IDENTIFYING POTENTIAL BIOMARKERS AND CLINICAL OUTCOMES FOR FUTURE CLINICAL TRIALS FOR SLC13A5 DEFICIENCY

CAPSTONE PROJECT REPORT

Presented to the Graduate Council of the

Graduate School of Biomedical Sciences

University of North Texas Health Science Center at Fort Worth

In Partial Fulfillment of the Requirements

For the Degree of

MASTER OF SCIENCE

IN CLINICAL RESEARCH MANAGEMENT

By

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Dallas, Texas

November 2022

ACKNOWLEDGEMENTS

I would like to thank Dr. Stephen Mathew, the program director, who guided me through this program and capstone project. Additionally, thanks to Dr. Jerry Simecka, my major professor, and Dr. Jennifer Cihlar, one of my committee members, for their time and thoughtful feedback.

I have greatly appreciated the enthusiasm and support at UT Southwestern Medical Center from Dr. Souad Messahel, my site supervisor, Dr. Kimberly Goodspeed, my site Principal Investigator, and Daniyal Kamal, a clinical research coordinator. Their expertise and advice that have helped me to accomplish this capstone project are a bonus to seeing their exceptional passion for clinical research and healthcare that I hope to emulate throughout my own career. I look forward to continuing to work with and learn from them at UTSW.

Additionally, I could not have accomplished this project without help and input from Kim Nye and Tanya Brown at the TESS Research Foundation, and Kristin Philips and Emily McGinnis at Taysha Gene Therapies. It has been inspiring to work with a diverse and passionate group with the same goal to advocate for and learn from families affected by rare diseases.

Finally, I would like to thank my family and friends for their support and encouragement throughout my academic career.

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CHAPTER I

INTRODUCTION

SLC13A5 deficiency is a rare autosomal recessive disorder in which a homozygous loss-of-function mutation in the *SLC13A5* gene results in frequent seizures within the first week of life, limited or slow motor progress, limited expressive language abilities, sleeping difficulties, teeth hypoplasia, and lifelong dependence on caregivers (Klotz et al., 2016; Hardies et al., 2015). This disorder affects both males and females and has been diagnosed in the USA, Europe, and South America for an estimated total of 120 reported diagnoses based on literature review and information from the TESS Research Foundation (Thevenon et al. 2014; Bainbridge et al. 2017; Klotz et al. 2016; Matricardi et al. 2020; Yang et al. 2020; Hardies et al. 2015). Diagnosis consists of genetic testing using commercially available epilepsy panels when seizures are refractory and other physiological factors have been ruled out (Goodspeed et al., 2022). SLC13A5 deficiency is a complicated and taxing disease for the affected individual and those who care for them. Only symptomatic management is available, which includes antiseizure medications, and regular therapies such as speech therapy, physical therapy, and occupational therapy at variable levels of success (Yang et al., 2020; Ozlu et al., 2021). There is not an available treatment for targeting the root cause of SLC13A5 deficiency, and there is a significant unmet need to address the developmental aspects of the disorder. However, there is current research and preparation of a gene therapy for SLC13A5 deficiency at UT Southwestern Medical Center in partnership with TESS Research Foundation and Taysha Gene Therapies.

A critical piece of the clinical trial development plan is solicitation of caregiver input to improve understanding of the burden of the disease and define clinically meaningful improvement. Caregiver input will help define meaningful improvement within a clinical trial due to their unique knowledge of and experience living with or caring for an individual with the condition of interest (Khodyakov et al., 2017). This perspective is valuable as the expectations and aspirations of the caregivers may differ from the focus of a medical provider or investigator during a clinical encounter, and therefore caregiver input will complement the design of the clinical trial by identifying additional measures to track for response to novel intervention (Hunt and Arar, 2001). The goals of caregivers often characterize what quality of life improvements would mean for themselves and their affected loved ones and including this information can help to ensure that the focus of the research is relevant and sensitive to the needs of those most affected (Khodyakov, 2017). Neglecting to consider caregiver perspective could limit the potential of a clinical trial to uncover unexpected yet meaningful disease-modifying properties (Brock et al., 2021). Furthermore, it is critical to address the questions and concerns of caregivers to create a collaborative foundation for research. The Food and Drug Administration describes that input from a diverse set of patients and caregivers contributes to improved study recruitment, retention, compliance, fewer protocol revisions, and more relevant data (Food and Drug Administration, 2022). Thus, collaboration between researchers and caregivers will ensure that the future clinical trial tests the effectiveness of the drug clinically while also collecting input to determine any quality-of-life changes for the caregiver or patient.

CHAPTER II

BACKGROUND AND LITERATURE REVIEW

First described in 2014, SLC13A5 deficiency, also known as citrate transporter disorder or developmental epileptic encephalopathy 25 (DEE25), is caused by the biallelic loss of function variants on the *SLC13A5* gene, which then causes the decreased activity of a sodium-dependent citrate transporter (NaCT) and reduced intracellular citrate (Ozlu et al., 2021). The resulting effects of this deficiency include infantile epilepsy, movement and balance difficulty, developmental delay, communication impairment, sleeping challenges, and eating difficulty (Bainbridge et al., 2017; Brown et al., 2021; Matricardi et al., 2020). Affected individuals undergo trial-and-error of several antiseizure medications and therapies to manage the disorder and the associated challenging symptoms throughout the lifetime of the affected individual. These interventions present their own challenges: for example, therapies such as speech or occupational therapies require hours of time and effort each week for the individual and their caregivers, and the antiseizure medications often come with side effects such as exacerbation of neurodevelopmental disability (de Lange et al., 2018). Additionally, patients with SLC13A5 deficiency may develop drug-resistant epilepsy (Ozlu et al., 2021). There is not a treatment for the genetic basis of the disease, which could directly correct the effects of reduced citrate transport activity.

Gene therapy technology presents a hopeful future for genetic-based epilepsy disorders such as SLC13A5 deficiency. Since the first successful human trial of gene therapy in 1990, the

potential of the technology has rapidly expanded (Onodera et al., 1998). Of particular interest for SLC13A5 deficiency researchers, gene replacement therapy (GRT) aims to restore cellular function by providing a functional copy of the gene that overcomes the effects of the biallelic loss of function variants (Goodspeed et al., 2022; Thevenon et al., 2014). There is current research and preparation for a potential gene therapy for SLC13A5 deficiency using an adeno-associated viral (AAV) serotype 9 (AAV9) vector developed by Rachel Bailey, PhD at the University of Texas Southwestern Medical Center in partnership with TESS Research Foundation and Taysha Gene Therapies (Goodspeed et al., 2022; Ozlu et al., 2021). The Food and Drug Administration and European Commission have granted Taysha Gene Therapies the rare pediatric and orphan drug designation for this AAV-based gene therapy for SLC13A5-related epilepsy. To receive the orphan designation from the European Commission, a medicine must be intended to provide a significant benefit for those affected by a disease that is life-threatening or chronically debilitating and affects no more than 5 in 10,000 children (European Medicines Agency, 2018). In the United States, the Food and Drug Administration grants the orphan designation for drugs that prevent, diagnose, or treat a disease or condition that affects fewer than 200,000 persons in the country, or those that will not be profitable within 7 years of FDA approval (Attwood et al., 2018). Achieving these designations comes with economic incentives for the research and development for therapies for these rare diseases (Bolislis et al., 2018; Miller et al., 2018). It is important to put effort into learning more about these rare diseases to support those directly and indirectly affected.

Although each disease is individually rare, the cumulative prevalence of rare diseases is globally significant (Hazal et al., 2020). There are an estimated 6,000-8,000 rare diseases in the world, affecting over 30 million Americans (Dodge et al.; Whicher et al., 2018). Many families affected by a rare disease often spend early and critical years searching for a diagnosis that is paramount to safely managing their disease but are often told that there is a lack of knowledge for how to manage their new diagnosis. Learning more about a rare disease like SLC13A5 deficiency will result in diagnostic journey improvement and unlock a wealth of resources for affected families (Wright et al., 2018). This capstone project seeks to contribute to the current understanding of the disorder, to be utilized by affected families and those aiming to treat them. This project aims to develop a disease burden model through solicitation of SLC13A5 deficiency caregiver input. In addition to this project, further research for understanding this disorder includes a 2-year natural history study that is underway to paint a picture on disease variability (Clinical Trials.gov: NCT04681781). This study will collect data points on seizure history, medication history, brain activity via routine electroencephalograms, cardiac activity via electrocardiogram, motor scale assessments, and developmental assessments at regular intervals over 2 years. Together, these efforts will contribute to the understanding of how SLC13A5 deficiency affects patients and their loved ones and bring the GRT to clinical trial.

Significance

Taysha Gene Therapies is developing a clinical trial to evaluate the safety, tolerability, and efficacy of a gene therapy treatment for those with SLC13A5 deficiency. The goal of the future clinical trial is to address the current unmet need for treatment, based upon input from the patients and caregivers. The primary goal of this capstone project is to determine what success looks like to these caregivers so that a clinical trial may be designed to capture those aspects of disease.

Meaningful improvement from a clinical perspective could include reduced seizure frequency, improved fine motor skills, and improved cognitive function, while caregiver perspective may additionally include the ability to be more independent in daily tasks, play with other individuals, and bathe and toilet without assistance (Brock et al., 2021). Taysha Gene Therapies and TESS Research Foundation conducted a market research study with a select group of SLC13A5 deficiency caregivers to characterize the disorder, identify specific aspects of disease burden, and gain insight into caregiver knowledge and opinion of clinical trials. When Taysha's patient engagement team interviewed a subset of SLC13A5 deficiency caregivers regarding a potential clinical trial, a participant asked, "What is considered success in terms of a gene therapy working?" This demonstrates a gap in expectations for future research plans and the need for transparency among stakeholders.

It is additionally important that health professionals consider and support the caregivers of individuals affected by developmental disabilities for the sake of caregiver wellbeing. While caregiving is a normal part of being a parent, providing the high-level of care that is necessary

for an individual with life-long limitations often produces additional levels of physical and psychological stress. Sources of psychological stress while caring for an individual with disabilities include leaving a fulfilling career for more time to take care of their child, worrying about their child's future depending on the support of others, paying thousands of dollars for equipment and medications, and fearful anticipation of their loved one's next seizure. Physical burden includes carrying their loved one who cannot walk, helping them eat, toilet, or bathe for many years, and losing sleep due to either their loved one's nocturnal awakenings or for fear of missing a seizure. Parents of children with disabilities experience increased levels of depression and anxiety and the majority of these caregivers meet criteria for clinical diagnoses of these conditions (Gallagher et al., 2008). There are some aspects that are more specific predictors of psychological morbidity. Predictably, high caregiver burden and poor sleep quality are associated with an increase in anxiety and depression for caregivers of people with intellectual disability, which are both highly associated with SLC13A5 deficiency (Brummett et al., 2006; Gallagher et al., 2008). Identifying and addressing the challenges that contribute to the caregiver burden will be significant in alleviating the stress of this disease for everyone directly and indirectly affected. Future clinical trials should include measurement of these important aspects of the disease to increase identification of meaningful clinical outcomes.

CHAPTER III

PROBLEM AND HYPOTHESIS

When designing a clinical trial, it is critical to define clinically meaningful endpoints and biomarkers that determine the efficacy of an intervention. In accordance with guidance from the Food and Drug Administration (FDA) and National Institute of Health (NIH), incorporating the patient community's opinions is crucial to gain an understanding of the burden of disease on the individual and family, and to foster cooperation and participation in the trial (Food and Drug Administration, 2022; Kaufmann et al., 2018). This study will explore the opinion of caregivers to determine potential clinical outcome measures and biomarkers for SLC13A5 deficiency, a rare neurological disorder that causes epilepsy and developmental problems, in anticipation for future clinical trials. While many symptoms of SLC13A5 deficiency are known at this point such as motor delay, seizures, and cognitive delay, it is important to understand which aspects of these symptoms affect the caregivers and contribute the most to their burden. Additionally, it is likely that there are relatively common problems that affect this population but are not being considered by the medical community and researchers.

Hypothesis and Specific Aims

I hypothesize that by directly surveying caregivers of individuals with SLC13A5 deficiency, a disease burden model can be developed that encompasses the concerns of the patient community. I expect that the caregivers will have similar responses, but that differences will arise between age groups. The primary study objective is to identify the most impactful symptoms of SLC13A5 deficiency from the caregiver perspective. The secondary study objective is to identify relevant and meaningful clinical outcomes for use in a future clinical trial for treating SLC13A5 deficiency that addresses the most impactful symptoms.

Hypothesis: Caregiver input will identify the most challenging aspects of SLC13A5 deficiency, which will contribute to development of an effective clinical trial protocol that addresses the concerns of patients and their support network.

Aim 1: Develop a caregiver-focused disease burden survey for SLC13A5 deficiency informed by market research study data.

Aim 2: Develop a disease burden model for SLC13A5 deficiency with a cross-sectional survey of TESS Research Foundation network caregivers.

Aim 3: Determine clinical outcome measures and biomarkers that are relevant to affected families and quantifiable within a gene therapy trial.

CHAPTER IV

RESEARCH DESIGN AND METHODOLOGY

This study was classified as Exempt Research and approved by the University of Texas Southwestern and North Texas Regional Institutional Review Boards as such. This study is an exploratory data analysis of information from caregivers of individuals with SLC13A5 deficiency. All study participants are part of the TESS Research Foundation caregiver network based on their relationship to a patient diagnosed with the disorder.

Data collection for this study consisted of two parts: 1) Review of an existing dataset and 2) Cross-sectional survey of all available caregivers of patients with SLC13A5 deficiency disorder. For part 1, we reviewed deidentified data generated through a market research study previously conducted by Taysha Gene Therapies. This study included online surveys and a 10-day asynchronous discussion with 13 caregivers in collaboration with the TESS Research Foundation. The objectives of the study were 1) to understand the diagnostic journey, 2) to identify challenging symptoms and unmet needs, 3) to understand the impact of seizures and other medical comorbidities, and 4) to understand community expectations for clinical trials. For the purposes of this capstone project and building a disease burden model, the focus was on the initial 3 objectives.

For part 2, an anonymous online survey was distributed via UTSW REDCap to the entire TESS caregiver network, which consists of over 100 caregivers worldwide. TESS distributed this survey by sharing the REDCap link via social media and direct email. The voluntary survey

consisted of a maximum of 110 questions and utilized branching logic to optimize the participant experience. The survey employed an open-ended, mixed methods approach (qualitative and quantitative) through a combination of short answer, multiple choice, Likert scales, and free response to investigate the themes observed from the market research of part 1 to capture the burden of disease in a larger population of caregivers. The survey allowed multiple submissions to facilitate caregivers with more than one affected child and included the question "what is your favorite movie?" for the purpose of grouping data from the same caregiver together without identifying the participant. The objectives of this survey were to define the goals and concerns of the caregivers, and to describe the experience of caring for an individual with SLC13A5 deficiency within a larger population of caregivers.

TABLE 1: Data collected in cross-sectional survey of part 2.

Theme	Data Collected
Historical data/demographics	Patient current age, age at diagnosis, gender; caregiver age, gender, number of affected patients they care for
Seizures	Frequency, duration, use of rescue medication, types, beathing difficulty during seizure, injuries, hospitalizations
Motor disability	Abilities to hold head up, sit up, crawl. stand, walk, pick up an object, eat, drink, clothe, toilet, and bathe independently; presence of contractures, muscle spasms, muscle weakness, balance difficulty
Communication and cognition disability	Communication ability, mode of communication, reading, comprehension
Sleep disturbances	Nocturnal awakenings, hours of sleep, frequency of snoring
Tooth abnormalities	Presence of tooth abnormalities
Excessive drooling	Presence of frequent excessive drool
Disease management	Duration, frequency, and type of therapies attended; number of health professionals regularly seen
Caregiver burden	Severity of impact from symptoms of seizures, motor disability, communication disability, cognitive disability, sleep disturbances, tooth abnormalities, excessive drooling, financial burden, emotional burden, and temporal burden; rank of most significant symptoms; most challenging symptoms; patient's greatest strength

In the cross-sectional survey for part 2, data captured included characteristics of seizures, motor development, speech and cognition, sleep disturbances, tooth abnormalities, drooling, and the caregiver burden that results from these symptoms. Seizure burden data included the frequency, duration, need for the administration of rescue medication, type, control, medication use, and seizure-related injuries, emergencies, and hospital visits. These data points were collected to demonstrate the heterogeneity of seizure characteristics within the SLC13A5 deficiency community. Motor development data points included the presence of contractures,

muscle weakness, spasms, and the abilities to stand, hold an object, crawl, stand, and walk to describe the differences in physical ability among the population. Communication and cognition abilities questioned included the abilities to communicate, read, and understand conversations. Information was also captured on sleep problems (number of nocturnal awakenings, hours slept on average, and snoring), feeding problems (ability to chew, swallow, or drink without aspiration), life skill abilities (bathing, toileting, dressing), the presence of tooth abnormalities, and excessive drooling to determine the extent of these symptoms for this population. Caregiver burden was also questioned regarding their own social, emotional, and financial burden, and the time spent managing the disorder, as well as the impact of the previously mentioned symptoms in question. For example, "Describe the impact of your affected child's tooth abnormalities on your quality of life as a caregiver" with answer responses including Severe, Moderate, Mild, None. We also captured historical data including the age at diagnosis, current age and gender of the affected individual, and current age and gender of the caregiver. This information was used to covariate in analysis as caregivers of different age or gender groups could have unique perspectives. For example, the assignment of responses to 3 age groups was rationalized by natural breaks in the patterns of data (e.g., developmental skills) and normal age-related milestones to ultimately result in the youngest age group at preschool-age (0-6 years), pre-pubertal age (7-14 years), and older teenage to adult age (15 years and older). Finally, we asked caregivers to rank their most challenging symptoms and provided free response sections to allow the caregiver to describe any symptom that was not mentioned in the survey or to elaborate on an answer they provided.

Due to the anonymous nature of participation in both surveys, it is impossible to know if the same caregivers participated in both parts of this capstone project. For this reason, the analyses of these parts are separated to avoid misleading duplication. In the analysis of the collected data, descriptive statistics (i.e., frequencies and percentages of categorical variables and mean/median of continuous variables) were used to summarize the demographics of the Taysha market research study of part 1 and the UTSW cross-sectional survey study of part 2.

All survey data received was stored on the REDCap website, on UT Southwestern Secure servers, which are protected by a firewall and only accessed through employee VPN. Only the principal investigator and IRB-approved research staff have access to the research information obtained. Responses were coded and no PHI was collected.

CHAPTER V

RESULTS AND DISCUSSION

The most significant differences in how SLC13A5 deficiency affects individuals and their caregivers are between patient age groups.

The initial market research study consisted of a total of 13 participant caregivers of 17 children. Participants who had more than 1 affected child were asked to answer questions based on their oldest child. TABLE 2 represents the children and caregivers represented by the responses of part 1.

TABLE 2. Participant demographics for part 1. [1]

Characteristic	Frequency	Percent
Affected current age		
0-6	7	53.85%
7+	6	46.15%
Total	13	100.00%
Affected gender		
Male	6	46.15%
Female	7	53.85%
Total	13	100.00%
Caregiver gender		
Male	2	15.38%
Female	11	84.62%
Total	13	100.00%

1. Caregiver age was not available from the data of the market research study.

The cross-sectional survey for part 2 received a total of 27 responses from the caregiver network, which represent 22.5% of the estimated total diagnoses. These responses consist of 25 caregivers, 2 of whom responded twice for the 2 affected family members they care for. The demographics of the participants and their affected children are illustrated in TABLE 3.

TABLE 3. Participant demographics for part 2.

Characteristic	Frequency	Percent
Affected current age		
0-6	13	48.15%
7-14	6	22.22%
15+	8	29.63%
Total	27	100.00%
Affected gender		
Male	14	51.85%
Female	13	48.15%
Total	27	100.00%
Caregiver current age		
30-39	13	52.00%
40-49	7	28.00%
50-59	5	20.00%
Total	25[1]	100.00%
Caregiver gender		
Male	3	12.00%
Female	22	88.00%
Total	25	100.00%

[1] Totals of affected and caregivers differ due to 2 caregivers taking the survey to represent their 2 affected children.

Overall, there were no apparent differences in reported severity of impact between the ages or genders of caregivers for any of the symptoms or aspects of disease management. The

patterns in how SLC13A5 deficiency affects patients and caregivers were apparent between patient age groups, but not between patient genders.

The median age at diagnosis for affected individuals over the age of 6 is 6.5 years reported from the part 2 study (n=14), which is equal to that of the part 1 market survey (n=6). The median age at diagnosis for children 6 years and younger is 1 year from the cross-sectional survey (n=13) and <1-year from the market survey (n=7). This reduction in median age of diagnoses between the age groups is likely attributable to the discovery of SLC13A5 deficiency in 2014 and subsequent improved awareness across the global medical community and inclusion of the disorder on commercially available epilepsy panels. This earlier diagnosis can lead to improved clinical outcomes with earlier medical intervention.

Patients' motor disability, speech delay, seizures, and cognitive delay have the highest impact on caregivers' lives.

Participants were asked to list which of their child's symptoms were most impactful on their lives as caregivers. The frequencies of the top 3 most impactful symptoms are illustrated in TABLE 4, grouped together by symptom theme. The older age group reported the impact of seizures less frequently due to this group's higher frequency of relative seizure control, including reduced and eliminated seizures. More caregivers in the older age group reported cognitive delay as an impactful symptom while anecdotally expressing that they worry their loved one will not be able to live an independent life and are frustrated that their loved one cannot complete daily tasks. Although there were different concerns between caregivers with children of different ages,

they collectively identified motor disability, communication disability, seizures, and cognitive delay as the most severely impactful on their lives.

TABLE 4. Frequency of high-impact symptoms in part 1.

Symptom Theme	Number of caregivers listing symptom within top 3 to eliminate/manage		
	Age 0-6	Age 7+	**Total**
Motor disability	7	4	11
Communication disability	4	5	9
Seizures	5	2	7
Cognitive delay	2	4	6
Feeding, swallowing issues	2	2	4
Sleep disturbances	0	0	0
Teeth abnormalities	1	0	1
Drooling	0	1	1

Since the market survey indicated that all symptom groups significantly impacted at least 1 respondent, the cross-sectional survey for part 2 included questions to evaluate the severity of impact for all symptoms in the larger population. Furthermore, motor development and movement, speech delay and communication issues, and seizures, as the most frequently mentioned symptom groups with severe impact, warranted more extensive and detailed questions.

TABLE 5. Frequency of high-impact symptoms in part 2.

Symptom	Number of caregivers listing symptom within top 3 to eliminate or manage			
	Age 0-6	Age 7-14	Age 15+	**Total**
Communication disability	9	5	5	19
Motor disability	9	5	3	17
Seizures	7	0	6	13
Cognitive delay	4	4	5	13
Feeding, swallowing issues	1	0	0	1
Sleep disturbances	3	0	1	4
Teeth abnormalities	0	1	1	2
Drooling	0	0	0	0

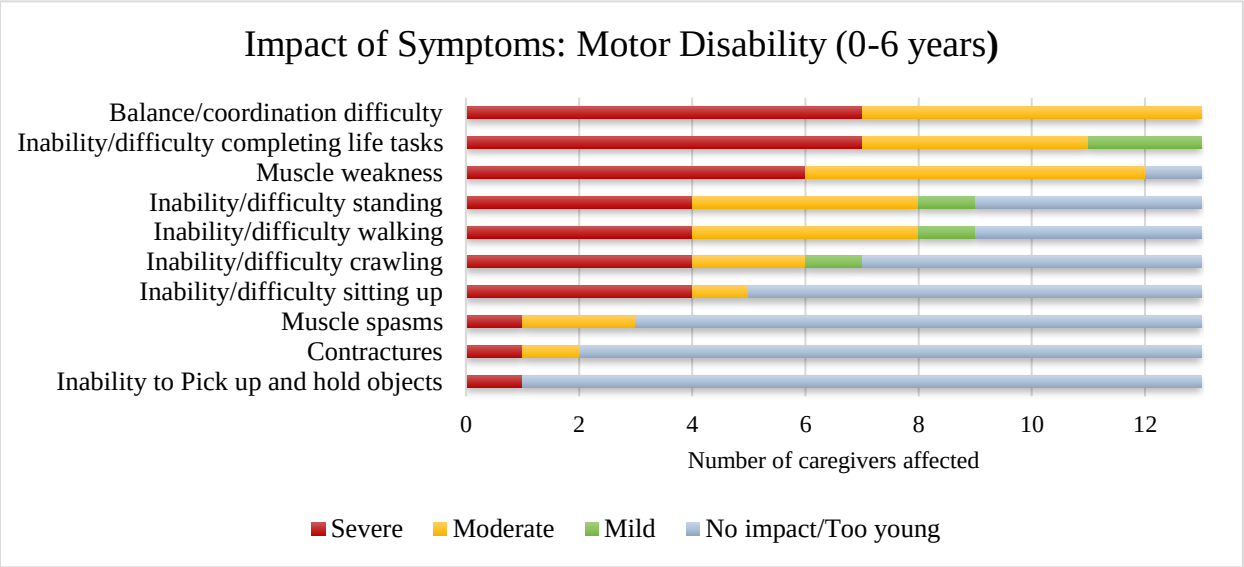
The first 5 symptom groups are equal in rank between both surveys as demonstrated in TABLES 3 and 5. Interestingly, 0 respondents of part 1 reported sleep disturbances as a serious concern, compared to the 4 of part 2.

Balance and coordination difficulty and the inability to complete life tasks highly impact nearly all caregivers.

Some of the most reported high-impact symptoms fall into the motor disability category. None of the affected individuals under the age of 7 can independently complete life tasks, which include bathing, toileting, and clothing. Overall, most of the affected individuals 15 years and older have more motor capabilities, however one caregiver of an affected child in this group

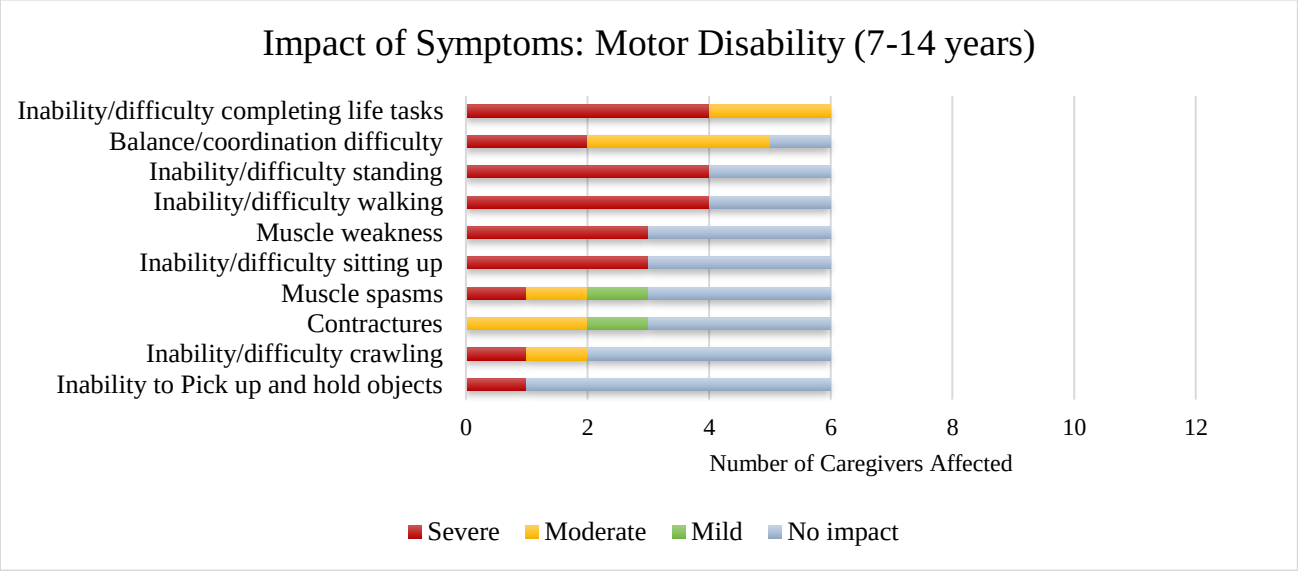
noted that their son had recently experienced motor regression and lost all of these motor skills, which is reflected in FIGURE 3.

FIGURE 1



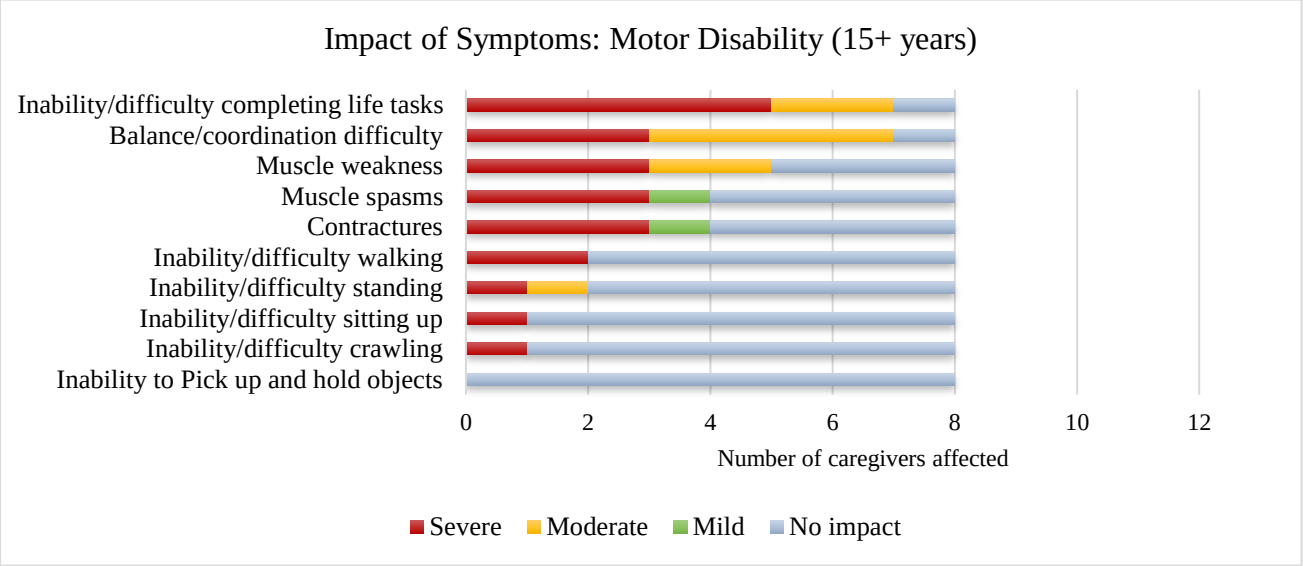
Severity of motor disability impact for caregivers of children aged 0-6 years. Balance/coordination difficulty and difficulty completing life tasks affected all caregivers of children in this age group, with the majority severely affected. Muscle weakness affects nearly all caregivers moderately to severely.

FIGURE 2



Severity of motor disability impact for caregivers of children aged 7-14 years. The patients' difficulty completing life tasks affects all caregivers of children in this age group. Balance/coordination difficulty, and the inabilities to stand or walk affect most respondents for this age group. All caregivers that are affected by their loved one's muscle weakness or challenges with independently walking, standing, or sitting up are severely impacted.

FIGURE 3



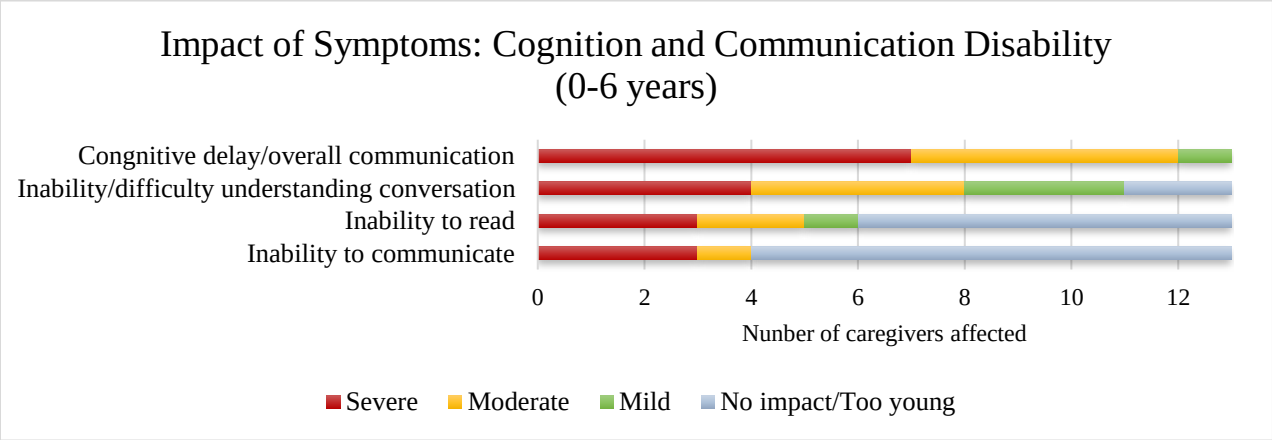
Severity of motor disability impact for caregivers of patients aged 15 years and older. Balance/coordination difficulty and difficulty completing life tasks affected the most caregivers in this age group moderately to severely, closely followed by muscle weakness. Fewer than half of caregivers in this age group reported that their loved one is unable to sit up, crawl, stand, walk, or pick and hold up an object.

Of the caregivers of children aged 0-6 years, 7.6% reported that their child can hold their head up, sit up independently, crawl, stand independently, walk independently, and hold an object. As may be expected, motor abilities increase with age. However, compared to the other age groups, fewer caregivers of the youngest age group reported severe impact from motor delay compared to the older age groups as demonstrated in FIGURES 1-3. This could be attributed to either the relative ease of supporting smaller children as they move, or that fewer caregivers expect more advanced motor abilities from younger children.

Nearly all caregivers are highly impacted by their loved one's cognitive delay and communication disability.

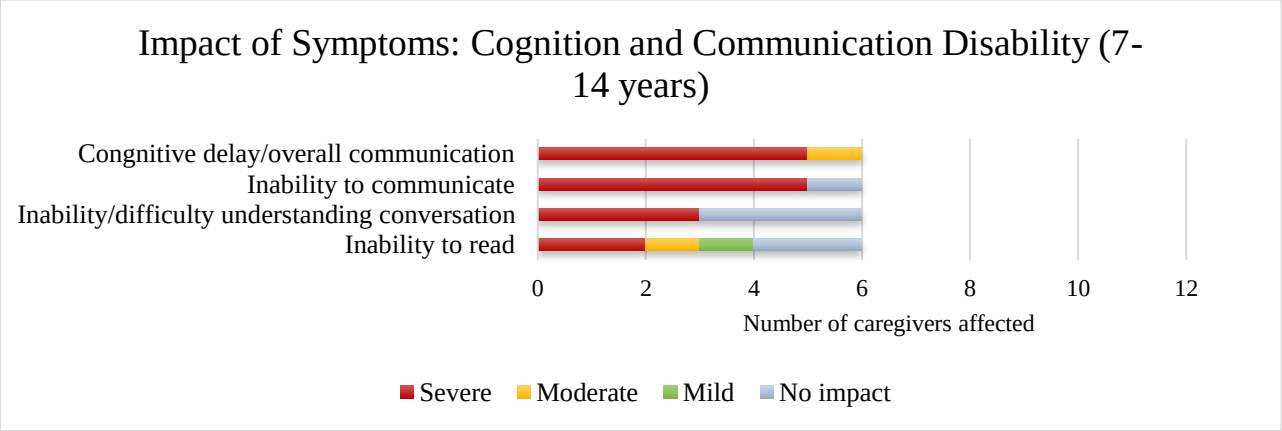
All but one participating caregiver reported moderate to severe impact from cognitive delay or broad communication difficulty (FIGURES 4-6). When asked to comment on this impact, most caregivers described the mutual frustration that results from difficulty understanding the patient's requests. This frustration is often accompanied by aggressive behavior from the child who uses physical behaviors to supplement their impaired expressive communication. When asked to state the most challenging symptom experienced as a caregiver, 4 caregivers cited a communication-related symptom.

FIGURE 4



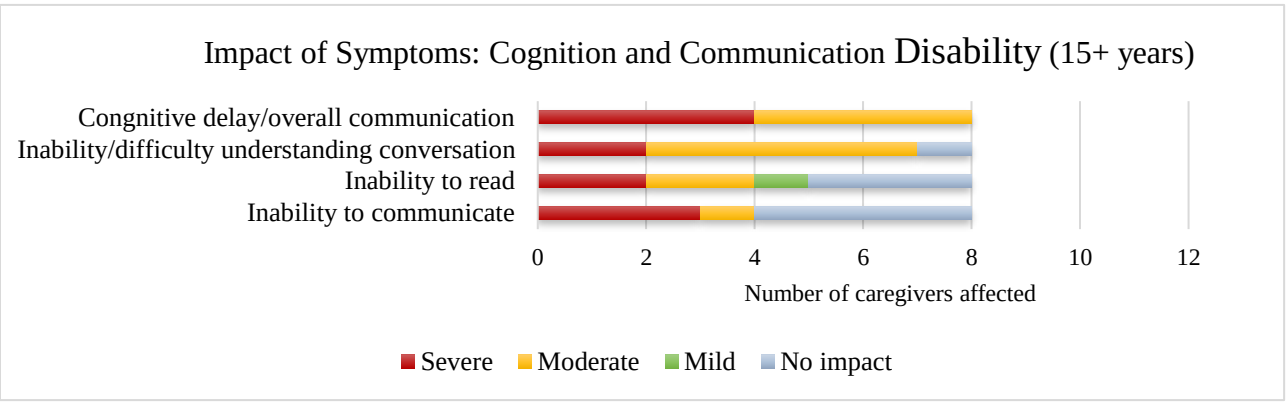
Severity of cognition and communication disability impact for caregivers of children aged 0-6 years. All caregivers reported impact from cognitive delay/overall communication disability, with the majority reporting severe impact. Fewer than half of the caregivers reported impact from the inabilities to read or communicate, as some of their loved ones are too young to do so.

FIGURE 5



Severity of cognition and communication disability impact for caregivers of children aged 7-14 years. Nearly all caregivers of this age group are severely affected by their loved one's cognitive delay and overall communication inability.

FIGURE 6



Severity of cognition and communication disability impact for caregivers of children aged 15 years and older. The majority of caregivers of this age group are impacted by their loved one's cognitive delay, overall communication disability, difficulty understanding conversation, and inability reading. Cognitive delay and overall communication have the most severe impact on these caregivers.

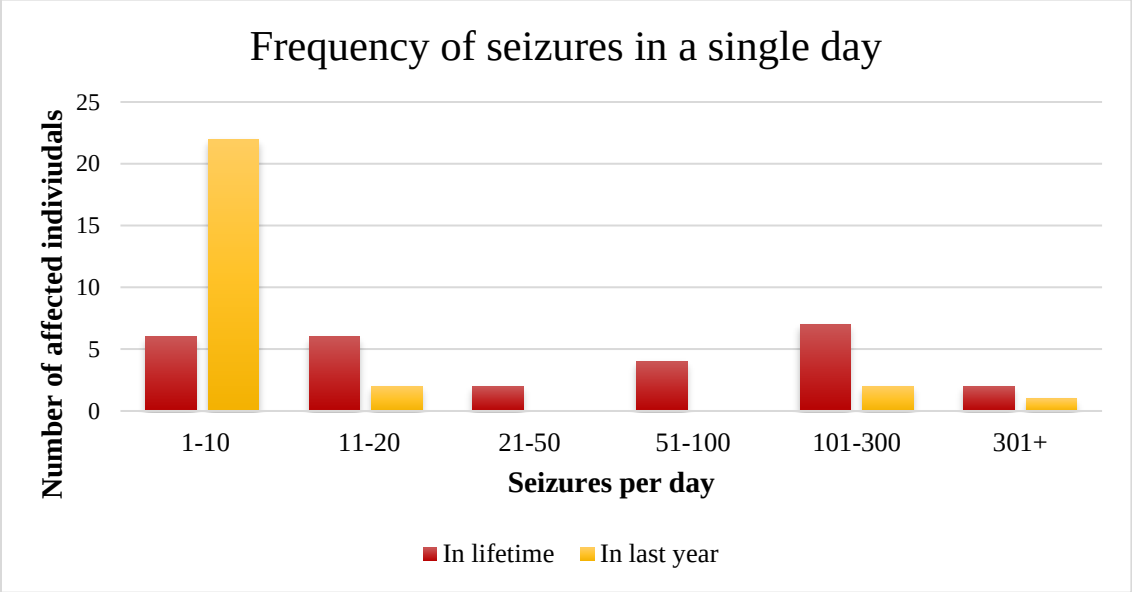
The inability to communicate impacted the fewest caregivers across all age groups. Though most SLC13A5 deficiency patients are unable to clearly speak words and phrases, 10 of their loved ones can communicate through various combinations of signs and specific gestures (n=8), assisted communication devices (n=5), word approximations (n=4), and a few spoken words (n=1). Although communication is a challenge for SLC13A5 deficiency patients and those around them, the patients are often able to learn alternative methods of communication.

Seizures are seen as life-threatening and remain a concern after the affected individual achieves seizure control.

Seeing a loved one experience a seizure is an emotionally challenging experience, and caregivers of loved ones with seizure control remain fearful of breakthrough seizures, accounting for the remaining severe burden. The majority of affected individuals, 24 of the 27, were reported to have partial or full control of their seizures.

FIGURE 7 illustrates the difference in distribution of seizure frequency across the lifetime of the affected individual versus frequency in the last year. When asked for the highest number of seizures the patient has had in a single day ever, the responses were generally evenly spread, highlighting a visible reduction in seizures within the last year as the data skews toward 1-10 seizures in a single day in FIGURE 7. This is indicative of many families achieving some level of seizure control by medication. Just under half of the affected individuals, 13 of the 27, have tried at least 6 different anti-seizure medications in their lifetime to reach this control.

FIGURE 7



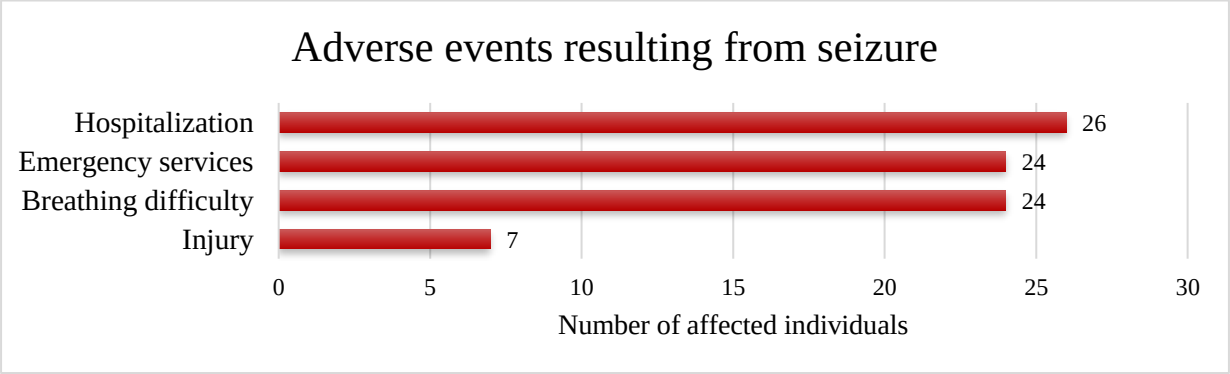
Frequency of seizures in the patient's lifetime versus in the last year. Caregivers were asked to provide 2 ranges regarding seizure frequency: the most seizures their affected loved one has ever experienced in a single day, and the most seizures their affected loved one has experienced in a single day over the past year. Considering the patient's entire lifetimes, the distribution of seizure frequency is fairly equal, but skews toward fewer (1-10) seizures in a day within the last year.

Other aspects of seizures associated with the disorder that significantly affect the patient and their family include extended duration, need for rescue medication, and adverse events that result from a seizure. Nearly half of the affected individuals, 14 of the 27, experienced a prolonged seizure (> 5 minutes) within the last year. Of these 14, 7 reported that the time to recovery back to the child's "normal self" in terms of cognition and alertness after a prolonged seizure was over 24 hours, with 2 of these 7 reporting over 1 week for recovery. In the last year, 15 of the caregivers administered rescue medication during a seizure with a mean of 6.46 doses and maximum of 18 doses. When asked to define "good seizure control" for their loved one, the

most common responses described a reduction in seizures (n=10), no seizures at all (n=7), or seizures that do not require rescue medication or hospitalization (n=4).

Adverse events associated with severe seizures are summarized in FIGURE 8. Nearly all respondents reported necessary hospitalization for their loved one as the result of a dangerous seizure. These often frequent and extended hospital stays for the family are reported to be accompanied by a combination of severe emotional distress from helplessly seeing their loved one suffer, and relief that their loved one is being cared for by professionals. Several caregivers mentioned that their daily lives and even holidays are planned around remaining close to a hospital in case of an emergency.

FIGURE 8



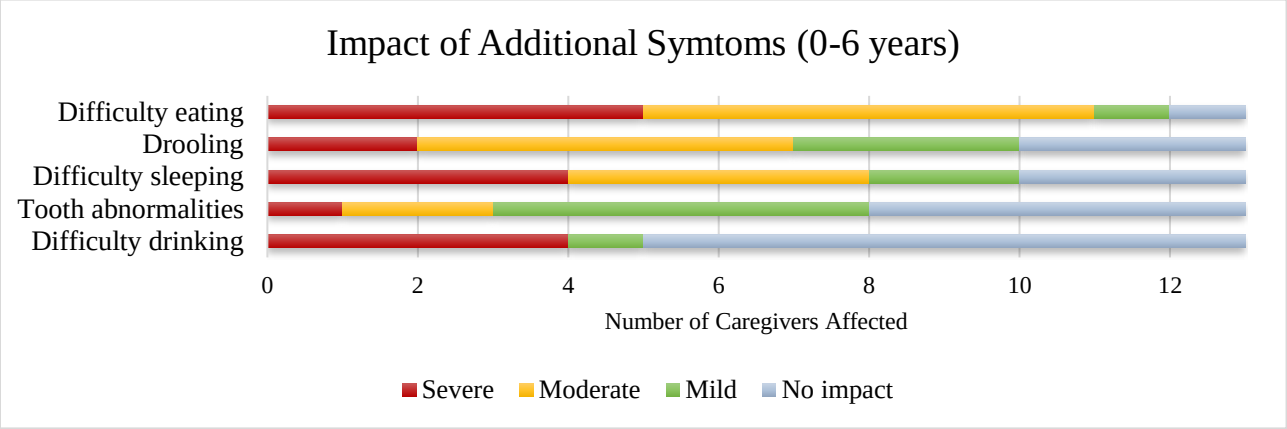
Frequency of adverse events that result from a seizure. Caregivers were asked whether their affected loved one had ever experienced breathing difficulty, been injured, been hospitalized, or required emergency services as the result of a seizure. Nearly all caregivers reported their patient had been hospitalized after a seizure. Most caregivers have witnessed their loved one experience breathing difficulties during a seizure and have contacted emergency services due to a seizure. Nearly 25% of participants reported injury resulting from a seizure.

Of those with some level of control, 13 reported the seizures still having a severe impact on their caregiver's lives and 7 experiencing a moderate impact. Comparatively, every caregiver that reported no seizure control reported severe seizure impact.

Other symptoms such as difficulty eating, drooling, sleep disturbances, and tooth abnormalities affect most of the population, but varied in severity between patient age groups.

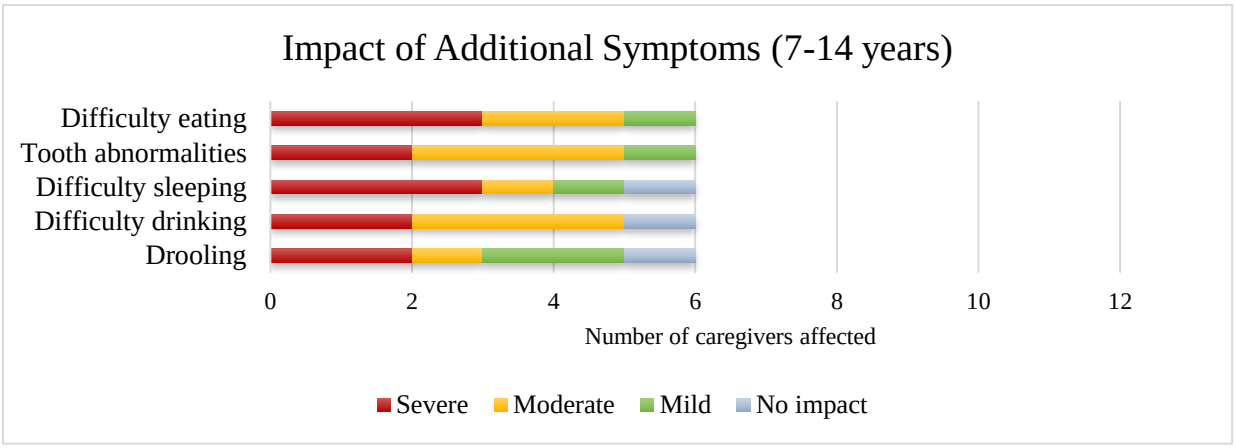
Sleep challenges were reported for 21 of the affected individuals, which include nocturnal awakenings, sleeping too much or too little, and snoring. Of the 21 affected, 20 of these individuals experienced nocturnal awakenings, 5 of which averaged over 6 awakenings each night and 15 wake up 1-5 times each night. The majority of each age group reported impact from sleep disturbances. Only 61.5% of caregivers of children younger than 7 reported impact from their loved one's tooth abnormalities, as opposed to the 100% of each of the older groups (FIGURES 9-11). This could be explained by some of the children not having teeth yet, or that tooth hypoplasia generally gets progressively worse over time. Though the presence of tooth abnormalities was nearly equal for both genders, 64.3% of caregivers of female patients reported moderate to severe impact compared to 38.5% of caregivers of male patients.

FIGURE 9



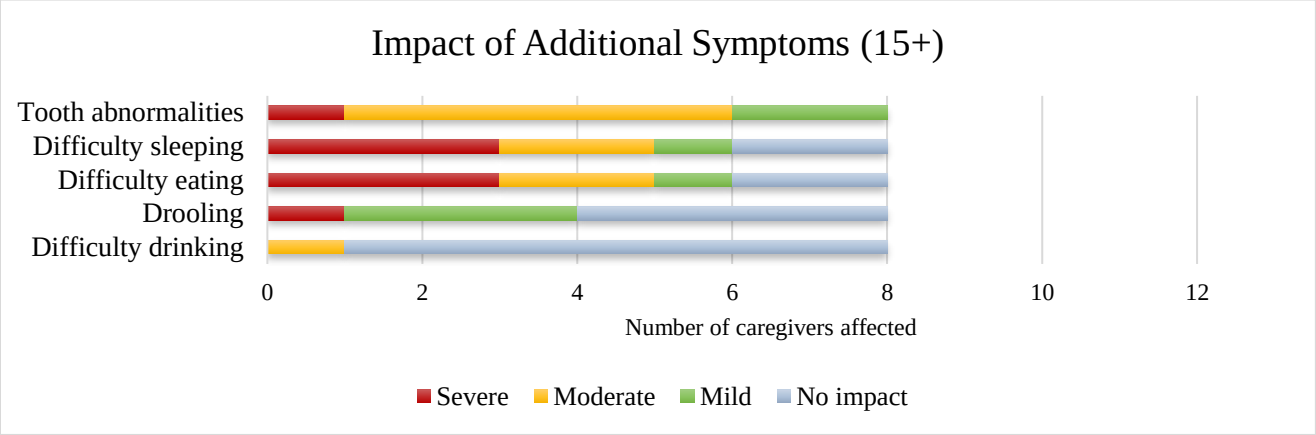
Severity of additional symptom impact for caregivers of children aged 0-6 years. Difficulty eating, drooling, sleeping challenges, and tooth abnormalities affected the majority of caregivers of this age group, but with varying reported severity.

FIGURE 10



Severity of additional symptom impact for caregivers of children aged 7-14 years. All caregivers reported impact from difficulty eating and tooth abnormalities. Most are moderately to severely affected by difficulties sleeping and drinking.

FIGURE 11

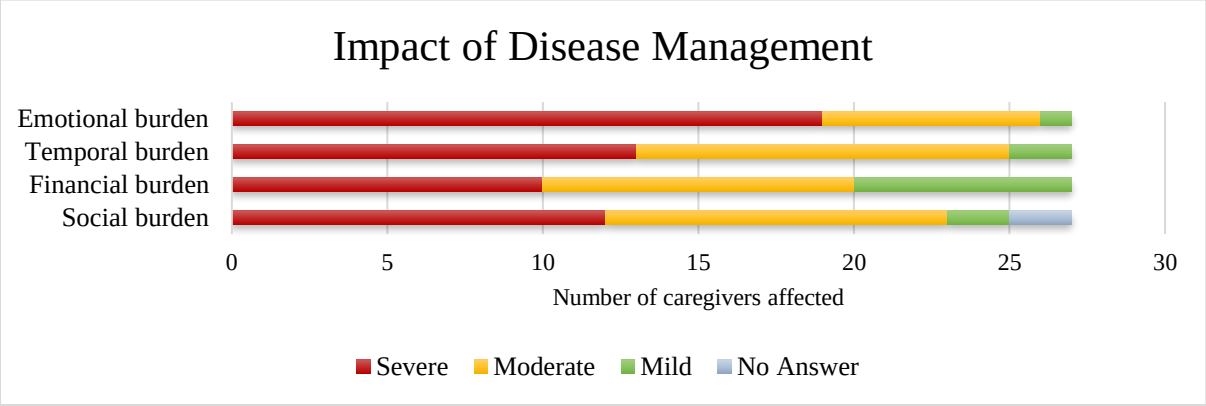


Severity of additional symptom impact for caregivers of children aged 15 years and older. Tooth abnormalities are the only symptom to affect all caregivers in this age group, with 1 affected severely. Difficulty sleeping and eating severely affect the most respondents (n=3) of this age group.

The financial, social, temporal, and emotional burdens of caregiving highly impact nearly all respondents.

Aside from 1 incomplete response, every respondent reported some impact from each aspect of disease management that was questioned: temporal, social, emotional, and financial. The most widespread severe impact for caregivers stemmed from emotional burden. Common themes include depression, anxiety, caregiver burnout, and anger. Two caregivers reported anger for how it not only affects their child with SLC13A5 deficiency, but also their healthy children and entire family, confirming the importance of investigating family impact to improve care that benefits all affected.

FIGURE 12



Severity of disease management impact for all caregivers. All participating caregivers reported impact from all aspects of disease management. One caregiver did not indicate severity of impact for social burden. Emotional burden most significantly affected the caregivers, closely followed by the temporal burden. Financial burden impacted all caregivers, but with the most variable severity.

The temporal burden for caregivers of SLC13A5 deficiency includes the time spent with healthcare professionals to manage their loved one's disease. According to the cross-sectional survey, caregivers take their affected loved ones to a mean of 5.37 healthcare professionals at least once per year, with the most common being neurologists, pediatricians, dentists, and orthopedic specialists. Additionally, each child attends a median of 278 minutes of therapy each week, with a maximum of 1,770 minutes per week. The therapies attended by the most affected individuals include physical (n=24), speech (n=18), occupational (n=18), social (n=5), and aqua therapy (n=4). These activities to manage SLC13A5 deficiency not only consume a significant amount of time for the caregiver but are often associated with high costs. Furthermore, moderate to severe impact of social burden is accompanied by stories of not having the time to leave their

affected loved one to attend an event and struggling to connect with others who do not understand their loved one's disease and their commitment to it. The disparity in severity of financial burden between caregivers shown in FIGURE 12 can be attributed to variation in access to universal healthcare or other government benefits, private health insurance, and the ability of family members to maintain their career.

Variability of impact severity reporting can be attributed to differences in perceived burden from the caregiver. For example, when asked to describe their emotional burden, there was variety between respondents and a mild answer is surprising. Some who reported severe impact noted that they are overwhelmed, extremely exhausted, and have been diagnosed with anxiety, and the mild impact was accompanied by comments that they are able to manage and share the experience as a family. There was no apparent pattern in symptom severity between these sides of the spectrum.

CHAPTER VI

SUMMARY AND CONCLUSIONS

Employing caregiver responses specified which care gaps exist for those with SLC13A5 deficiency, and which of these gaps most significantly affect themselves. In this project, this perspective provided the context to determine which aspects of SLC13A5 deficiency most significantly impact their daily lives, and therefore this study has identified which symptom characteristics are important to track in a clinical trial. Based on the prevalence of severe caregiver impact resulting from motor disability symptoms and speech and cognition symptoms, the most significant clinical outcomes would demonstrate an improvement in these symptom groups. Notably, most affected individuals found some degree of success in seizure management, and so the gap in treatment primarily lies with the motor, speech, and cognition challenges. The highest-impact clinical outcomes are described in TABLE 6.

TABLE 6. High-impact clinical outcomes for clinical trials of SLC13A5 deficiency.

Symptom Group	Benefit	Clinical Outcome
Communication Disability	Caregiver: Improved ability to care for their loved one Patient: Improved social abilities, reduced frustration	Communicating with specific gestures
		Using an assisted communication device
		Approximating words
		Speaking words
Motor Disability	Caregiver: Improved temporal burden, reduced need to provide physical support Patient: Reduced injury risk, more independence	Sit up independently
		Stand independently
		Walk more than 2 steps independently
		Feed themself
		Toilet themself
		Bathe themself
		Dress themself
Cognitive Disability	Caregiver: Reduced frustration Patient: Able to learn independently, more aware of social cues	Understanding 1-step commands
		Understanding 2-step commands
		Reading
Seizure Control	Caregiver: Reduced emotional and financial burdens Patient: Fewer antiseizure side effects, reduced injury risk, less time in hospital, improvement in cognition and motor ability	No need for rescue medication
		No need for emergency services or hospitalization
		No prolonged seizures (>5 minutes)
		Reduction in seizures
		Seizure control without medication
Tooth Hypoplasia	Patient: Reduced pain and sensitivity	Slower tooth deterioration
		Healthy teeth
Sleep Challenges	Both: Improved rest	Fewer nocturnal awakenings

The clinical outcomes of the abilities to complete life tasks such as toileting, bathing, and dressing would represent an improvement in both motor skills and cognition, as well as alleviate the physical burden for caregivers across all age groups. Such an improvement would lead to

improved independence for the child and a time saver for the caregiver. Additionally, improvements in balance and coordination would represent significant improvement across all age groups, particularly a reduction in injury risk. Improved motor skills could also alleviate the burden stemming from the difficulty when eating, which caregivers of all ages are affected by.

A clinical outcome that would improve the relationship between affected individuals of all age groups and their loved ones would be improved communication ability. At its best, a treatment could facilitate the affected individual's ability to speak words, but it could also lead to success in word approximations, gestures, and assisted communication devices. Improved communication would positively impact caregivers and individuals across all affected age groups. Further improved communication could come from increased cognitive ability and subsequent ability to understand conversation.

Though most of the participants reported some level of seizure control by medication, concern for antiseizure medication side effects persists. Seizure control beyond modern antiseizure medication would be significant for all caregivers. Reduction of seizure frequency and severity not only has the potential to improve other clinical outcomes such as cognition and motor development, but it would also positively affect the emotional burden of caregivers who live in fear of the symptom.

Other clinical outcomes of note include the progression of tooth hypoplasia as the subject ages and change in nocturnal awakenings.

This study demonstrated that families of people affected by SLC13A5 deficiency value clinical outcomes in more nuanced ways than medical professionals, highlighting the importance of including their perspective in treatment development.

Limitations

In an effort to not overlap with the ongoing natural history study and prevent "survey fatigue", the cross-sectional survey refrained from asking more quantitative and specific questions about symptoms, for example specific seizure semiology. This capstone project is meant to complement the data obtained in this clinical study to progress SLC13A5 deficiency understanding overall. Limitations also include the small number of families available in the community, which was further limited to those who understand English. Additionally, the survey responses could have suffered from recall bias. Caregivers of children with SLC13A5 deficiency and other rare diseases are often balancing many tasks to care for themselves and their families, so it is expected that details are forgotten. Furthermore, only one parent for each child was surveyed, of which 88% were female, resulting in the possibility of gender bias. Finally, selection bias could have resulted as participation in the study was entirely voluntary and caregivers most interested in clinical research would have been more inclined to participate.

Future Directions

Future research should continue to value the input from the patient community and seek the voices of other families affected by rare disease. Information from such research should be shared with families affected to encourage participation in the rare disease community, which then leads to more research and improved relationships between families, researchers, and providers all with the same goal of improving care. There are many more disease communities that can benefit from these relationships.

CHAPTER VII

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CHAPTER VIII

CAPSTONE PROJECT EXPERIENCE

Project site

My capstone project was conducted at the University of Texas Southwestern Medical Center in Dallas, Texas. Within UTSW, the Perot Foundation Neuroscience Translational Research Center at the Peter O'Donnell Brain Institute conducts clinical trials to learn more about neurological health. The Gene Therapy Program primarily conducts clinical trials for rare pediatric diseases and disorders.

Journal summary

During my capstone project, I was the Clinical Data Specialist within the Gene Therapy Program and Pediatric Neurology. I was responsible for submitting the study to the Institutional Review Boards, building the electronic survey, extracting the data from REDCap, and analyzing the data from the redacted data from Taysha Gene Therapies and my own survey.