

GENE THERAPY STUDIES FOR CYSTINOSIS

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The lysosomal cystine accumulation that characterises cystinosis arises from mutations in *CTNS*, the gene encoding cystinosin, the lysosomal cystine transporter. Currently, cystine levels are reduced by the drug cysteamine. Cysteamine freely enters lysosomes and cleaves cystine into cysteine and a cysteine-mixed disulphide, both of which can exit the lysosome using transporters other than cystinosin. Cysteamine treatment has dramatically improved the life of cystinosis patients. However, due to its physical constraints and side effects, we are exploring the possibility of viral-mediated *CTNS* gene therapy as an alternative or complementary treatment. Gene therapy treats the cause of a disease rather than the symptoms by re-introducing the absent (or defective) gene into the body. The *in vivo* model for our studies is cystinosin-deficient (*Ctns*^{-/-}) mice.

We generated *CTNS*-expressing adenovirus vectors and tested their ability to reduce cystine levels *in vitro* from i) human *CTNS*^{-/-} fibroblast cell lines and ii) primary hepatocyte cultures from *Ctns*^{-/-} mice. Firstly, we obtained a 5-fold reduction in cystine levels following gene transfer into *CTNS*^{-/-} fibroblasts as compared to control cells. Secondly, we obtained a 5-fold cystine reduction (to wildtype levels) following gene transfer in hepatocytes from 3 month-old *Ctns*^{-/-} mice as compared to control cells. In contrast, we obtained a smaller reduction (2-fold) in cystine levels in hepatocytes from 5 to 7 month-old *Ctns*^{-/-} mice, regardless of an equivalent efficiency of gene transfer. Subsequently, we validated these observations *in vivo* by targeting the liver of *Ctns*^{-/-} mice. We reduced cystine levels ~2-fold in young mice, whereas we did not reduce cystine levels in older month-old mice.

Taken together, our results suggest that gene transfer is feasible for reducing cystine levels. However, we were able to reduce cystine levels more efficiently in young versus older mice. As cystine levels are higher in older mice, further studies are needed to determine whether a longer period post-gene transfer is required to further reduce levels in these mice. If this is not the case, it would suggest that gene therapy may be preventive but not curative in some tissues, which would highlight the importance of targeting tissues before cystine build-up.

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Mexican Association of Cystinosis
Experience in Mexico

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Mexican association of Cystinosis was founded in January 22nd 2002, Families and patients were part of this support group, their main objective was get together and make Mexican physicians conscious about cystinosis, that this rare disease do exist and many Mexican patients were affected by these diagnosis.

By the middle of 2003, this group organized an important meeting, four doctors from the National Institute of Pediatrics were invited, the main purpose was to talk about how important was that an organization get involved in these rare disease and the participation of the physicians. Just one doctor attended that meeting, but she was so interested in our project that immediately accepted to work as a medical part of it.

So by the end of that year Mexican support group of cystinosis become an important organization in Mexico City. Since the beginning our main objectives were:

SUPPORT TO FAMILIES AND PATIENTS

MEDICAL ASSISTANCE

EDUCATION & AWARENESS TO MEDICAL COMMUNITY

MAIN RESOURCE IN LATIN AMERICA, SPANISH SPOKEN

Today Mexican association of cystinosis is an important organization who has done 7 medical cystinosis conferences in Mexico, Helped patients to receive cystagon, printed several information about cystinosis by booklets, brochures and posters, medical assistance twice a year.

Also we have received several e-mail messages from Venezuela, Colombia, Chile, Argentina, Brazil, España, and most of them were answered, now, we are in touch with many doctors from these countries and have detected more cystinosis patients.

Mexican Association of Cystinosis will continue working to help all cystinosis patients living in Latin-America.

We want to say thank you to all the organizations who helped us before to make possible our goals.

**THIRD TRANSPLANT OF KIDNEY!!!!
A NEW LIFE FOR GERARDO: IT IS POSSIBLE**

Leticia Belmont MD, Victor Gómez
Mexican association of Cystinosis A.C.

Gerardo was born November of 1961, 25 for the first time, with 3 kilos, it is the first son, ate apple and banana in paps and he ate everything milled until the 4 years that he ate his first cookie. When he/she was 1 year old 10 months, it was programmed for an amigdalectomy to present frequent infections of the breathing roads, and they found him glucose and proteins in the urine exam, also had a lot of thirst, little appetite, flaw to grow, carves it lowers, ricketts, was diagnosed Glomerulonephritis, Syndrome of Fanconi was documented and he was diagnosed Cystinosis to the 3 years. In 1976 to the fifteen year-old age, he received their FIRST kidney transplant, of cadaverous donor, and this was their second birth. This first kidney lasted him up to 1985, that is to say 9 years, and in that same year, he received its SECOND transplant of cadaverous donor's kidney, with big risks, it presented unemployment cardiorrespiratory, but again Gerardo returned to the life. This second kidney was working up to 1999, that is to say 13 years. Later on required hemodialysis during eight years and that they believe!!! That the 25th April of 2007, Gerardo Mendoza Valles he received his THIRD kidney of cadaverous donor to the 45 years of age and if of chance you mark the telephone of his he marries he finds a recording that he says "Hello: these speaking to Gerardo's house Mendoza, am I the same but renovated" and is a great happiness listened that few times it is listened in a recording of telephone. We really unite to the great happiness that this implies for Gerardo that also in the year of 2005 he/she received a transplant of it Horns. Gerardo is the Director of the National Foundation of Transplants was transplanted more than 4,300 in México!!!!, he is an implacable promoter of the donation of organs, dynamic and very hard-working. It is necessary to mention that alone she had a smaller sister, with I also diagnose of Cystinosis, she received renal transplant to the 15 years, but I present rejection to the 15 days and it died to the 20 years. Gerardo's father died from colón cancer and who continue fighting they are the and his mom who live to the maximum every day and giving the best thing to many people that require help. To have cystinosis is not easy, to get a kidney is not easy, to receive a kidney is not easy, but to receive THREE, and to continue lives, with a new opportunity of life, without having never taken before Cystagon it is a prowess. Gerardo has already begun for the first time in his long trajectory of patient with cystinosis he is necessary to take cystagon and we hope it continues taking advantage of this new opportunity and promoting the donation of organs for many patients in Mexico, and obviously we will continue working in favor of the patients with Cystinosis to who we can offer our hand, our help, our friendship and our heart.

Development of a Cysteamine *in situ* gelling system for the treatment of corneal crystals in Cystinosis

Abstract

The objective of this project is to produce a once daily cysteamine prolonged delivery system for the topical treatment of corneal crystals in paediatric patients with cystinosis. Various formulations will be screened *in vitro* and the optimised one will be evaluated *in vivo* in rabbits and finally clinically. For the development of this new ophthalmic preparation of cysteamine, the rationale is that increased ocular contact time of the drug by the using an *in situ* gelling and mucoadhesive polymer will reduce lacrimal drainage and thereby increase bioavailability. This should lead to decreased frequency of administration which should improve compliance greatly and decrease the morbidity linked with actual treatment.

Bola Lawal; Catherine Tuleu,PhD; Ken Nischal,MD; Olufemi Rabiou,PhD; Rajnish Sekhri,MD; William Van't Hoff,MD.

Renal phenotype in the cystinosis mouse model is dependent upon genetic background

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Cystinosis is an inherited disorder due to mutations in the *CTNS* gene, encoding a lysosomal transporter of cystine, cystinosin. Defective cystinosin leads to an intralysosomal accumulation of cystine, which is associated with major kidney defects and a multisystemic disease. A mouse model of cystinosis has previously been generated on a mixed 129Sv x C57BL/6 genetic background by inactivating the *Ctns* gene. These mice accumulated cystine and developed ocular, muscular and bone abnormalities but no kidney symptoms. Here, we generated two congenic *Ctns*^{-/-} strains on C57BL/6 and FVB/N genetic backgrounds. Although both strains accumulate cystine, only the C57BL/6 *Ctns*^{-/-} mice present with renal symptoms. At 15 months C57BL/6 *Ctns*^{-/-} mice develop renal failure and incomplete tubulopathy characterized by polyuria and aminoaciduria, preceded by histological lesions with focal tubular atrophy observed from 9 months. The lesions worsen with age, leading to wide areas of fibrosis and cellular infiltration without tubules at 18 months. The FVB/N *Ctns*^{-/-} mice do not develop any renal dysfunction, hence demonstrating the effect of genetic background on the renal phenotype of these mice. The availability of an animal model of cystinosis that develops renal disease will aid in the identification of the mechanisms involved in renal impairment in humans with cystinosis.

Design and Synthesis of Novel Prodrugs for the Treatment of Cystinosis.

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Introduction

Cystinosis is a rare autosomal recessive disease characterised by raised intracellular levels of the amino acid cystine. Treatment of cystinosis involves the administration of cysteamine, an aminothioliol which possesses an offensive taste and smell. Cysteamine and its metabolites are excreted in breath and sweat causing halitosis and body odour and frequent oral dosing may cause gastric irritation. As a result, patient compliance may be poor, Gahl *et al*, (2001), Cairns *et al* (2002). In an attempt to overcome these difficulties, a series of odourless and tasteless prodrug forms of cysteamine were designed, synthesized and evaluated. Prodrugs are pharmacologically inactive derivatives which are designed to decompose within the body to release the active moiety. The advantage of using prodrugs is that their enhanced lipophilicity often confers a more favourable pharmacokinetic profile on the prodrug than on the active.

Methods

A library of approximately 50 water insoluble fatty amide prodrugs of cysteamine (and its disulphide cystamine) was synthesised using a combination of both solid and solution phase organic synthesis. The compounds were prepared in good yield, purified by a combination of recrystallisation and chromatography then fully characterised by mass spectroscopy and ¹HNMR.

The cytotoxic effect of the synthesized prodrugs was determined in cultured MCF7 and human umbilical vein endothelial cells using an Alamar blue assay. Due to the insoluble nature of the prodrugs, co-solvents of 1% ethanol or DMSO were used.

A number of methods for the quantitative detection of thiols are available in the literature (Camera, and Picardo, (2002) and refs therein). Using a combination of these methods, a novel reverse phase HPLC assay for the *in-vitro* determination of cysteamine and cystine was established employing a thiol specific UV tagging agent synthesized and characterized in our laboratories. This assay allows us to evaluate the cystine-depleting ability of our prodrugs using cultured cystinotic cells (Coriell, NJ, USA).

Conclusions

A number of water insoluble amide prodrugs of cysteamine and cystamine were synthesised, fully characterised and their cytotoxicity determined using MCF7 and HUVEC cell lines. The compounds were odourless and a small number have proved tasteless. Cytotoxicity results indicate that the compounds were no more toxic than the co-solvent vehicle up to 50 μ M. Studies to determine the ability of the compounds to deplete the high levels of cystine found in cystinotic cells are currently underway in our laboratories.

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Decreased intracellular ATP levels in conditionally immortalized proximal tubular cells from cystinotic patients

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Objectives of study

The hallmark of nephropathic cystinosis is lysosomal cystine accumulation, primarily leading to Fanconi syndrome. Although all tissues have elevated cystine levels, it is not known why the kidney is first affected.

It is postulated that decreased ATP production in cystinosis results in defective proximal tubular reabsorption, a process driven by Na,K-ATPase. To study this hypothesis, we have monitored ATP levels and viability in conditionally immortalized proximal tubular cells (ciPTC) of cystinosis and healthy controls.

Methods

Urinary sediment of cystinotic patients and healthy controls was suspended in supplemented culture medium. Primary cultures were transfected with SV40 tsA58 T antigen allowing proliferation at 33°C and maturation at 37°C. To confirm the proximal origin of the cells expression of aquaporin-1 (AQP1), dipeptidyl-peptidase IV (dpp-IV) and ZO-1 was demonstrated using immuno labeling techniques. PTC were matured at 37°C for 0-10 days, followed by cystine measurement using HPLC and ATP determination using luciferase assay. Results are expressed as nmol/mg protein.

Results

Colonies of cystinotic and control cell lines (n=2) with cobblestone morphology developed after 2 weeks and expressed AQP1, dpp-IV and ZO-1 confirming their proximal origin. In cystinotic PTC, cystine levels increased up to 7.8 after 10 days at 37°C compared to 0.1 in controls. Intracellular ATP decreased in cystinotic PTC during 10 days from 8.8 to 1.6, while ATP levels in controls remained stable (range 9.7-13.7).

Conclusion

Decreased ATP levels in ciPTC during 10 days maturation suggest that alterations in ATP levels are involved in tubular dysfunction in cystinotic patients.

An Innovative Genomics Approach to Identifying Novel Genes Involved in Cystinosis

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Mutations in the cystinosin gene, *CTNS*, are a central determinant in the development of Cystinosis. While the *CTNS* gene was identified by a classical genetic approach, there has been only minimal scientific investigation into the broader effect that genetic variation in the *CTNS* gene has on other downstream phenotypes that may be more directly involved in pathology. The overall goal of our research is to determine how genetic variation in *CTNS* affects the function of other genes. To this end, we have recently adopted an innovative genomic approach where we employ normal human variation as a model for pathological human variation, thus obviating the immediate need for large families of individuals affected with Cystinosis. In order to determine the larger role of cystinosin, we have exhaustively enumerated normal human variation in the *CTNS* gene and then tested to see whether this genetic variation influences the quantitative expression of any other gene (via the measurement of genome-wide gene expression in lymphocytes). At least 400 genes were identified that showed statistically significant correlation with *CTNS* gene expression. Future research will focus on determining whether these genes have a functional role in Cystinosis.

In order to verify and extend these studies, the next phase of our research program involves the collection of genetic material from Cystinosis families (approximately 250 individuals). DNA and RNA will be isolated from white blood cells collected from individuals affected by Cystinosis and from unaffected family members. We will resequence the *CTNS* gene to find polymorphisms in all individuals then use the RNA to perform whole genome transcriptional profiling. This data will thus provide genetic correlations between polymorphisms in the *CTNS* gene and genes expressed in lymphocytes. This will ultimately give us important information on the cystine pathway in general and on the role of cystinosin in particular. It is likely that novel genes, previously unknown to be involved in this pathway, will be discovered. These genes could then be targeted for pharmacological intervention in the future.

EARLY INTERVENTION TRIAL FOR VISUAL PROCESSING DEFICIT IN CYSTINOSIS

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Category: Research/Clinical

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We give permission for the poster abstract to be published with conference materials and to be posted on the CRN website.

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Background: Children with cystinosis have a high incidence of visual spatial deficits which may lead to academic difficulties. The aim of this study was to determine whether a unique program of computerized visual stimuli, presented in slowly increasing speed of presentation and complexity, would improve visual processing in children with cystinosis.

Methods: A computer-based program of exercises using visual spatial tasks of increasing difficulty was provided to children with cystinosis. Parent and child were trained on the program, and were instructed to have the child work on the program daily (5 days per week) for at least ½ hour per day for 12 weeks. Children were tested on specific visual processing tasks before and after the training program was completed in order to determine whether an improvement in visual spatial function could be demonstrated.

Results: We had great difficulty in recruiting families to participate in this study. Despite ads placed in cystinosis newsletters and contacting many families by telephone, only 8 families agreed to participate. Of those, only one was very compliant and 2 more were partially compliant (i.e., logged on to the program at least 1/3 of the time). We were unable to demonstrate any significant difference in visual processing performance following the intervention trial.

Conclusions: This study demonstrated how difficult it is to place additional demands on families that are already coping with chronic illness. Despite the fact that children with cystinosis have documented cognitive and academic difficulties, both recruitment and adherence posed significant problems for this study. Perhaps one solution would be to incorporate an intervention into the child's school day such that he or she would receive the benefit of intensive cognitive training without its interfering with other after-school or weekend routines.

Parent Ratings of Executive Functioning in Cystinosis: A Window into Behavioral Regulation and Problem Solving

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Background: Cystinosis is a genetic metabolic disease that affects many areas of the body, including the brain. The disorder presents a specific cognitive profile of visual spatial deficits with intact language and intelligence. Executive functioning (e.g., problem solving, planning, organizing, and monitoring behavior) is involved in many critical aspects of everyday life. The area of executive functioning has not been examined in cystinosis.

Methods: The Behavior Rating Inventory of Executive Function (BRIEF), a comprehensive parent rating scale of executive functioning, was collected on 21 children with cystinosis and 17 matched controls (ages 6 – 17 years).

Results: Results indicate that in daily life, children with cystinosis demonstrate a significantly greater degree of executive functioning difficulty compared to controls (although not in the “Clinical” range) on the Global Executive Composite and the Metacognition Index. There was no significant difference between cystinosis and control groups on the Behavioral Regulation Index or its component scales.

Conclusion: Children, adolescents, and adults with cystinosis demonstrate subtle but significant difficulties in the metacognitive aspect of executive functioning. This suggests that the daily lives of these individuals, both at home and at school, may be affected. These data have implications for designing appropriate interventions.

This project was funded by the Cystinosis Research Foundation (UCSD # 2005-3008).

Planning, Problem Solving, and Organizing Information: Executive Functioning in Cystinosis

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Planning, Problem Solving, and Organizing Information: Executive Functioning in Cystinosis

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Background: Cystinosis is a rare genetic metabolic disease. Many areas of the body, including the brain, are affected by the disease. Neuropsychological studies have found that, as a group, individuals with cystinosis have average intelligence but may have deficits in the areas of arithmetic, visuospatial processing skills, and social-behavioral skills. The cognitive area of executive functioning (e.g., problem solving, planning, and attention) is also associated with these skills and has not been examined in cystinosis.

Methods: The Delis-Kaplan Executive Function System (D-KEFS), a comprehensive test of executive functioning, was administered to 23 individuals with cystinosis and 21 control participants (ages 8 – 34 years).

Results: Compared to age- and SES-matched controls, the cystinosis group had a significantly higher rate of impairment on several of the D-KEFS tasks. Further analysis suggests that executive functioning tasks involving visual skills, or visual and verbal skills combined, yielded higher rates of impairment within the cystinosis group than did those only involving verbal skills.

Conclusion: Individuals with cystinosis have a greater incidence of executive dysfunction, particularly when tested on items involving purely visual skills, or visual and verbal skills combined, when compared to matched-controls. The present study has implications for the design and implementation of interventions.

This project was funded by the Cystinosis Research Foundation (UCSD # 2005-3008).

Managing the Psychosocial Effects of Cystinosis: A Family System Approach

Objective: To support the psychosocial management of Cystinosis by understanding the predictable effects on the family. We will review research on other chronic illnesses to gain insight on effective management strategies for the family.

SIGNIFICANCE OF PSYCHOLOGICAL ISSUES IN THE FAMILY.

The psychological impact of cystinosis can and does affect each person in the family. These effects are experienced differently for each person depending on how they interpret and respond to stressful or traumatic situations, their role within the family, and the amount of other life stressors..

When a family is confronted with the diagnosis of Cystinosis it is normally stressful and traumatic. It is a critical incident that changes the family. In Critical Incident Stress Management training we are taught a critical incident is defined as:

- Any situation that has the potential to overwhelm a person's sense of vulnerability and/or control. (Roger Solomon, Ph.D.)
- An event which is outside the usual range of experience and challenges one's ability to cope, and has the potential to overwhelm one's usual psychological mechanisms. (Jeff Mitchell, Ph. D.)
- According to the DSM IV a traumatic incident is defined as, "The person experienced, witnessed, or was confronted with an event that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others."

A diagnosis of cystinosis or any other chronic illness is traumatic to the family and by definition is "outside the usual range of life experiences." There are numerous type 1 diabetes studies that have addressing the psychosocial effects of this chronic disease on the family. The first studies show the children or adolescents themselves who have type 1 diabetes have an increased risk for the development of psychiatric problems. Many children have adjustment problems within the first few months after their diagnosis (Jacobson et al., 1986; Kovacs, Feinberg, et al., 1985). Although the majority of these adjustment problems resolve within the first year, children who do not resolve these problems are at risk for poor adaptation to diabetes, including regimen adherence problems, poor metabolic control, and continued psychosocial difficulties (Grey et al., 1995; Kovacs, Ho, & Pollack, 1995). In addition, many mothers of newly diagnosed children are at risk for adjustment problems of their own, with significant depressive symptoms observed in approximately one-third of mothers; the majority of these abate within the first year after their child's diagnosis (Kovacs et al., Finkelstein, et al., 1985). A recent study found that 24% of mothers and 22% of fathers met the criteria for posttraumatic stress disorder 6 weeks after their child had been diagnosed with diabetes (Landolt et al., 2002).

Posttraumatic stress is a normal reaction in a normal person to an abnormal event.

In critical incident stress management we learn that many types of situations can be stressful but not defined as traumatic or a critical incident. The initial diagnosis of Cystinosis can be considered a critical incident because of how it is defined.

Critical Incidents:

- Are sudden and unexpected
- Disrupt our sense of control
- Involve the perception of a life-damaging threat
- May involve emotional or physical loss
- VIOLATE ASSUMPTIONS/BELIEFS ABOUT HOW THE WORLD WORKS:

“THIS IS NOT SUPPOSE TO HAPPEN”

The world is benevolent!	(“Bad things will not happen to me”)
The world is meaningful!	(World is predictable, fair, and controllable)
The self is worthy!	(“Bad things don’t happen to good people”)

How we respond to a traumatic event depends on our perception of vulnerability, control over the situation, and the personal meaning. Our perception of vulnerability would question your PRESENT SAFETY (I am vulnerable, I am not safe). Our loss of control over the situation would question LACK OF CONTROL OR CHOICES (I am powerless, I have no control). The personal meaning of the incident would question ISSUES OF: RESPONSIBILITY/SELF DEFECTIVENESS (I did something wrong or something is wrong with me).

There are factors that will affect the magnitude of our individual and family member response (Adapted from Eric Nielson, Ph.D.):

1. THE NATURE OF THE EVENT
 - Extent of personal involvement
 - Degree of control
 - Degree of threat or loss
 - Disruption of expectations
2. DEGREE OF WARNING
3. EGO STRENGTH/COPING STYLE
4. PRIOR MASTERY OF EXPERIENCE
5. PROXIMINTY – EMOTIONAL LINK
6. THE AMOUNT OF STRESS IN ONE’S LIFE-AND HOW ONE IS COPING WITH IT
7. NATURE AND DEGREE OF SOCIAL SUPPORT
 - The amount of help/support available immediately after the event and the extent to which the person is receptive to that help.
 - Accessibility to outside social support.
 - Extent to which family is helpful and supportive, and the openness of person in communicating with loved ones.

EFFECTS OF FAMILY DYNAMICS

The impact of the cystinosis diagnosis is not limited to the child with the disease. From siblings struggling with guilt and jealousy, to parents managing new responsibilities, to grandparents suddenly changing their patterns with young ones, the disease has an effect on everyone. Daily routine that once was simple suddenly becomes a complicated task in cystinosis management for the whole family.

There are many things that change for the siblings when one of the children is diagnosed with cystinosis. Through the process of coming to the diagnosis, parents disappear into the hospital setting with the sibling. You wait and worry, thinking about not only your sibling’s wellbeing, but your place in the family. You become jealous of all the attention and then guilty because they know their sibling is sick. It is hard for parents to know what would be normal in sibling rivalry.

When parents are faced with a sick child they can become united by the common quest for answers or can be divided by the stress. We know most parents will respond differently to the diagnosis of cystinosis. In Dr Grey's book, "Men Are From Mars and Women from Venus", we gain insight in male and female communication and stress responses. A dad will "go into his cave and begin problems solving", to gain some rational sense out of the diagnosis. They will naturally pull away from the family to gain some sense of control. Many times they will become busy at what makes sense or what they are good at to cope with the stress. In contrast, moms will want to talk about the diagnosis with others to gain the support and understanding they need to cope. They do go into problem solving mode at times but mainly crave the emotional connections for support.

Grandparents and extended family know just what to do: send gifts and warm thoughts. But when you get home and life begins again, often time extended family does not know what to do next. They are afraid of saying or doing the wrong thing, so they will back off.

WHAT TO DO?

There is a normal grieving process we go through when we realize our child is different. We face the realization that what we hoped for may not be for our child. How our child deals with it may have a lot to do with how we react to the news. It is natural for our children to sense our moods and attitudes, not just by what we say, but by our reactions.

Individually, there are healthy ways to cope with stress:

- Talk it out/Write it out – Journaling
- Access personal support systems – seek support, assistance, and help from others.
- Maintain routine/structure – It helps us regain a sense of control and stability.
- Get the help you need/when to access professional help? SYMPTOMS OF DISTRESS: **Bold More Severe**

1. Cognitive (Thinking) Distress

- Sensory distortion
- **Confusion ("dumbing down")**
- Inability to concentrate
- **Difficulty in decision making**
- Guilt
- Preoccupation (obsessions) with events
- **Inability to understand consequences of behavior**
- **Suicidal/homicidal ideation**
- **Psychosis**

2. Emotional Distress

- Anxiety
- Irritability
- Anger
- **Panic**
- **Vegetative Depression**
- Fear, Phobia, **Phobic Avoidance**
- Posttraumatic Stress (PTS)
- Grief (mourning associated with loss)
- **Pathological Grief when:**
 1. Associated with severe guilt
 2. Lasts too long
 3. So intense as to impair ability to function

Vegetative Depression (depressed mood plus)

1. **decreased appetite**
2. **decreased energy**
3. **decreased sleep**
4. **decreased libido**

4. Behavioral Distress

The following tips concern general family management for the families of cystinosis children (Adapted from Diabetes article).

Information is power. When life is out of control, having a plan or information reduces fear and brings life back in order. Broaden and deepen perspective – learn about what you are scared about. Example: Emergency procedures for NASA and all private pilots.

Agonize behind close doors. We have talked about the stress and trauma of the diagnosis, but it is never wise to let your child see this. Children get terrified when they see their parents scared.

Child first, cystinosis second. Remember you child is still a child, with all the normal concerns of other children who are growing up – socially, physically and emotionally. Encourage you child to begin or continue social activities and stress the similarities rather than the differences between her/him and other children.

Personal Health Records

Presenter: Carol Hughes (Lorna Smith, standby)

Category: Patient/Family

Poster Size: 36' X 24"

Method of display: Easel, small table or portion of table space (3ft width)

Need small table or part of table top (could share with another poster session) to display a sample Personal Health Record (PHR) in 3 ring binder and a one page handout summarizing resources for the different methods of keeping these medical records and costs involved. Costs range from FREE to hundreds of dollars.

If easels are scarce, the poster could be propped up on table using the wall, if necessary.

ANALYSIS OF THE *CTNS* GENE IN NEPHROPATHIC CYSTINOSIS MEXICAN PATIENTS.

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ABSTRACT

Objective: Identify *CTNS* gene mutations in nephropathic cystinosis Mexican patients.

Subjects and Methods: Nine patients with infantile nephropathic cystinosis and two siblings with the juvenile phenotype were studied. The common 57-kb deletion was detected by PCR multiplex (LDM-2/exon 4). Alleles without the 57-kb deletion were screened by SSCP and subsequent direct sequencing.

Results: We detect four severe mutations still not reported: c.379delC, c.1090_1093delACCAinsCG, c.986C>G (p.T216R) and c.400+5G>A; in addition, five mutations previously reported were identified (57-kb deletion, c.985_986insA, c.537_557del, c.357_360delGACT and EX4_EX5del). One patient was initially misdiagnosed as homozygous for 57-kb deletion when using LDM-2/exon 4 primers, but subsequent studies showed a [57-kb deletion] + [EX4_EX5del] genotype.

Conclusions: Although our sample was small, seems that the spectrum of *CTNS* mutations in Mexican patients is heterogeneous in contrast to that observed in European or North American populations. The identification of novel mutations could be indicating the presence of exclusive Amerindian *CTNS* alleles in Mexican population. In order to prevent false positive assignment of 57-kb deletion genotype due to another type of intragenic *CTNS* gross deletion, we propose include a different control *CTNS* exon in PCR multiplex to those originally proposed, especially when parental DNA samples are not available.

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Adolescence and Cystinosis: Coping with the Many Challenges

David Glaize, Ed.D.

Of all of the stages in human growth and development, most experts agree that adolescence presents the most challenges. For young people to become competent, well-adjusted adults, they must meet a multitude of critical developmental milestones; socially, academically, emotionally, educationally, and in career development. Without developing essential skills in each of these areas, a young person will not be able to manage adulthood. Young people with Cystinosis, and other chronic diseases, are not only faced with these challenges in adolescence, but also must face the many physical, social, emotional and health issues presented by their illness. Poster will list the developmental tasks, Cystinosis interference, and suggested interventions.

Feeding Therapy

Whitney Glaize, CCC-SLP

This poster will focus on the sensory motor approach to feeding therapy. It will discuss specific oral motor exercises that are used to both decrease sensitivity to food and increase strength and range of motion in the oral mechanism which in turn helps to increase tolerance of food. It will outline specific steps that are recommended when introducing new foods. Food textures and consistencies and how they relate to food tolerance will be addressed. This poster will also touch on some prerequisites to oral intake of solid food.