to supplement amino acids, and to avoid the consequences of low protein diet like osteoporosis. Less worry also means also not having to think about the implications that high homocysteine levels may have on the body with anxiety, depression, cognitive deficit, ophthalmic issues, blood clots and strokes– something that is always in the back of a patient's and parent's mind. The availability of an effective therapy could also enable a lower HCY goal to be reached safety for patient which may have health benefits. In summary, the quality of life for patients and their families could change dramatically if an effective, safe and convenient therapy were available for HCU.

Partner organization

HCU Network America is a registered 501c3 non-profit organization dedicated to helping patients and their families affected by Homocystinuria (HCU), Methylenetetrahydrofolate reductase (MTHFR) and select cobalamin deficiencies.

HCU Network America's mission is to inform and provide resources for patients and families, create connections and support advancement of diagnosis and treatment for HCU and related disorders.

Disclaimer

Discussions in FDA Rare Disease Listening Sessions are informal. All opinions, recommendations, and proposals are unofficial and nonbinding on FDA and all other participants. This report reflects the HCU Network America's account of the perspectives of patients and caregivers who participated in the Rare Disease Listening Session with the FDA. To the extent possible, the terms used in this summary to describe specific manifestations of Classical Homocystinuria, health effects and impacts, and treatment experiences, reflect those of the participants. This report is not meant to be representative of the views and experiences of the entire Classical Homocystinuria, patient population or any specific group of individuals or entities. There may be experiences that are not mentioned in this report.