Dietary Considerations for Infantile Nephropathic Cystinosis

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Infantile nephropathic cystinosis is a very rare and serious genetic disorder that manifests in infants, usually before their first birthday; it affects 500-600 children in the United States with approximately 20 new cases each year (Nesterova & Gahl, 2012). Feeding and hydration issues abound in these children so proper nutrition is critical for survival. While it is known that a nutritious diet, one that is rooted in fresh, whole foods can have a positive impact on one's health; there is very little information regarding an appropriate and supportive diet for this population. This paper proposes a whole foods diet approach that will make optimal nutrition obtainable for those living with cystinosis.

Cystinosis is an autosomal recessive inborn error of metabolism caused by a mutation of the *CTNS* gene (Gahl & Nesterova, 2010) (Gahl, Thoene, & Schneider, 2002) (Nesterova & Gahl, 2013) (Wilmer, Emma, & Levtchenko, 2010). The *CTNS* gene encodes for the protein cystinosin, a lysosomal membrane protein and cystine transporter (Elenberg, 2013) (Kalatzis, Cherqui, Antignac, & Gasnier, 2001). In the lysosome, cystinosin oxidizes cysteine into cystine. In healthy individuals cystine can leave the cells and enter the cytoplasm where it is rapidly converted into free cysteine by reducing agents, mainly glutathione (Kalatzis,et al., 2001) (Wilmer, et al., 2010). However, in cystinosis patients, the lysosomes of cells cannot transport cystine out of the cell and because cystine has low solubility, it will form crystals in various cell types thus damaging vital organs, namely the kidneys and eyes (Elenberg, 2013) (Gahl & Nesterova, 2010) (Kalatzis et al., 2001) (The National Organization for Rare Disorders [NORD], 2011).

A major complication of cystinosis is renal tubular Fanconi syndrome, the failure of proximal tubular epithelial cells ability to reabsorb nutrients and minerals (Gahl & Nesterova, 2010) (Fathallah-Shaykh, 2013) (Wilmer, et al., 2005) (Wilmer, et al., 2010). Symptoms include

polyuria, polydipsia, dehydration, and acidosis due to the loss of excessive amounts of solutes in the urine, accompanied by the loss of water (Fathallah-Shaykh, 2013) (Nesterova & Gahl, 2012) (Wilmer, Emma, & Levtchenko, 2010). Other complications include failure to thrive, rickets, muscle weakness, hypokalemia, progressive glomerular failure, and ultimately end stage renal disease (ESRD). If cystinosis is left untreated, it is not uncommon to see renal failure in these children before they reach ten years of age (Gahl & Nesterova, 2010) ([NORD], 2011) (Wilmer, et al., 2010).

Current Treatment

Currently, there is no cure for cystinosis or the resulting Fanconi syndrome. The only treatment is for patients to take the cystine depleting medication cysteamine bitartrate (trade name Cystagon) (Bouazza, et al., 2011) (Gahl & Nesterova, 2010) (Nesterova & Gahl, 2012) (Wilmer, et al., 2011). Early and disciplined cysteamine therapy has dramatically improved the prognosis for those with the disease by enhancing growth and staving off inevitable kidney transplantation, sometimes into the second or third decade of life (Gahl, et al., 2002) ([NORD], 2011) (Nesterova & Gahl, 2012) (Wilmer, et al., 2010). The drug is not without issues as it has an off-putting odor and taste, can cause gastro-intestinal distress, and dosing is strict (every 6 hours), and lifelong (Gahl & Nesterova, 2010) (Nesterova & Gahl, 2012). Earlier this year, the FDA approved Procysbi (cysteamine bitartrate) delayed release capsules that provide consistent cystine depletion over a full 12-hour dosing period (FDA Approves Procysbi, 2013). Hopefully, this new version of cysteamine bitartrate will provide some relief from the previous rigid dosing schedule.

Dietary recommendations address replacing the excessive urinary losses of amino acids, glucose, phosphate, calcium, magnesium, sodium, potassium, carnitine, bicarbonate, and water

via supplementation and enteral feeding (Gahl, et al., 2002) (Nesterova & Gahl, 2012). Unrestricted access to water and salt is strongly encouraged as these children will have extreme thirst and crave salt, usually in the form of the "four P's" pizza, pickles, pretzels, and potato chips (Gahl, et al., 2002) (Nesterova & Gahl, 2012). While these foods may be considered "kid friendly", there is a cause for concern as they are not nutrient dense and are high on the glycemic index. Foods with a high glycemic index, like pretzels, are rapidly digested and can cause substantial fluctuations in blood sugar. Furthermore, a diet based primarily on high glycemic items such as processed foods has been proposed to be a contributing factor toward developing type II diabetes and heart disease (Gropper & Smith, 2013, pp. 77-79). While the sodium issue might be addressed by letting the child have these foods, a whole world of vital nutrients will be missed.

The cystinosis page on Medscape's website suggests the following recommendations; they are somewhat vague and could apply to almost any metabolic condition:

> "Dietary recommendations should follow daily Dietary Reference Intake (DRI) requirements (ie, 60% carbohydrate, 10% protein, 30% lipids), and caloric intake should aim to achieve weight gain. When the patient becomes free of acute GI symptoms (ie, no longer having frequent episodes of vomiting, gagging, abdominal pain, or diarrhea) and is able to eat well, restart the patient on a regular diet, supplementing individually determined amounts of sodium, potassium, bicarbonate, and phosphate to achieve reference range serum levels" (Elenberg, 2013).

These children do not make saliva in a normal fashion so chewing and swallowing can be problematic and dysphagia is always a consideration (Gahl, et al., 2002). Still, oral intake is

strongly encouraged so as not to lose the ability to chew and swallow (Cystinosis Research Network [CRN], 2012) (Gahl & Nesterova, 2010) (Gahl, et al., 2002). However, it is possible that some suffer from myopathy and will lose function of their oropharyngeal muscles making aspiration a dire complication (Nesterova & Gahl, 2013). In these extreme cases, tube feeds might be the only option.

A majority of infants and toddlers with cystinosis are fed via a feeding tube, either G or J due to the reflux, nausea, and vomiting that can occur as side effects of the cysteamine therapy (Cystinosis Research Network [CRN], 2011) (Gahl & Nesterova, 2010) (Elenberg, 2013). Early weaning from tube feeding is encouraged and is possible with good adherence to cysteamine therapy (Nesterova & Gahl, 2013). EleCare Jr is one example of a commercial formula and per their website, their products are amino acid based, allergen free, and supply complete nutrition. Unfortunately, like most commercial feedings EleCare Jr contains some less than desirable ingredients. A review of the EleCare Jr ingredient label revealed corn syrup solids as the first ingredient and even more concerning, the vanilla flavor contains the following artificial sweeteners, acesulfame K, aspartame, and sucralose (http://elecare.com/child-food-allergy-formula). These chemical additives are not easily processed by the digestive system and can cause gastrointestinal upset. They are not supportive of optimal health in anyone, especially children, regardless of health status (Mullin & Swift, 2011).

Many additional medications are used in the treatment of cystinosis as well; proton pump inhibitors (PPIs) are frequently used due to the hypercholhydia caused by the cysteamine therapy ([CRN], 2012). This is unfortunate as there has been interesting research regarding the havoc these drugs can wreak on proper nutrient digestion and absorption and how long term use can contribute to C. difficile infection (Nesterova & Gahl, 2012) (Yang & Metz, 2011). PPIs have

been shown to contribute to deficiencies in iron, vitamin B-12, magnesium and calcium thus affecting the health of blood and bones (Mullin & Swift, 2011, p. 63).

One Day, Whole Food Diet Approach

One of the main concerns is that these children are in extreme need of massive hydration and electrolyte replacement. I do not believe there is any one nutrient that would be of most benefit to focus on solely therefore I am suggesting a synergistic approach, focusing on making every precious bite as nutrient dense as possible. I was fortunate enough to learn of one cystinosis patient where this approach has been successful. Since making a conscious effort to incorporate fresh, seasonal, and unprocessed foods into his diet, this young man has noticed better health and an increase in energy. He has learned how to successfully deal with his nausea by eating his meals around the same time as taking his medications. He is fortunate to have no trouble chewing and only minor issues with swallowing. He credits this to eating well as a child and not requiring a feeding tube. He does take supplemental doses of Vitamins, C, D, and a B complex (A. Hoffmann, Personal communication, October 23, 2013).

Children living with cystinosis are encouraged to drink plenty of water; this can lead to a feeling of fullness that might leave little room for food. Because of this fact, every ounce of fluid taken in should be of the upmost quality, nutritionally speaking. This can be accomplished by encouraging the intake of freshly juiced fruits and vegetables which are excellent sources of vitamin C. Vitamin C is necessary for carnitine and collagen production as well as bone health (Gropper & Smith, 2013). Coconut water is an excellent source of potassium; homemade bone broths are rich in minerals such as calcium, magnesium, and phosphorus. Soups made with fermented miso can also be nourishing and will have the extra benefit of being salty. Any of

these foods can be thickened appropriately if there are swallowing issues that need to be addressed.

In the diet there should also be a focus on whole, intact grains that are rich in B vitamins for proper breakdown of glucose, fiber for bowel health, and protein for growth and development (Gropper & Smith, 2013). Quinoa, a high energy and versatile protein packed grain, actually has more calcium than milk and is loaded with other vitamins and minerals (Katz & Edelson, 2008). Adding ginger to foods and sipping on ginger teas can help relieve nausea and stimulate gastric motility (Katz & Edelson, 2008) (Mullin & Swift, 2011). Energy levels may be increased with the addition of coconut oil, rich in easily absorbed medium chain fatty acids (MCFAs) (Jacob, 2013).

Meals for a Day

Breakfast:
Steel Cut Oats with Fruit Compote (Katz & Edelson, 2008, p. 116)
Poached Egg
Fresh Fruit/Vegetable Juice

Lunch:
Hearty Miso Soup with Quinoa (Floyd & Barry, 2012, p. 162)
Vegetable Sticks and Avocado Cream (Katz & Edelson, 2008, p. 115)

Dinner:
Light and Crispy Chicken Bites (Floyd & Barry, 2012, p. 183)
Mashed Ginger Sweet Potatoes with Fresh Nutmeg (Katz & Edelson, 2008, p. 72)
Sautéed Summer Squash

Desserts and snacks:
Creamy Banana and Coconut Shake (Katz & Edelson, 2008, p. 98)
Mango Coconut Ice Pops (Floyd, 2011, p. 179)
Homemade Ginger Ale with Grape Cubes (Katz & Edelson, 2008, p. 94)
Inside Tract Smoothie (Mullin & Swift, 2011, p. 287)

Beverages:
Coconut water
Kombucha
"Recharge" by Knudsen brand (a commercial product superior to other sports drinks)
Herbal teas such as peppermint or turmeric
Mint Lemonade (Floyd, Eat Naked, 2011, p. 171)
"Homemade Ensure Substitute" (R. Snow, Personal Communication, September, 2012)

Conclusion

All disease stems from some type of cellular dysfunction and while there is no cure for cystinosis at this time, it has become a much more manageable condition due to responsible cystine depleting therapy. While the current information regarding diet relies heavily on commercial supplementation; there needs to be room at the table for a solid supportive nutrition plan, one based on wholesome foods. Starting these healthy habits early would be of great benefit to these children and would continue to support them as they grow into adulthood.

References:

FDA Approves Procysbi. (2013, April 30). Retrieved October 6, 2013, from Drugs.com: http://www.drugs.com/newdrugs/fda-approves-procysbi-nephropathic-cystinosis-3772.html

Bouazza, N., Tre'luyer, J., Ottolenghi, C., Urien, S., Deshenes, G., Ricquier, D., & Chadefaux-Vekemans, B. (2011). Population pharmacokinetics and pharmacodynamics of cysteamine in nephropathic cystinosis patients. *Orphanet Journal of Rare Diseases, 6*(86), 1-8. Retrieved from http://www.ojrd.com/content/6/1/86

Cystinosis Research Network [CRN]. (2011). *Living With Cystinosis: Survey Results.* Survey, CRN. Retrieved October 14, 2013

Cystinosis Research Network [CRN]. (2012, October). *Cystinosis Parent Handbook.* Retrieved September 20, 2013, from Cystinosis Research Network: https://cystinosis.org/images/research/article-library/overview/CRN_Parent.pdf

Elenberg, E. (2013, May 13). *Cystinosis.* (C. B. Langman, Ed.) Retrieved October 6, 2013, from Medscape: http://emedicine.medscape.com/article/981650-overview

Fathallah-Shaykh, S. (2013, April 16). *Fanconi Syndrome*. (C. B. Langman, Editor) Retrieved October 8, 2013, from Medscape: http://emedicine.medscape.com/article/981774-overview

Floyd, M. (2011). *Eat Naked.* Oakland, California: New Harbinger Publications, Inc. Retrieved October 16, 2013

Floyd, M., & Barry, J. (2012). *The Naked Foods Cookbook.* Oakland, California: New Harbinger, Inc. Retrieved October 21, 2013

Gahl, W. A., & Nesterova, G. (2010). Cystinosis-The post-transplant era. *European Nephrology, 4*, 55-61.

Gahl, W. A., Thoene, J. G., & Schneider, J. (2002, July 11). Cystinosis. *New England Journal of Medicine, 347*(2), 111-121. Retrieved from www.nejm.org

Gropper, S., & Smith, J. (2013). *Advanced Nutrition and Human Metabolism* (6th ed.). Belmont, California: Wadsworth.

Jacob, A. (2013, October). Coconut oil: Learn more about this superfood that contains healthful saturated fats. *Today's Dietitian, 15*(10), pp. 56-60. Retrieved October 7, 2013

Kalatzis, V., Cherqui, S., Antignac, C., & Gasnier, B. (2001). Cystinosin, the protein defective in cystinosis, is a H+ -driven lysosomal cystine transporter. *The European Molecular Biology Organization Journal, 20*(21), 5940-5949.

Katz, R., & Edelson, M. (2008). *One Bite at a Time:Nourishing Recipes for Cancer Survivors and Their Friends* (2nd ed.). New York, New York: Random House, Inc. Retrieved October 21, 2013

Mullin, G., & Swift, K. M. (2011). *The Inside Tract: Your Good Gut Guide to Great Digestive Health.* New York, New York, United States of America: Rodale. Retrieved September 2013

Nesterova, G., & Gahl, W. (2013). Cystinosis: The evolution of a treatable disease. *Pediatric Nephrology, 28*, 51-59. doi:10.1007/s00467-012-2242-5

Nesterova, G., & Gahl, W. A. (2012, June). *Infantile Nephropathic Cystinosis Standards of Care*. Retrieved September 18, 2013, from Cystinosis Research Network: https://cystinosis.org/images/family-support/resources/CRN_Standards_12pgloRes.pdf

The National Organization for Rare Disorders [NORD]. (2011). *Rare Disease Database.* Retrieved September 30, 2013, from NORD: http://www.rarediseases.org/rare-disease-information/rare-diseases/byID/59/viewAbstract

Wilmer, M. J., de Graaf-Hess, A., Blom, H. J., Dijkman, H., Monnens, L. A., van den Heuvel, L. P., & Levtchenko, E. N. (2005). Elevated oxidized glutathione in cystinotic proximal tubular epithelial cells. *Biochemical and Biophysical Research Communications, 337*(2), 610-614. doi:10.1016/j.bbrc.2005.09.094

Wilmer, M. J., Emma, F., & Levtchenko, E. N. (2010, September 8). The pathogenesis of cystinosis: Mechanisms beyond cystine accumulation. *American Journal of Physiology-Renal Physiology, 299*, F905-F916. doi:10.1152/ajprenal.00318.2010

Wilmer, M. J., Kluijtmans, L. A., van der Velden, T. J., Willems, P. H., Scheffer, P. G., Masereeuw, R., & ...Levtchenko, E. N. (2011). Cysteamine restores glutathione redox status in cultured cystinotic proximal tubular epithelial cells. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease, 1812*, 643-651. doi:10.1016/j.bbadis.2011.02.010

Yang, Y.-X., & Metz, D. C. (2011, October). Safety of proton pump inhibitor exposure. *Gastroenterology, 139*(4), 1115-1127. doi:10.1053/j.gastro.2010.08.023