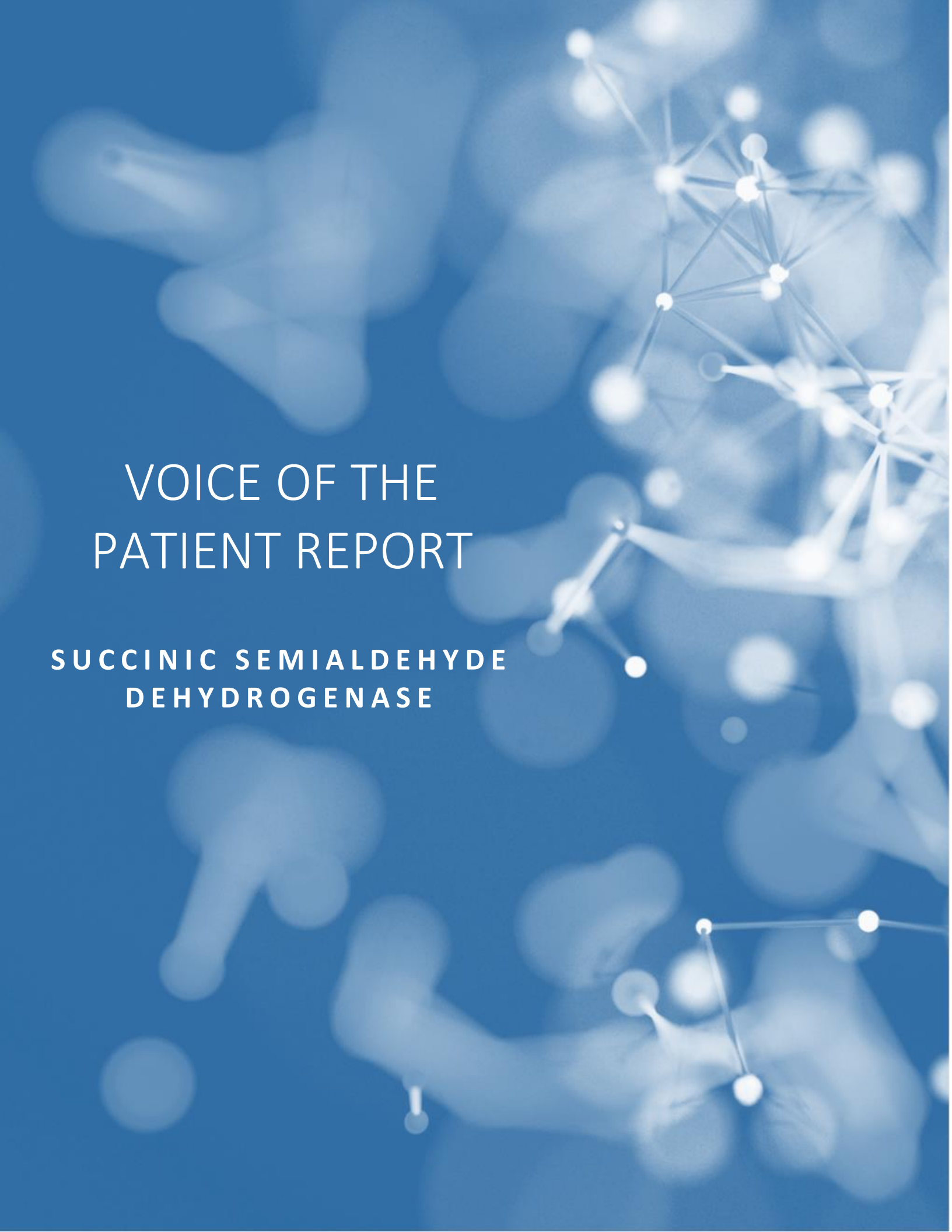

VOICE OF THE PATIENT REPORT

SUCCINIC SEMIALDEHYDE DEHYDROGENASE

SSADHD VOICE OF THE PATIENT REPORT COVER PAGE

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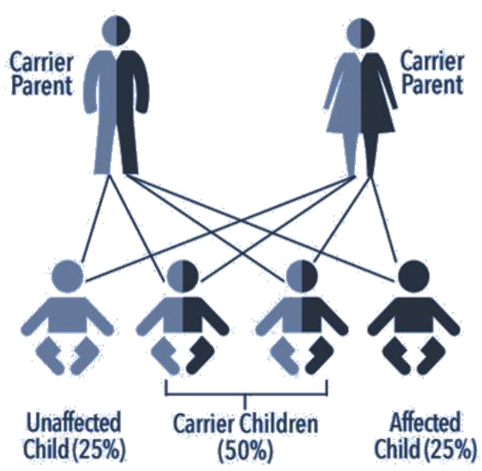
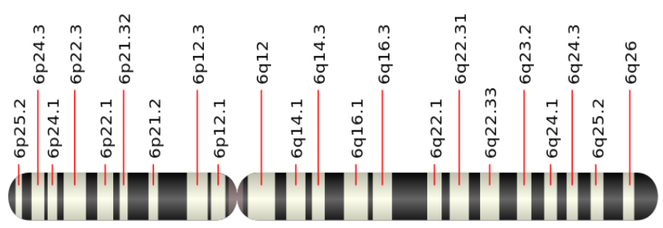
SUCCINIC SEMIALDEHYDE DEHYDROGENASE DEFICIENCY

SUCCINIC SEMIALDEHYDE DEHYDROGENASE DEFICIENCY (SSADHD) IS A RARE PEDIATRIC INBORN NEUROTRANSMITTER DISORDER OF GABA METABOLISM.





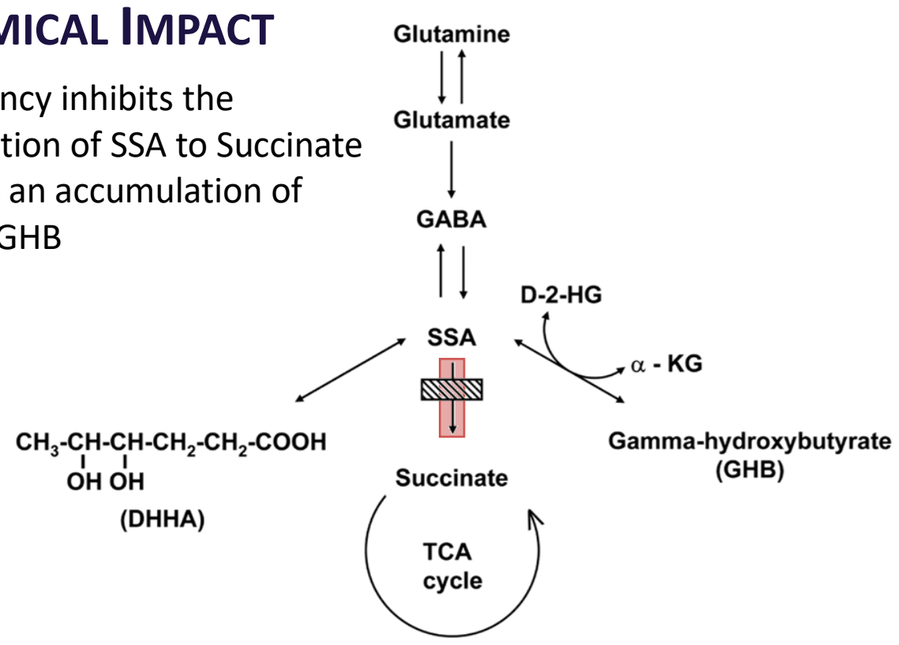
SINGLE GENE 6P22

ALDH5A1

AUTOSOMAL RECESSIVE

BIOCHEMICAL IMPACT

The deficiency inhibits the transformation of SSA to Succinate and causes an accumulation of GABA and GHB



1 IN 340,000

Less than 10% of SSADHD patients are properly diagnosed

DIAGNOSIS

"It's been a long journey…it's been like throwing darts and trial and error, and along with those throwing darts, we're also throwing money and emotions and energy and a lot of prayers."

SSADHD is detectable with just a few drops of bloods at birth but currently isn't screened for by any newborn screening program

IT IS ESTIMATED THAT THERE ARE OVER A 1,000 UNDIAGNOSED PATIENTS WITH SSADHD IN THE US

SPEECH IMPAIRMENT

"He got really, really frustrated because he couldn't express himself—we have holes in the walls to demonstrate that. He had challenges with behavioral issues as a result of not being able to express himself."

INTELLECTUAL DISABILITY

"We continue to have reading sessions and we'll get somewhere, but then we lose it. We get it, and then we lose it. We don't keep after it. I mean, you can have (what seems like) a miracle with spelling and then you turn around the next day and it is as if they never saw the word, 'the', ever."

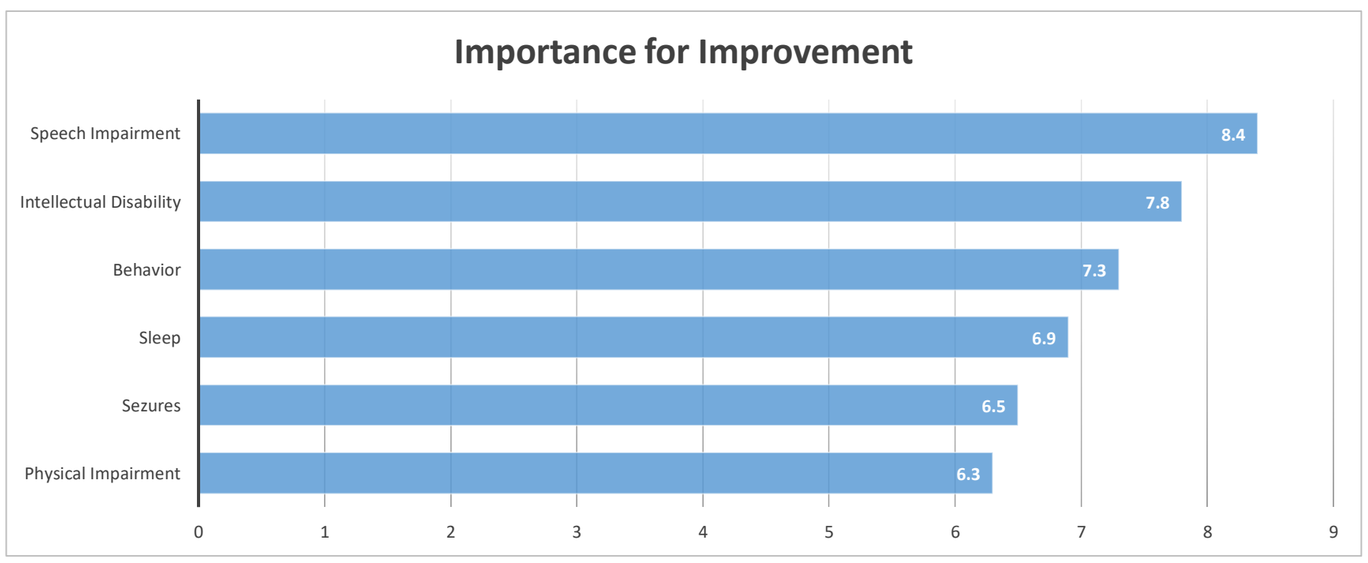
BEHAVIORAL & PSYCHOLOGICAL

"[Our child] has basically no friends. Sometimes, neighbor kids tolerate him, but he doesn't really get involved into play."

SLEEP DISTURBANCE

"When [our child] was little, he slept all the time; he was only awake for about 30-minute intervals and would sleep for about an hour to hour and a half, then wake up for another 30 minutes."

MOST BURDENSOME SYMPTOMS



PHYSICAL IMPAIRMENT

"[Our child] was super hypotonic and couldn't do much of anything—crawl, walk, all of it. This led to shallow hip sockets, and the ligaments in her knees and ankles didn't develop properly."

SEIZURES

"The other issue is the fact that he's lost his independence. He'll never walk alone again—simple as that. He is mobile, he can walk .... but if he's out of his wheelchair I hold him to make sure he doesn't fall."

Adult reports indicate worsening epilepsy and high Sudden Unexpected Death in Epilepsy risk.

Watch the entire meeting on YouTube

INTRODUCTORY REMARKS

On July 8, 2022, I had the distinct privilege to look out at a banquet room full of Succinic Semialdehyde Dehydrogenase Deficiency (SSADHD) families and welcome them to the SSADHD Externally Led-Patient Focused Drug Development (EL-PFDD) meeting. The room was full of over a hundred patients, caregivers, researchers, and clinicians who came together from around the world to share the impact that this rare disorder has on their daily life. Additionally, we were joined remotely by families, from across the world, whose patients were too fragile to travel and attend the meeting in-person.

This meeting was a culmination of over a year's work including smaller group meetings, caregiver and patient interviews, and an extensive survey which was shared with all registered members. SSADHD is highly underdiagnosed and has a varying phenotype, making it difficult to focus on just 6 specific symptoms to best utilize the time we had together at the meeting.

The size of the group was truly a reflection on the commitment that this community has towards finding better treatment options, eliminating the diagnostic odyssey and ultimately finding a cure for SSADHD. I'm beyond grateful to those families and patients who took on the challenge of voicing their perspective knowing how hard it is for them to travel, speak freely of their personal difficulties and disrupt their routines by spending time outside of their own environment.

I'm thankful to William Lewallen, FAC-P/PM, International Program Analyst for the International Programs and EL- PFDD Staff/Strategic Initiatives and Michelle Campbell, PhD, in the Office of Neuroscience, Office of New Drugs at the US Food and Drug Administration for guiding us through this process and personally joining us to see and hear firsthand the complexities that SSADHD patients and caregivers face on a daily basis.

I know that the EL-PFDD Meeting could have gone on for days rather than just 8 hours and I would have still felt the limitation in voicing the full impact of SSADHD. Although we focused on just 6 specific symptoms, there are 6 more that immediately come to mind, 6 more that pale in comparison to larger issues, and 6 more that we are undoubtedly facing as our patient ages.

Lastly, I would like to extend my sincere gratitude to Alice McConnell for her energy and enthusiasm in bringing this project to fruition. Thank you to Mousumi Bose, Ph.D., Associate Professor, at Montclair State University, along with her team, for their continued commitment to rare diseases by coordinating this project and facilitating our interviews, survey, polling and meetings. Gratefully the unwavering support and vast knowledge of Jean-Baptiste Roullet, PhD and K. Michael Gibson, PhD, FACMG, emeritus, from Washington State University is reflected in every aspect of this project. Last but not least a thank you to our industry partners who supported the meeting, GC BioPharma and Speragen.

I'm hopeful that this project will bring an effective treatment option to the forefront for SSADHD patients.

Sincerely

Carolyn Hoffman

Co-Founder

SSADH Association

EXECUTIVE SUMMARY

Succinic semialdehyde dehydrogenase deficiency (SSADHD) is an ultra-rare, inherited disorder of GABA metabolism, caused by pathogenic variants in the ALDH5A1 gene. Currently, approximately 200 patients have been diagnosed worldwide, but this number is likely to be higher due to underdiagnosis and misdiagnosis. Members of the global SSADHD community joined together over the last year to describe the effects of SSADHD on their lives, the burdens of the disease and its lack of treatments, and unmet needs in a meeting convened as part of the U.S. Food and Drug Administration's Externally Led Patient-Focused Drug Development program.

This report focuses on the findings from the externally led patient focused drug development meeting held on July 8, 2022. It identifies topics, symptoms, and challenges deemed most impactful by patients, families, and caregivers. The report also contains insightful survey responses and personal stories of individuals impacted by SSADHD. Due to speech and cognition challenges in SSADHD, the majority of the information collected for this effort was gathered from family caregivers (parents and legal guardians) of patients with SSADHD.

A total of 104 individuals participated in the meeting. Eighty-two community members attended in person, with thirty-one others participating virtually via Zoom conference. These included individuals diagnosed with SSADHD, parents, siblings, community advocates, and professionals in the field. There were some families with more than one member living with SSADHD, and disease severity ranged from mild to profound impacts on daily life. Existing treatments were generally reported to have varying success in terms of managing symptoms, with many experiencing unmet medical needs. Forty-six caregivers attended in person along with fourteen individuals with SSADHD.

From our discussions with family caregivers, the process of getting an accurate diagnosis was lengthy and frustrating, with serious consequences for individuals and families affected by SSADHD. The length of the diagnostic odyssey of patients varied, from just a few months to longer than 20 years, despite the appearance of symptoms in infancy and early childhood. Misdiagnoses were common, which sometimes led to ineffective, costly, and time-consuming therapies. Provider-family interactions also significantly impacted the delayed diagnosis many patients experienced in their diagnostic odyssey. In retrospect, early diagnosis would have stopped the painful diagnostic odyssey, given patients and caregivers access to early intervention, the SSADHD community, and the resources and support that come with it. Furthermore, the difficulty in obtaining an accurate diagnosis suggests a large population of undiagnosed patients. Tools such as newborn screening and inclusion of SSADHD-causing pathogenic variants in symptom-specific genetic screening panels would improve the ability to better understand the disease and improve future clinical trial participation.

The symptoms affecting patients with SSADHD fall into six primary areas, including intellectual disability, behavioral and psychological symptoms, seizure disorder, sleep disturbances, speech and communication impairment, and mobility and other physical symptoms. Among these, speech and intellectual disability were reported as the most burdensome symptoms, followed by behavioral and psychological symptoms, and seizure activity. Seizure types included myoclonic, tonic-clonic, atonic, and absence seizures. Seizures can eventually lead to sudden unexpected death in epilepsy. Anxiety, obsessive compulsive disorder, attention deficit disorder, oppositional defiant disorder/aggression, and depression were all reported as behavioral/psychological symptoms of the disorder. Symptoms of sleep disturbances included restlessness, insomnia, and sleep attacks. Speech and communication impairment was characterized by delayed or abnormal speech development, apraxia, and dysarthria. Mobility impairment and physical symptoms of SSADHD included low muscle tone, difficulties with gross and fine motor skills, balance, scoliosis, and movement disorders.

The impacts of these symptoms are profound, and affect independent activity, social interactions, education, employment, safety, and emotional wellbeing. Furthermore, these symptoms create significant emotional, social, and financial burdens for caregivers and extended family.

Current overall management of SSADHD is solely symptomatic, and primarily include pharmacological treatment, supportive therapies, and assistive resources. Various medications are currently prescribed to patients with SSADHD for the treatment of behavioral/psychological symptoms, sleep disturbances, and seizure activity. These treatments are often met with mixed success, with inconsistent effectiveness on symptoms, often requiring the need for multiple medications, with various adverse side effects as well. Rehabilitative therapies such as occupational and physical therapy have been shown to improve gross motor skills and some fine motor skills, but speech therapy for verbal communication has been less consistently effective in SSADHD. Assistive tools for speech and language have also been useful in communication, but relatively limited in scope due to availability and utility, depending on the circumstances. Assistive devices such as orthotic shoes, braces, and gait trainers have been useful in mobility.

Many patients have been enrolled in previous and ongoing clinical trials for SSADHD, and families of these patients have learned that thorough and timely communication between the clinical research team and families with enrolled patients is imperative for sustainable clinical trial participation. Families require researchers and staff members that effectively communicate the intent of each study, expected outcomes, and potential adverse effects to the patient and families prior to enrollment. Families also require collaboration from the research team to ensure that patient needs are met given their existing challenges, with the goal to minimize any undue stress during the clinical trial process.

Specific outcomes for future clinical trials, according to patients and caregivers, should depend on improvement of symptoms that have the most impact. These include improved communication through increased enunciation, word and sentence formation, improved executive function through increased frequency of task completion (such as activities of daily living) or concrete decision making. Other specific outcomes should include decreased behavioral/psychological symptoms, increased sleep hours during the night and increased wakefulness during the day, decreased mood swings, decreased seizure activity, less time to walk to specific destinations, decreased reliance on assistive devices and resources, and improved emotional wellbeing.

This first-of-its-kind meeting for the SSADHD community identified the biggest impacts of the disorder, guidance for future clinical trial design and outcomes, as well as strategies to improve accessibility to clinical trials for patients and families. Due to the fact that current treatments for SSADHD are exclusively symptomatic, there is a considerable need for better treatments for SSADHD that comprehensively address the broad variation of symptoms and its impacts on daily life, independent activities, and overall quality of life. Additionally, because SSADHD is vastly underdiagnosed and often misdiagnosed, there is an urgent need for more research and education regarding screening and diagnosis. Improved screenings and the inclusion of SSADHD on newborn screening panels as well as other symptom-based genetic testing panels can aid in earlier diagnosis and improved care for individuals with SSADHD.

In providing this opportunity for greater understanding of SSADHD and current needs, families expressed great hope for the future of the SSADHD community. Attendees also benefited from the opportunity to learn from others' lived experiences and strengthen community networks. The shared needs and experiences identified at this meeting are important steps to significant progress and an improved quality of life for patients and families affected by SSADHD.

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L I M I T A T I O N S

The current prevalence studies for SSADHD show that in comparison to cases reported in the literature and known in the patient registries, that less than ten percent of the patient population has been diagnosed. This is particularly true for patients of non-European heritage. From the literature the median age at diagnosis is 3 years (Brown, 2020) and it is common for patients to be diagnosed in their teens, twenties, or post-mortem. The critical newborn and infancy periods are not understood since the patients are not diagnosed at birth. At the extreme ends of the phenotype, the most severe die in infancy and the mildly affected are never diagnosed. With less than ten percent of the patient population diagnosed the full spectrum of the disorder cannot be fully represented in this report.

The phenotype of SSADHD is broad. The symptoms that affect patients vary greatly, even between sibling sets. The symptoms of SSADHD can be quite severe. Symptoms that would be significant if presented alone to a healthy individual may not even be considered an area of concern for patients with SSADHD and their caregivers. In addition, given the broad spectrum of symptoms, the undiagnosed patient population, the time, regional, and cost limitations of data collection - this report cannot address all of the significant symptoms that patients may experience.

Patients with SSADHD and their caregivers have grown accustomed to the burden of the disorder and have created adaptations, accommodations, and coping skills to deal with the daily difficulties. The symptoms of SSADHD are chronic and can be progressive. Unlike the experience with acute symptoms, patients with SSADHD have to modify their lives to accommodate; it becomes their new normal. While a patient or caregiver may not consider all chronic symptoms to be severe, modifications and adaptations are necessary to manage day to day activity. Symptoms might not be judged by the patient and caregiver as burdensome, as if it happened to an unaffected person in more acute circumstances. For example, in managing a speech impairment, a common symptom of SSADHD, some patients and caregivers learn sign language or use a computer aided device to communicate. Once this way of communicating becomes the new normal it is not reported as burdensome because it is chronic and routine and not a sudden onset.

Patients with SSADHD do not live in a vacuum. The condition affects their families, caregivers, and community greatly. Although the patients live with the symptoms of the disorder their families, caregivers, and the community at large also carry the burden of the disorder. For many caregivers and family members it consumes their lives causing physical, relationship, social, financial and emotional stress. The patient focused drug development process captures the patient's experience of the disorder but doesn't capture the global adverse effects of the other lives impacted by the disorder – we have tried our best to also include the impacts on the lives of the family members and caregivers who live with and care for patients.

SSADHD EXTERNALLY-LED PFDD MEETING DESIGN

The overarching goal of the SSADHD Externally Led Patient Focused Drug Development (EL-PFDD) meeting, in addition to the preliminary meetings and surveys, was to specifically identify what individuals with SSADHD and their families (as opposed to clinicians monitoring individuals with SSADHD) need in terms of therapeutic benefits, especially with respect to clinical trials for SSADHD. To reach this goal, we engaged as many patients and caregivers from within the SSADHD population as possible and had them describe the impact of their condition on their lives – how they feel, function, and survive. They identified the disease features that patients are the most eager to be treated for, how much they are willing to be personally involved in the drug development process, and the risks they are willing to take to help develop such treatments.

The insight gained from this meeting and related preliminary sessions will ensure that patient input is an integral part of future trial designs and drug development strategies, along with the information obtained from the pre-meeting interviews and caregiver surveys, and the meeting polling results.

DATA COLLECTION FOR MEETING AND PRELIMINARY SESSIONS

There are very few studies that report on the individual or family experience with SSADHD. Our group recently published a qualitative preliminary evaluation of the daily impacts of SSADHD, as reported by family caregivers (parents) to individuals with SSADHD. In this study of 5 caregivers representing 7 individuals with SSADHD, difficulties with physical function (as described by mobility, fatigue, seizures and sensory processing), cognitive and intellectual function, social and emotional function, psychological and behavioral function were found to have effects on daily living and quality of life in living with SSADHD. Additionally, caregivers reported that SSADHD had impacts on their own daily lives, including the burden of tasks related to managing the care of an individual with SSADHD, and on maintaining relationships with friends and family. The results of this study were used as a preliminary template for the organization of topics for the EL-PFDD meeting (Bose, 2021).

In preparation for the EL-PFDD meeting in July 2022, starting in September 2021, preliminary caregiver focus groups (3 total, with 4-6 caregivers per group), individual caregiver interviews (2 total), and individual patient interviews (5 total) were completed through May 2022. During the caregiver focus groups and interviews, participants were asked questions related to the specific ways that SSADHD affected their child's life, and what their family needs are with respect to clinical trial participation. For the patient interviews, participants were asked questions about the difficulties for the individual related to the disorder, what they wish to see improved in their abilities if there were a treatment for

the disorder, and how they feel about medical tests and going to the doctor. These meetings provided the foundation and framework for the preliminary survey that was distributed to caregivers and care providers of individuals with SSADHD prior to the meeting. Taken together, these preliminary sessions and survey results identified the specific symptom categories and related burdens of SSADHD that significantly impacted most patients and caregivers, according to their perspective. These categories were: seizure disorder, intellectual disability, behavior problems, sleep disturbance, speech challenges, physical limitations, and diagnostic odyssey. Many other symptoms and related burdens were identified during the discussions, however, in the interest of time and resources, we kept the focus of the EL-PFDD on the most common and universally impactful symptoms for the majority of individuals affected by SSADHD.

During the EL-PFDD meeting, we invited two caregivers per category to briefly share their experience in dealing with disease burdens with personal stories. For the speech and diagnosis sessions, individuals with SSADHD were invited to accompany their caregiver and participate in the discussion. We also included an additional category discussing experiences and needs regarding clinical trial participation. The speakers represented diverse perspectives, including a spectrum of age categories (for both the individual with SSADHD and their caregivers), geographic region, and specific disease experiences.

For each category that was covered during the EL-PFDD meeting, the speaker stories were followed by live polling and a subsequent 30-min discussion with all attending patients and caregivers (in person or virtually).

ATTENDEES AND PARTICIPANTS

There were 82 people in attendance at the meeting and 31 others participated in the meeting via Zoom conference. Two members of the FDA came to the meeting to hear directly from families affected by the disorder, 11 more FDA members participated online. Given the considerable impact that SSADHD has on an individual's cognitive and communication ability, in most cases caregivers spoke on behalf of their family members with SSADHD.

Forty-six of the people who attended the in-person meeting were family caregivers of an individual with SSADHD; 14 of these individuals were in attendance as well. Seventeen caregivers participated online. There were 9 clinicians/researchers present in-person, and 2 participating online, and 12 other stakeholders participating either in person or online. In total, there were 104 individuals that participated in the meeting.

BACKGROUND ON SSADHD

WHAT IS SSADHD?

Succinic semialdehyde dehydrogenase deficiency (SSADHD) is the most prevalent inherited disorder of GABA metabolism (Lapalme-Remis, 2015; Rodan, 2015; Malaspina, 2016; Attri, 2016). It is an ultrarare condition caused by homozygous or compound heterozygous pathogenic variants in the *ALDH5A1* gene (OMIM 610045) on chromosome 6p22 resulting in impaired degradation of succinic semialdehyde and accumulation of both γ-aminobutyric acid (GABA) and γ-hydroxybutyric acid (GHB) (Martin, 2021).

Watch the History of SSADHD

DIAGNOSIS OF SSADHD

Early diagnosis of a rare, genetic condition provides the best opportunity for treatment and the most likely chance for positive outcomes to improve quality of life for the individuals living with the condition and their families. Early diagnosis requires knowledge of disease – including genetic variants contributing to disease and the associated biomarkers. Approximately 200 patients have been reported worldwide. However, the true prevalence is likely higher considering the nonspecific neurological phenotype and potential for misdiagnosis. A recently published study estimated the world-wide disease prevalence of 1:340,000, with the disorder being as high as 1:258,000 in East Asian populations in the U.S., with a population of ~330 million, estimates suggest there are ~1000 individuals in the U.S. with SSADHD (Martin, 2021).

Thus, the estimated prevalence is likely an underestimate of the global carrier frequency and disease incidence due to the lack of knowledge related to the function of missense variants in *ALDH5A1*. Disease burden may also be higher in some populations than currently reported, requiring improved screening and access to care worldwide.

Diagnostic challenges begin with access to screening. The two most commonly used methods to diagnose SSADHD are an organic acid urine screen looking for elevated levels of GHB or by molecular analysis identifying pathogenic variants in the *ALDH5A1* gene. These tests can be costly and are not widely available throughout the world.

In addition to accessibility, there are limitations for both methods. Urine organic acid screen cases are frequently missed (Gasconet, 2007), and for molecular testing, the ALDH5A1 gene is not always included on all of the panels that include symptoms of SSADHD (intellectual disability, ataxia, seizures, developmental delays, ADHD, OCD, and others). Whole exome sequencing also has limitations (Gilissen, 2014). In addition, we know that at least 5-10% of individuals who undergo clinical genetic testing (genomic sequencing) have more than one identifiable genetic diagnosis. This situation may result in the lack of a pursuit of a second diagnosis, even if the individual has features beyond what may be typically observed in someone with that initial diagnosis.

The challenge with any metabolic disease is fully capturing the spectrum of the phenotype and communicating and educating the medical community to aid in diagnosis. Severity of disease ranges from mild-moderate to profound in SSADHD, and this breadth of phenotypic presentation and lack of health provider knowledge about SSADHD and about metabolic screening often complicate and delay diagnosis. Unfortunately, even individuals with severe disease symptoms are often not efficiently diagnosed, and mild disease may never be diagnosed or patients may not even seek care, not realizing their situation is not typical.

Efforts to expand screening for SSADHD are sorely needed. Potential barriers to childhood screening include the need for clinician education at all levels about SSADHD and how to obtain appropriate screening. While screening at any age should be considered, newborn screening for SSADHD is a significant need. Efforts are underway to develop the resources, education, and tools to facilitate newborn screen for disorders of GABA metabolism. Earlier diagnosis is critical for the individual and their family—newborn screening is the best mechanism to obtain an early, accurate diagnosis. Newborn screening occurs for every infant born in the U.S. regardless of socioeconomic status, insurance coverage, or geography. Removing or reducing barriers to care by enhancing newborn screening to include SSADHD is cost-effective, expeditious, and non-invasive – and will reduce health disparities in both diagnosis and care. Newborn screening for SSADHD and other GABA metabolism disorders can be done by MS/MS technology using a dried blood spot, similar to current newborn screening methods. The cost-effective approach that state-supported newborn screening services provide is the optimal approach to early screening and diagnosis.

As described, we expect that SSADHD is currently underdiagnosed and represents a broad range of phenotypic severity. This delay in diagnosis leads patients into long diagnostic odysseys, which are often expensive and require unnecessary invasive and painful testing often over the course of many years. It also disenfranchises them from participating in the SSADHD patient community, advocacy work, natural history studies, clinical trials, and even the patient focused drug development process.

SYMPTOMS OF SSADHD

Epilepsy is a common source of morbidity in Succinic Semialdehyde Dehydrogenase (SSADH) deficiency. Adult reports indicate worsening epilepsy and high Sudden Unexpected Death in Epilepsy (SUDEP) risk (DiBacco, 2018).

According to reports in the medical literature, initial or “presenting” symptoms vary from case to case. However, initial symptoms often include delays in achieving certain motor milestones (e.g., crawling, sitting unaided, walking without assistance), reduced muscle tone (hypotonia), and/or intellectual or language delays. In some cases, additional presenting symptoms may be present, such as an impaired ability to coordinate voluntary movements, episodes of uncontrolled electrical activity in the brain or seizures, and/or certain abnormalities during early infancy, including failure to cry or respond to certain visual stimuli. Although symptom onset is usually detected during infancy or childhood, the disorder sometimes does not get diagnosed until later in life, and frequently not until adulthood. Symptoms associated with SSADHD may be mild, moderate, or severe and often vary greatly from case to case even between siblings. The symptoms of SSADHD include the following manifestations:

Delayed gross motor development, delayed mental, development, delayed fine motor skill development, delayed speech and language development, hypotonia, seizures, hyporeflexia, ataxia, behavioral problems, feeding difficulties, hyperkinesis, sleep disturbance, neonatal problems, EEG abnormalities, psychoses, MRI or CT abnormalities, gastrointestinal problems, oculomotor apraxia, microcephaly, macrocephaly, hyperreflexia, somnolence, autistic features, choreoathetosis, myopathy.

CURRENT TREATMENTS

It is widely accepted that the neurometabolic consequences of SSADHD (increased GABA and GHB, decreased GABA receptor expression) are key determinants of clinical severity and disease burden, and disease burden is extreme for both the individuals with SSADHD and caregivers (Bose, 2021). It follows that developing treatments with curative potential are warranted to address considerable and urgent medical needs.

Unfortunately, there is no cure for SSADHD, and treatments are exclusively symptomatic (reviewed in Didiasova, 2020). Pharmacologic treatment is generally aimed at alleviating symptoms of the disease, primarily seizures and psychiatric sequelae. Currently employed symptomatic interventions primarily target seizures, behavioral symptoms (ADHD, OCD, anxiety), sleep and GI disorders. Individuals with SSADHD are also taking numerous dietary supplements, the efficacy of which in treating disease-related symptoms remains unconfirmed. The antiepileptic vigabatrin is sometimes used, but it is a last-recourse drug for refractory seizures because of a significant risk for ocular toxicity. The use of valproic acid, another antiepileptic drug, is also limited because of the potential for inhibition of residual SSADH activity.

THE GREATNESS OF SSADHD

"My son is incredibly funny. He is nonverbal so he is great at slapstick!"

"My daughter is the kindest, most open, loving person that I know. She accepts people how they are and has the sweetest soul. "

"My son is very kind and caring."

"My daughter is so full of love and cuddles. She is everyone's favorite person."

"My son has a great sense of humor and he even makes up his own jokes and is the first to laugh at them. The best part is, if you don't laugh, he will explain to you why it's funny! "

"My son is very charming and gets everybody to do what he wants 😂😍 "

"My daughter loves to chat and spend time together"

"My daughter is always ready for a good laugh! And very friendly "

"My son is very happy and positive baby 🥰 "

"My son's dress and clothing selection always surprises everyone - he is an adult."

"My son is very loving and always greets every person he comes into contact with."

"My daughter is happy and determined."

"My daughter has the best sense of humour. She is great at practical jokes! "

"Despite the many challenges SSADHD provided, my son's infectiously joyous perspective on life was guided by one simple word – 'Happy'."

"My son is sweet, tender and affectionate with everyone"

"My son is a very sweet, positive guy, with a great sense of humour, caring, generous and kind. With a great desire to communicate and be with people."

"My son is an expert in all things trains or Pokémon! He's kind, polite and loves his family! He works hard at his job and was just nominated for the Volunteer of the Year at our local food bank!"

PERSPECTIVES ON SSADHD

PERSPECTIVES ON DIAGNOSIS

When talking about the perspectives of diagnosis, one caregiver started the conversation by briefly defining what a diagnostic odyssey was in the context of SSADHD. This definition also included the impacts of the diagnostic odyssey in SSADHD:

"I just wanted to briefly talk about what the diagnostic odyssey is, because I didn't really know what it was. Diagnostic odyssey is the time from when signs or symptoms of disease first appear until an accurate diagnosis is made. During that time, patients can see several different providers or specialists and undergo a variety of medical testing only to be left with no clear diagnosis. The diagnostic odyssey is especially common for those with rare diseases like SSADH, who can end up spending several years seeking answers; this can put patients through unnecessary tests and procedures, cause delays in effective treatments, and result in misdiagnosis."

Watch the Diagnosis Panel

The steps to an accurate diagnosis were often a considerable process for caregivers and patients. Multiple caregivers described their experience as a ***"journey"***:

"It is a costly, exhausting, and emotional journey for patients and their families to endure."

"It's been a long journey…it's been like throwing darts and trial and error, and along with those throwing darts, we're also throwing money and emotions and energy and a lot of prayers."

DIAGNOSTIC ODYSSEY

Our preliminary caregiver survey found that the majority of the respondents representing patients with SSADHD (22%) reported that they received their accurate SSADHD diagnosis in between 2 and 5 years of age, and a similar percentage of respondents (19%) reported that they received their accurate SSADHD diagnosis when their child was greater than 5 years of age. This was supported by other caregivers in both the preliminary focus groups and at the meeting. Some caregivers reported that their child with SSADHD was given a correct diagnosis before their child's first birthday. In one case during the meeting, a caregiver described in detail the journey that took 12 years before an accurate SSADHD diagnosis, stating:

"[My child is] 13 years old. He was just recently diagnosed with the condition eight months ago."

These specific experiences are described below as different aspects of the diagnostic odyssey and offer insight into potential explanations for the length of time to diagnosis.

It is estimated that less than 10% of the SSADHD population is properly diagnosed

APPEARANCE OF SYMPTOMS

The recognition of symptoms was often the first step towards diagnosis. For most caregivers, these symptoms appeared in infancy and early childhood, usually as low muscle tone, delayed milestones in development and/or excessive sleepiness/fatigue. Reported delays included those in initial reflexes, motor development, speech and feeding. This would lead families to seek out help from their providers.

PROVIDER-FAMILY INTERACTIONS

Assessment and interpretations of physicians or other medical care providers are imperative in obtaining access in diagnostic testing for SSADHD. However, according to caregivers, this determination for testing varied from provider to provider based on provider's knowledge, caregiver advocacy, and interactions between the provider and the caregiver. These factors also contributed to the delayed diagnosis in SSADHD. In one case, a caregiver shared those errors made

and subsequent indifference towards these errors on the part of the medical care provider delayed the correct diagnosis of SSADHD in their child.

> ***"When they got [the test results] back, they [realized that they] didn't do the right test. So, the neurologist said, 'Well, we never get any results from that anyway, so we don't need to do that.'"***

Other caregivers discussed how medical care providers were dismissive or unwilling to listen to caregiver concerns over determining an accurate diagnosis:

> ***"I think all the doctors thought I was crazy at first…"***

> ***"Our pediatrician kept saying he was fine and there was no issue. His feet were turned in and we were concerned about that, with [our child's] muscle tone, and he said, "oh no, he's fine; some of the fastest runners in the world have toes that are turned in or heels that are turned out.'"***

> ***"We kept getting word from the pediatrician saying, 'No, don't worry about the speech, they'll have a burst of words; boys are slower to develop in speech' or 'Don't worry with walking; all of a sudden, they'll take a bunch of steps.'"***

> ***"Our pediatrician was saying, 'Oh no, just give it time,' you know, 'Failure to thrive' and those types of answers."***

One caregiver described the arbitrary nature by which SSADHD diagnostic testing was ordered for their child:

> ***"So, they had us take him to [the hospital] through the emergency room. We thought he was ill. It just so happens there was a genetics fellow in the emergency room on that exact day—at around 10 o'clock at night—and she said, 'We want to know what it is. Your baby is not sick; he has a genetic disorder and we're going to admit him just for an MRI.' They admitted us. After the MRI came back initially, they said, 'We'll go ahead and send you to genetics, but it's going to be a year and a half for an appointment.' A flood came and we were stuck at the hospital, and because we were stuck, the doctors were stuck too; the patients couldn't get in and the doctors couldn't get out for about three days. They were coming in rounds. Genetics came through and did an overhaul on him. They said, 'We want to know what your baby has. We don't think we've ever seen anything like it. [the hospital] is going to pay for a full West test." That's the only reason we know what he has. Afterwards, we were told by his genetics doctor at [the hospital], who specializes in metabolics, that with the way he presented, especially as a little one, they probably would have never tested him for SSADH."***

ASSESSMENTS AND TESTING

During the diagnostic odyssey, patients were subjected to a variety of diagnostic procedures, including laboratory testing, neuroimaging, and genetic testing. Specific tests prior to an accurate diagnosis commonly included testing for autism and pervasive developmental disorder-not otherwise specified (PDD-NOS). Additionally, caregivers reported testing for spinal muscular atrophy (SMA), Tay-Sachs disease, Fragile X syndrome, and Sotos syndrome. In one case, a caregiver shared that their child was tested for SMA four times.

Testing and other evaluations were performed by a number of specialists, including developmental pediatricians, neurologists, geneticists, and genetic counselors.

The testing and visits to various specialists added a considerable amount of time to the diagnostic odyssey. One caregiver shared their experience:

> ***"We experienced two years of going through tests and trying several neurologists."***

MISDIAGNOSES

A recurrent theme in the diagnostic odyssey for SSADHD patients was misdiagnosis. Our preliminary caregiver survey found that 26% of the SSADHD patients represented in the survey had received other diagnoses prior to receiving the

correct SSADHD diagnosis. The lack of an accurate, true diagnosis is key. Clinical diagnoses such as Autism, PDD-NOS and global developmental delay were the most common diagnoses that delayed an accurate diagnosis.

According to one caregiver, misdiagnosis halted the efforts of medical care professionals to characterize the causes of symptoms in their child with SSADHD, ultimately resulting in an increased time to the correct diagnosis, as well as a significant emotional impact on the caregiver:

> ***"After receiving the autism diagnosis at five years old, [my child's] physicians no longer suggested any additional testing or possible alternative diagnoses. I came to terms with the autism diagnosis since I had been searching for answers for so long and I felt defeated. I thought that it must be the only answer that there is."***

Misdiagnoses often prompted caregivers to begin treatments that were costly, time-consuming, and ultimately ineffective. These treatments included various therapeutic services, as well as diet changes. Caregivers of an adolescent child with SSADHD described the logistic and financial burden of managing these treatments:

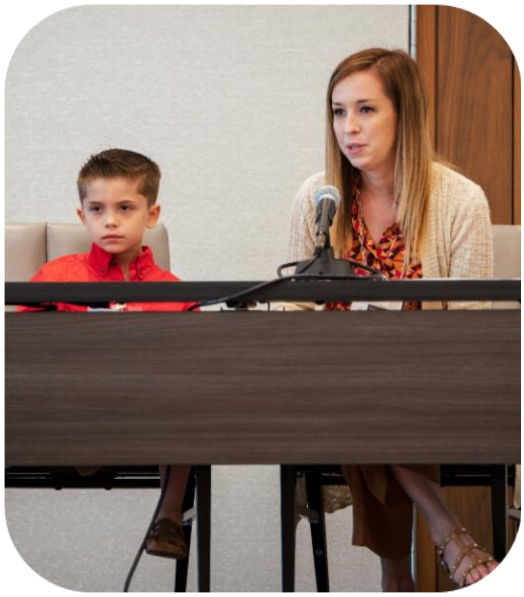
> ***"They're (doctors) recommending 35-40 hours of therapy a week, and [our child is] two. So, bottom line as parents, you're trying to decide, and thinking that we want him to have a life, but we don't want him to fall behind. I think we settled on 15 or 20 hours of various therapies, and then all of us changed our diets."***

Additionally, therapies to treat the misdiagnosis, as expected, were predominantly ineffective at alleviating symptoms and related impacts in individuals with SSADHD, leaving patients with no reprieve from symptoms, and caregivers feeling that they have wasted valuable time and money in efforts to administer treatments. Two caregivers shared their thoughts:

> ***"We've tried so many different therapies and medications and nothing has worked very well for [my child]."***

> ***"All the while, [we were] still not getting any results."***

OTHER BARRIERS TO CORRECT DIAGNOSIS



Aside from misdiagnosis, caregivers described other factors that contributed to a delayed diagnosis. In one case, a caregiver stated that testing for SSADHD was not included in common genetic screening panels, such as autism, at the time her child was tested.

This caregiver also shared that the financial cost of genetic testing was also a barrier to diagnosis, in conjunction with a lack of insurance coverage for such testing:

> ***"[My child's] geneticist recommended whole exome sequencing, but it was denied by our insurance company. The geneticist filed an appeal to the insurance company, but they denied the appeal. At that time, the out-of-pocket cost for the whole exome sequencing was approximately $6,500, and I did not have the financial means to afford it."***

NEED FOR CAREGIVER ADVOCACY

Many caregivers described having a strong sense or intuition that continued efforts were required to better characterize their child's symptoms. This was an important impetus for caregiver advocacy efforts on behalf of their child:

> ***"As parents, we knew that there was something going on, but we didn't have the knowledge to be able to speak to exactly what was happening."***

"However, I always had a feeling that there was something else going on and I knew it was possible for those with autism to have a co-occurring disorder."

Collectively, these factors and the consequent delays in diagnosis had a considerable emotional impact on caregivers. This emotional impact on caregivers had subsequent effects on the care of the individual with SSADHD, both negative and positive. In one case, the president of the SSADH Association recounted a conversation with a caregiver whose adult child was recently diagnosed at 21 years of age:

"She was so upset that it took her 21 years to find us, and she refused my help and never registered. She walked away. That's the cost of not having newborn screening. In some cases, by the time they find us, they're so heartbroken that we can't even help them."

In other cases, this emotional impact prompted many caregivers to be proactive in trying to address their challenges. In multiple cases, caregivers reported that advocating for more testing and assessment was a driving force in finally obtaining a correct diagnosis for their child with SSADHD:

"So, at 12 years old—in November of 2021—I randomly decided to do some research of my own on genetic testing to see how it's evolved over the years…I learned more about whole genome sequencing, which I didn't even know existed at the time…If it weren't for pursuing whole genome sequencing, I would not be here today telling you [my child's] story."

"This is an encouragement for all of us—we had to be our child's advocate. So, we switched pediatricians. We were in a rural part of Virginia at the time and had to drive an hour down…from where we were...Within 20 minutes, the new pediatrician said 'No, I agree that there's something going on.'"

"But with the insistence of my wife…we pushed for him to do the test again…When those results came back, we actually got the diagnosis."

ADVOCACY FOR POLICY AND PRACTICE CHANGE

As caregivers advocated on behalf of their child with SSADHD, many transitioned into advocating for policy and practice change aimed at increasing overall access to diagnostic testing for SSADHD and decreasing the length of time for the diagnostic odyssey. One caregiver spoke at length on the need for better access to genetic testing:

" I think that speaks volumes to the probability that there are many people living with SSADHD who are underdiagnosed. I think whole genome sequencing should be the gold standard testing, and it should be covered by insurance. Families should be able to get the answers that they seek and the help that they desperately need. Our diagnostic odyssey took 12 years before finally receiving an accurate diagnosis. Genetic testing needs to be more accessible to patients so that they can receive the right diagnosis. I think that we must end the diagnostic odyssey and advocate for newborn screening; the earlier an accurate diagnosis is made, the earlier the patient can begin receiving treatment, and the more individuals that are recorded into the database with rare diseases and we know have SSADH, more people will be able to participate in clinical trials and be a part of this important journey to advocate for available SSADHD treatments. "

IMPACT OF LACK OF NEWBORN SCREENING

Many caregivers specifically advocated for SSADHD diagnostic testing to be added to the newborn screening panel. One caregiver shared the risks that undiagnosed patients with SSADHD face with the current state of the newborn screening panel:

> ***"Newborn screening cards are medical devices that are regulated by FDA, but they come with no labeling for [patients]. It doesn't tell the parents or the families that these cards screen for less than one percent of the 7000 rare disorders that there are… Newborn screening cards need to come with a black box warning that says, your child may have a deadly disease, and this card—this screening program—does not cover all of the possibilities. Our neurologist kept saying '[our child] couldn't have a metabolic disorder because [their] newborn screening was normal.'"***

This caregiver went on to describe the impacts of a delayed or no diagnosis on the understanding of natural history and the execution of future clinical trials:

> ***"[There may be] one thousand families [without a diagnosis]; imagine if we had one thousand families [for this meeting], we would be in a giant auditorium, we could fill any clinical trial that came up, we would have such a voice and such a presence. People would know SSADHD like they know CF (cystic fibrosis). Just imagine if we had that kind of reach if we were properly diagnosed."***

> ***"The FDA wants us to have a natural history study as part of our drug development program, but how are we supposed to get the entire phenotype of the disorder if we have less than ten percent of our patients diagnosed? We miss the babies that die early, we miss the mild cases, we miss all of the in between. So, even when we are listening to people today and we learn how different the phenotype for the disorder is, imagine what the representation would be if we had a thousand patients. I cannot say that enough—one thousand patients! We would have so much more of a voice."***

IMPACT OF DIAGNOSIS

When patients were finally diagnosed correctly with SSADHD, according to our preliminary caregivers' survey, the vast majority of respondents (81%) reported that their child was diagnosed with SSADHD via urine analysis of gamma-hydroxybutyric acid (GHB) levels. A smaller percentage (31%) was either followed up with genetic analysis or diagnosed solely through genetic testing.

EMOTIONAL IMPACT OF RECEIVING DIAGNOSIS

Once receiving the correct SSADHD diagnosis for their child, one of the first impacts that caregivers reported was the tremendous emotional effect on themselves and the entire family. While the specific initial emotions varied between feelings of shock, relief, hope, etc., many caregivers noted the intensity of that emotional impact:

> ***"When we got the SSADHD diagnosis, my wife cried, and I was happy. I thought, "well, at least we know what it is."***

> ***"I was completely shocked by the results of the test, and I felt so many different emotions."***

> ***"To speak to how that switched, regarding the moment of diagnosis to Googling SSADHD and then…. all those emotions."***

> ***"I'm trying to remember the feelings of relief and all the emotions that we went through when we got that diagnosis. There was happiness, sadness, and all those things."***

Several caregivers alluded to initial feelings of confusion and uncertainty during the meeting as well as in the focus groups and preliminary caregiver interviews, primarily due to the fact that SSADHD is an ultra-rare disorder with little information available compared to more common disorders:

> ***"We didn't know what we didn't know."***

"I had never heard of the disorder before, and I couldn't even pronounce it…I've met with his doctors since receiving the diagnosis and they don't know much about the disorder. It seems like they don't know what kind of treatments to even suggest."

"She was…. diagnosed through the Neurology Department at the University of Virginia, and I remember the neurologist saying, 'Well, we don't really know what this is…'"

"A lot of doctors at that time had no clue what it was—they had never heard of it."

Two caregivers described feeling hopeful after receiving the diagnosis:

"We were told by his genetics doctor at Texas Children's, who specializes in metabolics, that with the way he presented, especially as a little one, they probably would have never tested him for SSADH. We are so grateful. We now have so much hope."

"As soon as we had the diagnosis, everything kind of opened up for us... There was somebody else out there and that brought us hope, which I think several people have said. The hope was there…"

ACCESS TO RESOURCES TO MANAGE SSADHD

One common impact of having a correct SSADHD diagnosis was that it provided improved access to a variety of resources and services to help manage their child's condition. This included improved access to medical treatment, educational accommodations, as well as the information and emotional support of a community organization of families with the same diagnosis.

With respect to improvement of medical care, caregivers described improved access to and insurance coverage of targeted care and management, especially due to having access to medical care providers that had expertise in SSADHD:

"Having that diagnosis, we can then take it to the next level with getting treatments, therapies, etc., and it's very critical."

"With knowing that [our child] has SSADHD, we could actually react…We could then pick the appropriate therapies."

"I want to mention that anesthesiology is different for our kids. Having the diagnosis has really made us able to work with anesthesiologists at the first instance. They will read the literature and find the best type of anesthesiology mixture, because otherwise [in some cases] it causes seizures in our kids. So, I think there are all these other repercussions with understanding the diagnosis—to putting a name on it, so that you can stay away from other things that could happen."

"How did it improve? She was finally diagnosed…and I remember the neurologist saying, '... We've heard of it and can help with treatments and related things, but there is a doctor, and his name is Philip Pearl, and he's in DC which is only a couple hours away.'"

"Now, we have the ability to go through insurance and have that diagnosis to go back to. But then getting hooked up with Dr. Gibson, and then Dr. Pearl coming in and doing some more clinical stuff, has really helped with being able to understand the different facets of it. Even though there's no treatment for SSADH."

One caregiver shared a story about their child receiving necessary priority care as a result of have an SSADHD diagnosis, when they hospitalized for an acute infection:

"Now, to speak on the treatment and the medical care since [our son] got a diagnosis. This year, he had a severe case of E coli, and when we got to the emergency room, he was having a difficult time because his system has a difficult time recovering (in general). When we got there and told him he has SSADH, they immediately took him in, and he got the best of care. We had to be admitted two different times because of it, but genetics was in there and they put us to the front of the line, which is

what he needed. If we would have just had the PDD-NOS diagnosis that they told us, we would have never gotten that treatment."

Several caregivers spoke to the impact of a correct SSADHD diagnosis on receiving school-based accommodations and services for their child with SSADHD:

"Having the proper diagnosis for school opens so many doorways. We can tell the school that our child has SSADH, I can bring in one of the [peer reviewed] papers, I can say, "here's the symptoms of it" and nobody fights us for services when it gets to that point. We tell them [they present with] ADHD, and they provide an additional service. We tell them she needs OT; 'students in middle school don't get OT', but when we say that she needs it, they do it without problem."

"If we would have just had the PDD-NOS diagnosis that they told us, we would have never gotten that treatment. The same applies with the special school that he's in."

"So having that diagnosis pointing to different things, especially as we went through school, has helped the people around him and provided the support to be able to help him through life."

Many caregivers shared how their child's SSADHD diagnosis allowed them to connect to the SSADH Association, which provided both current information on the management of SSADHD as well as emotional support from other caregivers of individuals diagnosed with SSADHD. This sense of community that families received from the SSADH Association, through online support groups and in-person meetings of families, addressed feelings of isolation that many caregivers described as part of their overall experience as well as fear about the future of their child with SSADHD:

"As soon as we had the diagnosis, everything kind of opened up for us, as far as being associated with the Association and finding the group on Facebook."

"I think that since that time, having the diagnosis has really helped us with connecting with other families and being able to learn about the disease."

"Also, just being able to know you all and friendships that are developed with the families, the long-term support we have throughout our children's lives, and being able to ask [another caregiver], 'What do I need to plan for when [my child] is 30?' Or the ability to ask [another caregiver], 'How did you do guardianship for [your child]?.' Even without a treatment, you feel like you have family and you're not alone. Thank you."

"We came here [from another country] in 2016 to see older children, which gave us insight into [our child's] future…and [we could] get consulting from families that went through all this 10 years ago, maybe, which was very helpful to us."

In one case, the community that was available through the SSADH Association following diagnosis inspired a caregiver to cultivate a community of SSADHD in their home country so that these families would have more accessibility to support and resources:

"With this knowledge, we built a website in German and an association in Germany so that we could inform other patients behind the language barrier."

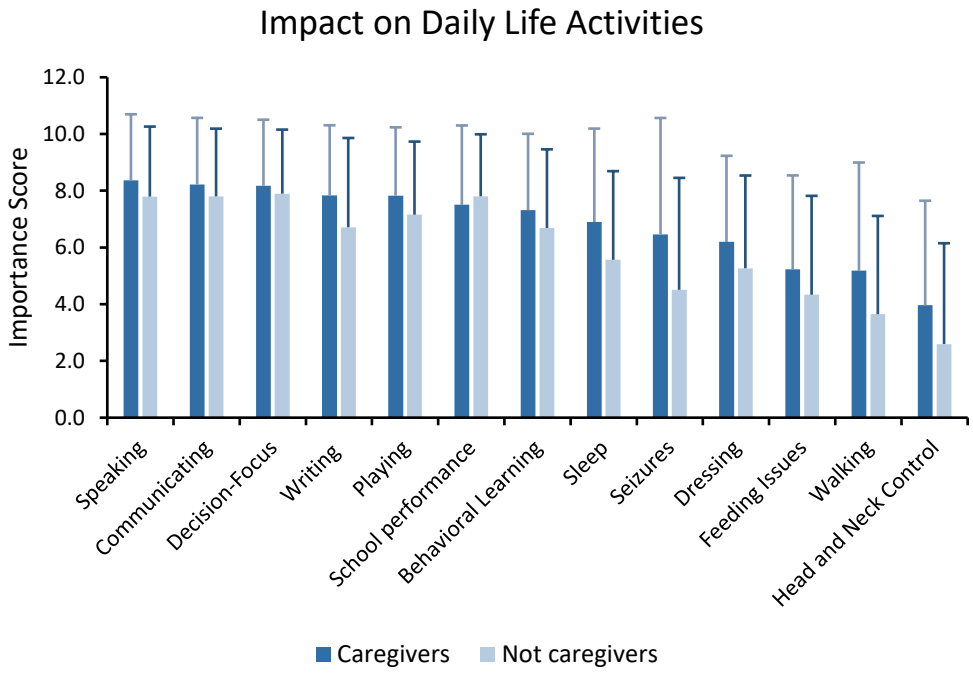
CONCLUSIONS

The time to diagnosis (diagnostic odyssey) is emotionally draining, costly, and exhausting for patients and caregivers. During the time without a diagnosis there is a lack of support, ineffective treatment, and limited access to school accommodations. The emotional toll the lack of diagnosis takes on the caregiver directly impacts the patient. Early diagnosis gives patients and caregivers access to early intervention both at home and in school, access to the SSADHD community, and along with that, access to the resources and support that come with the SSADHD community.

Efforts to expand screening for SSADHD are sorely needed. Potential barriers to childhood screening include the need for clinician education at all levels about SSADHD and how to obtain appropriate screening. While screening at any age should be considered, newborn screening for SSADHD is a significant need. Efforts are underway to develop the resources, education, and tools to facilitate newborn screening for disorders of GABA metabolism. Earlier diagnosis is critical for the individual and their family—newborn screening is the best mechanism to obtain an early, accurate diagnosis. Newborn screening occurs for every infant born in the U.S. regardless of socioeconomic status, insurance coverage, or geography. Removing or reducing barriers to care by enhancing newborn screening to include SSADHD is cost-effective, expeditious, and non-invasive – and will reduce health disparities in both diagnosis and care. Newborn screening for SSADHD and similar disorders can be done with technology similar to current newborn screening methods. The cost-effective approach that state-supported newborn screening services provide is the optimal approach to early screening and diagnosis.

SSADHD is currently underdiagnosed and represents a broad range of phenotypic severity. This delay in diagnosis leads patients into years-long diagnostic odysseys, which are often expensive and require unnecessary, invasive, and painful testing. It also disenfranchises patients and caregivers from participating in the SSADHD patient community, advocacy work, natural history studies, clinical trials, and even the patient focused drug development process.

FAMILY PERSPECTIVES ON SYMPTOM CHARACTERIZATION OF SSADHD



INTELLECTUAL DISABILITY IN SSADHD

Intellectual disability affects a broad range of individuals with SSADHD with respect to age, with the earliest impacts reported by caregivers during the meeting and the focus group discussions around 6 years of age and continuing on into adulthood. One caregiver during the meeting shared that increased age and growth of their child with ***SSADHD "polarize[d] the intellectual disability more"*** compared with the impact that was present at a younger age. During the meeting, one caregiver stated that their child's ***"intellectual disability impacts every moment of his life."***

This was in spite of the fact that many other symptoms of SSADHD presented with more distinct clinical characterizations. One caregiver shared their thoughts:

"I think the thing about intellectual disability is it sort of has a vagueness to it—in that it isn't as direct as the physical things, but it can still have the same devastating effects.

"So, they're unable to help, unable to perceive what's going to be going on, and I think that's huge in terms of their quality of life. I think that's a big deal and it occurs all the time."

Watch the Intellectual Disability Panel

SPEECH AND COMMUNICATION IMPAIRMENT IN SSADHD

Speech and communication impairment was a significant concern for many caregivers, as it impacted the patients' ability to function in a variety of settings. Many caregivers specifically distinguished the type of speech and communication difficulties that their child experienced in terms of their ability to interpret language from their physical ability to express language through speech. Caregivers shared some of these thoughts:

"The problem is that he has the information inside him, but he can't express it or repeat it—something blocks him."

"The biggest challenge is the balance between his receptive and his expressive abilities."

"We heard things from speech pathologists like, 'I've never seen a child like him before who knows everything but cannot speak.'"

Watch the Speech Panel

DELAYED OR ABNORMAL SPEECH/COMMUNICATION DEVELOPMENT

Multiple caregivers noted that their child experienced some level of speech/communication development issues. Some individuals with SSADHD never gained the ability to communicate verbally, although they were able to make sounds and use other modes of communication. Most caregivers alluded to a considerable delay in reaching speech and verbal communication milestones, as described by one caregiver:

"At the age of three and a half, the only sound that he could make with his mouth was 'ba'."

For those that developed verbal speech, they were quite limited in their vocabulary. One caregiver stated that their child with SSADHD speaks only ***"a little bit"*** and two others shared that their child used only a few words, even as adolescents and young adults. One caregiver shared that their child ***"…cannot even tell people their name."***

SPEECH APRAXIA AND DYSARTHRIA

Several caregivers stated that their child had the desire to speak and knew what they wanted to communicate, but could not form or articulate all of the words or parts of the words, as shared by one caregiver:

"[Our child's] apraxia just sounds like if you were to hold your tongue and talk, but also some words come out backwards and some other words only come out with just the consonant sound."

Additionally, many caregivers alluded to the fact that individuals with SSADHD struggle with dysarthria, or weakening of oral muscles used for speech.

The inability to control the muscles used for speech also contributed to vocal self-stimulatory behavior (stimming), such as unprompted shrieking or groaning. Verbal stimming behavior was described by one caregiver as a common occurrence in their child with SSADHD.

SEIZURE DISORDERS IN SSADHD

Caregivers reported that individuals with SSADHD started having seizures as early as 3 years old, with multiple individuals having seizures starting in later childhood (7 years old) and during adolescence. Individuals experienced various types of generalized seizures, including myoclonic, tonic-clonic, atonic, and absence seizures. Many seizures were described having lasted for long periods of time, from 10-20 minutes.

Watch the Seizure Panel

Triggers for seizures included sensory overstimulation, both visual and auditory, as well as being in environments or circumstances that were perceived as stressful. Our preliminary focus groups and interviews revealed that aspiration pneumonia due to acute illness was also a trigger for seizures for one individual.

Epilepsy is a common source of morbidity in Succinic Semialdehyde Dehydrogenase (SSADH) deficiency. Adult reports indicate worsening epilepsy and high Sudden Unexpected Death in Epilepsy (SUDEP) risk (DiBacco, 2018).

BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS IN SSADHD

Behavioral and psychological symptoms in SSADHD included symptoms related to anxiety, depression, obsessive-compulsive behaviors, oppositional-defiant behaviors, as well as other behaviors and symptoms related to inattentiveness, impulsivity, and hyperactivity.

ANXIETY

Two caregivers during the meeting discussed anxiety in their child with SSADHD. One caregiver mentioned that their adult child's anxiety was primarily ***"generalized"***, but also ***"event-specific"*** One caregiver suggested that sensory overstimulation could trigger anxiety in their child, stating:

Watch the Behavior Panel

> ***"The noises, the fireworks, the buses, too much crowd—they're not acceptable for him."***

Caregivers in our preliminary focus groups also reported that their children are overstimulated by their surroundings where there may be loud noises, or other sensory overstimulation. Additionally, they reported social anxiety when interacting with others. A family member of an individual with SSADHD also discussed ***"attachment anxiety"*** in their sibling during the meeting; this anxiety was caused by a temporary separation from their parents. She described the following:

> ***"My parents had to go to a different country for a week.... [my sibling] was so attached to them at the time.... In her eyes, they were just gone out of nowhere, it affected her psychologically in a way that we didn't realize."***

Anxiety manifested in different ways in individuals with SSADHD. Several caregivers at the meeting and during the preliminary focus groups described freezing, independent of seizures, where individuals experience a temporary paralysis at times of crisis. One caregiver described a freezing spell in their child:

> ***"They (doctors) told us that it's not a seizure, but like a crisis of panic."***

> ***"His hands and feet start sweating and he has palpitations; he feels like there's an attack from somewhere, but because he cannot speak and tell us what he feels, we can't help.... So, we'll take him off to bed because his muscles also lose strength, and he can't walk very well."***

Another caregiver stated that their child ***"can't get out of bed most days"*** due to their anxiety. Other family members shared that their child's anxiety triggered or escalated other behavioral symptoms, such as obsessive/compulsive symptoms.

OBSESSIVE/COMPULSIVE DISORDER (OCD)

Multiple caregivers during the meeting, preliminary focus groups and interviews shared that their child with SSADHD experienced symptoms of obsessive compulsive disorder (OCD). Caregivers and other family members described individuals with SSADHD fixating on multiple things and situations, shared here:

> ***"You see it (in many ways), from obsessing about food sometimes, about objects, about people, behavior, stim, that sort of thing."***

> ***"I don't know how—it's like his Spidey tingles go off—but it's 4:30 and he knows the door upstairs is open, the bathroom door, and he'll just go up and shut the door, and then the cabinet; it doesn't matter the time, he somehow is hyper aware and realizes it."***

The intensity of the OCD symptoms varied from individual to individual and would also vary at specific time points within an individual, usually related to the triggers setting off the symptoms. During the meeting discussion as well as the patient interviews, caregivers stated or alluded to anxiety triggering OCD symptoms, specifically, asking questions repetitively as a way of seeking reassurance and validation. One caregiver during the meeting described their child's repetitive questioning, which was exacerbated by lack of sleep:

> ***"If we tell him the exact plan, for the next 10 minutes or for the entire day, he will still keep asking sometimes 20 times, sometimes 50 times—he's very repetitive in his asking and in his doing, and that gets even worse when he has a bad night."***

A sibling of an individual with SSADHD shared that the anxiety associated with their parents' absence temporarily triggered the compulsive hoarding of food items in their sibling's bedroom:

She started keeping all these things to herself. ***"She would hide ice cream, she would hide bananas under her pillows, and we wouldn't realize it until weeks later when we realized a rotting smell in the room."***

Although distinct from OCD behaviors, one caregiver described that their child struggled with impulsive behaviors, where their child would engage in activities without any foresight or awareness of the consequences of these actions. This caregiver described a specific example with their child:

> ***"She will get into our cabinets; there was a morning recently where my husband and I did not hear her wake before us and he went out to find multiple spices—jars of spices—all over the kitchen."***

A sibling of an individual with SSADHD also described this unawareness of certain impulsive behaviors in their sibling:

> ***"The moment I walk in, she stops and it's like she doesn't even realize what she was doing—she's just like, 'oh I'm sorry, I didn't know.'"***

ATTENTION DEFICIT/INATTENTIVENESS

Many caregivers described a lack of focus or inattentiveness, similar to symptoms of attention deficit disorder, as part of the behavioral/psychological symptoms of SSADHD. One caregiver stated that nearly all individuals with SSADHD have ***"difficulties with focus and with concentrating on activities"*** and shared that for their child, any sort of unexpected sensory stimulation would distract them, sharing that ***"[My child] gets distracted by sounds, by light, by movements, basically by everything."*** Oftentimes, the inattentiveness led to repetitive questions, such as that described among the OCD symptoms. Additionally, one caregiver stated that a lack of sleep and communication difficulties exacerbated the inability to focus in their child with SSADHD.

OPPOSITIONAL/DEFIANT/AGGRESSIVE BEHAVIORS

Caregivers reported that many individuals with SSADHD often expressed distinct opposition or defiance frequently. One parent described the following about their 7-year-old child during the meeting:

> ***"[My child] will become defiant and not listen to what we have to say or when we ask her to stop."***

During our preliminary focus groups, other caregivers described oppositional and defiant behaviors in their child with SSADHD. One caregiver stated that their adult child with SSADHD had ***"a look, like he hates you"*** when being defiant, and that during these moments, their child would ***"dig his heels in and won't listen."*** Another caregiver described ***"bursts of anger"*** where their 10-year child with SSADHD would ***"grit [their] teeth and growl at you".***

Some caregivers described physically aggressive behaviors in their child with SSADHD. Individuals with SSADHD were reported to be aggressive to their teachers, peers, and even caregivers. Behaviors included hair pulling, biting, and choking of other individuals.

One caregiver attributed these behaviors to external factors, such as lack of sleep or sensory overstimulation. During one of our preliminary focus groups, one caregiver also shared that the aggressive behaviors may be related to the emotional experience associated with SSADHD, such as frustration due to the intellectual disability or the inability to communicate.

DEPRESSION

Two caregivers described symptoms of depression in their child with SSADHD during the meeting. According to one caregiver, depressive symptoms in their child were characterized as ***"times where they don't want to talk to any of us and they just want to be by themselves."***

SLEEP DISTURBANCES IN SSADHD

Sleep disturbances affected individuals with SSADHD of all ages and often changed day-to-day and throughout the course of their life. One caregiver noted about their child's sleep patterns:

> ***"It frequently changes; sometimes [our child] sleeps a lot, and sometimes he does not sleep at all."***

RESTLESSNESS AND INSOMNIA

Some caregivers expressed that their child with SSADHD frequently experienced very restless sleep, involving unintended physical movements as well as fragmented sleep patterns. One caregiver described this restlessness as ***"a total inability to relax in a state of sleep" and "[a] kind of hyperactivity when [our child is] in a state of sleep."***

Several caregivers characterized this restlessness as constant movement of limbs during times of sleep:

> ***"It always felt like [our child's] body was constantly moving—either side to side, or she would always be kicking her feet."***
>
> ***"{Our child] is quite restless too—a lot of throwing her arms and her legs around and tossing and turning throughout the night."***
>
> ***"[Our child] sweats at night, twitches, and moves around a lot."***

Watch the Sleep Panel

Caregivers also described sleepwalking, teeth grinding, and talking during sleep as characteristics of sleep restlessness. Some individuals with SSADHD would speak words while others would make other audible noises while sleeping. Caregivers shared these observations:

"Very early in the morning, he starts to sleep talk—it sounds like he's imagining his adventure and thinking about the cartoons he's watching all the time."

"[Our child is] also a very noisy sleeper. It's almost like there's a humming or a murmuring sound that she makes while she sleeps—you can always hear it—it's almost like a buzzing in the background, like a toy that has a battery that was left in. There's always a humming or a sound…"

With respect to sleep patterns, caregivers described individuals with SSADHD either having difficulties falling asleep or sleeping only for a few hours at a time, waking up multiple times in the middle of the night, or at an early time during the morning. Many caregivers shared their experiences:

"Falling asleep is mostly the concern… it's mostly just falling asleep and then staying [asleep] in bed…"

"The problem is, it doesn't matter the time [our child] goes to bed, he wakes up very, very early in the morning every day."

"But during the night, [our child] wakes up about three hours in, and he's going around the bed without sleeping."

"[Our child] still gets up frequently in the middle of the night…"

Some caregivers noted that their children with SSADHD were very light sleepers and often arose to any minor disturbances:

"... [our child] doesn't ever seem to be in a deep state of sleep."

"[Our child] is a light sleeper; every time I go in at night to put the blanket up on her and give her a kiss, she stirs and usually wakes a bit dazed."

SLEEP ATTACKS

In contrast to the restlessness and insomnia issues, many caregivers reported sleep attacks as a common occurrence in individuals with SSADHD, in which they would suddenly fall asleep without warning. Caregivers described these sleep attacks occurring under a wide variety of circumstances, including during school, therapy sessions, meals, recreational activities, in transit, or at home. Several caregivers described both sleep attacks and insomnia/restlessness symptoms in their children with SSADHD. A few caregivers shared their child's experiences with sleep attacks:

"[Our child] also went to regular kindergarten with an assistant aide, and again she would often fall asleep on the ground or in the playground—kids would be walking around her."

"[Our child] fell asleep almost every therapy session."

PHYSICAL SYMPTOMS AND MOBILITY ISSUES IN SSADHD

The physical symptoms and mobility difficulties experienced by individuals with SSADHD appeared to be related to low muscle tone and strength and issues with balance. These symptoms contributed to difficulties with gross (e.g., crawling, walking, running, throwing, etc.) and fine motor (e.g., feeding, writing, putting on clothing, etc.) skills. The level of these skills varied from individual to individual, and most physical symptoms and their subsequent impacts ameliorated as the individuals grew older.

BALANCE

Physical balance difficulties among individuals with SSADHD were reported by caregivers during the meeting, likely due to the hypotonia and limited physical strength. These symptoms seemed to manifest while standing or moving. One caregiver reported that their child has a ***"wobbly gait"***. Another caregiver stated that their child could stand and walk competently, however, she would not be able to keep her balance if there were any

Watch the Physical Limitations Panel

additional obstacles to standing or walking, such as standing/walking on grass or carrying something while walking.

SCOLIOSIS

Caregivers as well as patients (with assistance from their caregiver) discussed the impacts of scoliosis. The low muscle tone in individuals with SSADHD was believed to be related to the occurrence of scoliosis in individuals, due to the hypotonia contributing to the inability to support typical spinal alignment. One caregiver shared their child's experience with scoliosis and its subsequent impacts:

> ***"[Our child] developed scoliosis because of the severe hypotonia, and that has also limited her physically. At one point, when it was first diagnosed, we were at [a curvature of] 40 degrees."***

MOVEMENT DISORDERS

Additionally, a few caregivers reported movement disorders such as choreoathetosis, dyskinesia, or dystonia in their children with SSADHD. Although the movement disorders were uncommon in SSADHD, they had a considerable impact on the patients and families that did experience them. No families of individuals with SSADHD that had a movement disorder were present in-person for the meeting, likely due to the difficulties with travel associated with the movement disorders. Two caregivers with children that experienced movement disorders were interviewed prior to the meeting. One caregiver shared that their child experienced both (non-convulsive) seizures and choreoathetoid movement ***"explosions"***, and the appearance of one of these symptoms tended to decrease the appearance of the other.

IMPACTS OF SSADHD ON PATIENTS AND CAREGIVERS

Of the symptom categories that were described, our live polling found that intellectual disability was the most burdensome symptom of all symptoms reported by primary caregivers of individuals with SSADHD, followed by speech/communication impairment and then behavioral and psychological symptoms.

When caregivers were asked (in our preliminary caregiver survey) to rate the daily impact of SSADHD symptoms on a scale of 1 to 10 (least to greatest impact, respectively), results showed that the greatest impact of SSADHD was related to speech and communication impairment (average impact score of 8.2 out of 10), followed by intellectual disability (average impact score of 7.9 out of 10), behavioral/psychological symptoms (average impact score of 7.5 out of 10), sleep disturbances (average impact score of 6.8 out of 10), seizure disorder (average impact score of 5.3 out of 10), and movement disorders (average impact score of 5.3 out of 10).

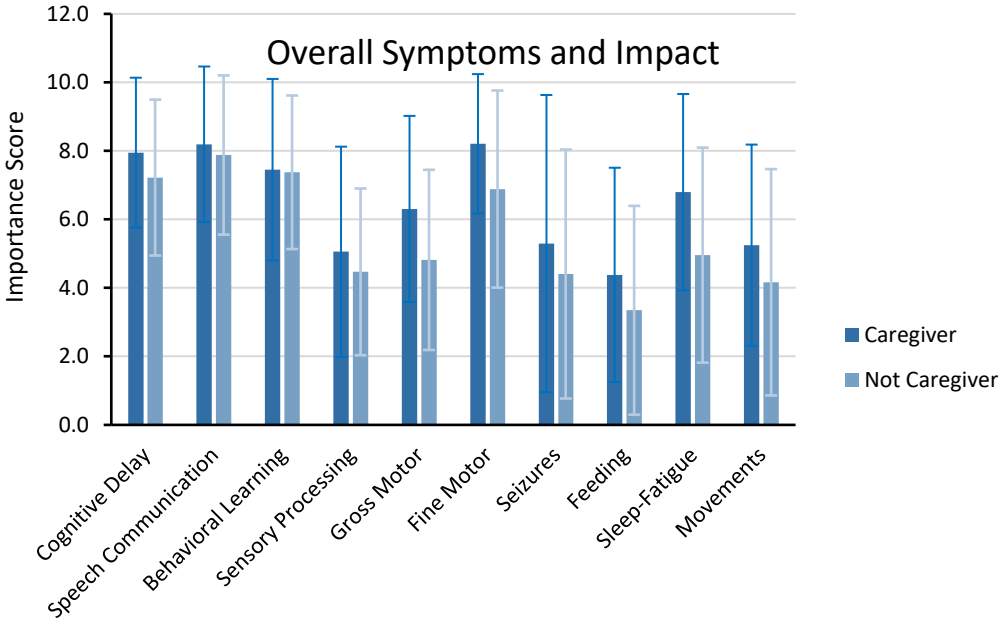
It should be noted that, although these rankings give an overall understanding of which symptoms have the greatest impact in the general SSADHD population, that the clinical heterogeneity of symptoms in SSADHD have variable impacts on individuals and families. For example, a seizure disorder is common but not frequent in SSADHD, therefore the impact of seizures was likely minimal in those patients and families that did not experience seizures at the time of the survey, but in patients with seizures, the impact was considerable and ***"life-altering"***, as told by one individual with SSADHD during the meeting. Similarly, movement disorders as common in SSADHD, however, one caregiver stated in a preliminary interview that the biggest impact of SSADHD has been managing the movement disorders, including the choreoathetosis and dystonia.

Additionally, although the physical symptoms were not ranked as most burdensome as compared to their daily struggles with some of the other symptoms by all caregivers participating in the live polling, it was evident that these impacts were significant in individuals with SSADHD during their early childhood years compared to older patients with SSADHD. Furthermore, when caregivers of these individuals were asked to rate the impact of various physical symptoms, limitations and mobility issues on a daily basis on a scale of 1 to 10 (least to greatest impact, respectively) in our preliminary caregiver survey, results varied across specific physical symptoms, with fine motor impairment being rated as having the greatest impact (average impact score of 8.2 out of 10), followed by gross motor impairment (average impact score of 6.3 out of 10), and then feeding difficulties (average impact score of 4.4 out of 10).

IMPACTS OF SSADHD ON PATIENTS

When caregivers were asked (in our preliminary caregiver survey) to rate the impact of SSADHD on specific daily life activities (scale of 1 to 10, least to greatest impact, respectively), several daily activities were considerably impacted by

SSADHD. Results showed that the greatest impact of SSADHD was on educational and work experience (average impact score of 8.5 out of 10), followed by executive functioning (average impact score of 8.2 out of 10), independent activity (average impact score of 7.6 out of 10), and then social interactions (average impact score of 7.4 out of 10). During the meeting, as well as in the focus groups and interviews, caregivers and patients discussed the different ways that the symptoms of SSADHD resulted in these and additional daily life impacts.



EDUCATIONAL AND OCCUPATIONAL IMPACTS

All symptom categories had impacts on educational experiences for individuals with SSADHD. Our preliminary caregiver survey showed that the average age of individuals with SSADHD in preschool, elementary, and high school was higher and had a greater range than typically developing individuals in those schools, suggesting that individuals with SSADHD may have started school at an older age than typically developing individuals in the same grade OR that they needed to repeat grades in school. One caregiver made the following comment on their child's educational experience in the context of being nonverbal:

> ***"So far, the lack of speech has driven [my child's] entire elementary school career, and it's just been a huge determiner in his life."***

ACADEMIC PERFORMANCE AND SKILLS

Caregivers and patients alike described how the different symptoms of SSADHD affected various aspects of academic performance, including reading, writing and math. In a preliminary interview, an adult with SSADHD stated that ***"reading is hard"***. Similarly, several caregivers described their child with SSADHD as being unable to read and write at their age-appropriate level, if at all. One caregiver reported that their adult son could ***"read at probably a second or third grade level"***. The difficulties with reading and writing were at least partially related to the decreased memory retention, as discussed by one caregiver:

> ***"We continue to have reading sessions and we'll get somewhere, but then we lose it. We get it, and then we lose it. We don't keep after it. I mean, you can have (what seems like) a miracle with spelling and then you turn around the next day and it is as if they never saw the word, 'the', ever."***

Two caregivers during the meeting shared that seizures affected their child's memory, both short-term and long-term.

The subject of math was also challenging for individuals with SSADHD. During a preliminary interview, one adolescent with SSADHD felt that homework was difficult because there was ***"a lot of math".***

Caregivers described the fine motor skill impairment in SSADHD resulting in difficulties with writing or the inability to write altogether. This was reported in individuals of various ages, as shared by their caregivers.

"Writing is very difficult, it's almost like a five-year-old's writing. Again, he's 12."

"Neither one [of our children with SSADHD] can write. [Our 19-year-old child] can scribe her name with five or six g's in there, but it's all across the page. [Our other child] scribbles up and down; at seven, she can't even do circles yet, and I don't think writing is going to happen for either of them."

"It's the fine motor (skills) that [our 25-year-old child] really has issues with, such as writing."

The fatigue from the sleep disturbances, seizures and the physical symptoms in SSADHD also affected the motivation and willingness of patients to engage in school activities. One caregiver shared that when at school, their child with SSADHD ***"doesn't want to participate."*** Additionally, one caregiver stated that the oppositional and defiant behavior in their child with SSADHD resulted in their refusal to participate in school activities.

MISSED SCHOOL ACTIVITIES AND ABSENCES

Caregivers reported that individuals with SSADHD were unable to engage effectively in their academic efforts due to the chronic fatigue and inadequate sleep caused by the sleep disturbances, and in some cases, seizures. Several caregivers shared their child's experiences:

"[Our child] also falls asleep at school and misses out on school instruction."

"[My child's] daytime sleepiness really limits what she can do during the day."

One caregiver also stated that the daytime fatigue and sleep attacks impacted the quality of therapy that their child received:

"We were doing lots of physical therapy, and that affected him because he would fall asleep during therapy, and therefore didn't get the quality of therapy that he needed."

Additionally, many caregivers described their child with SSADHD having to leave school frequently due to the occurrence of seizures in school. One caregiver shared:

"I got regular phone calls from the school, saying "[Your child is] having a seizure, come and get her…. So, I would say seizures for a long time limited what we could do."

DIFFICULTIES WITH STANDARDIZED TESTING AND EDUCATIONAL ACCOMMODATIONS

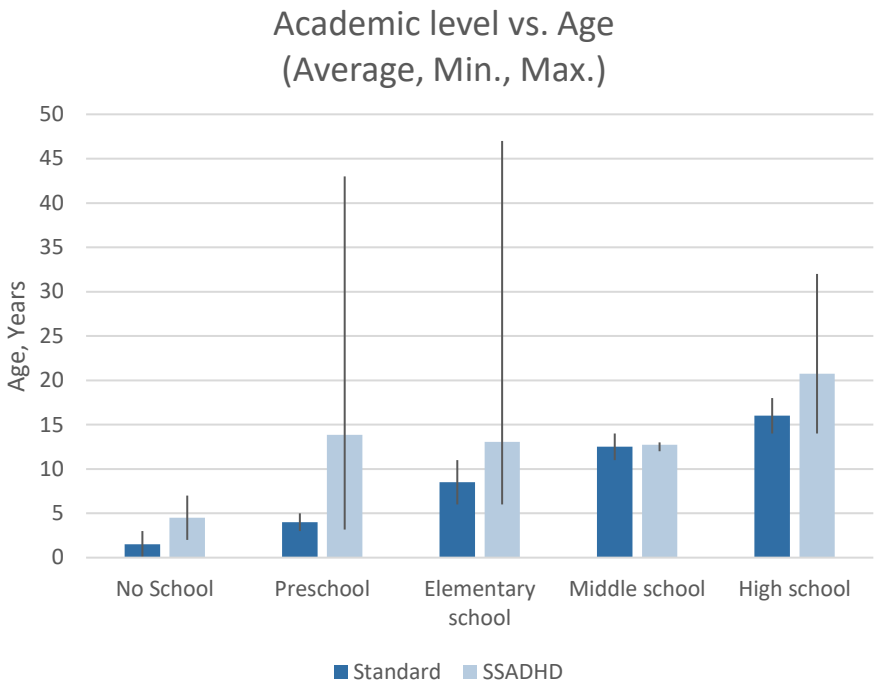
Another educational impact of SSADHD was related to obtaining the appropriate accommodations for patients. These challenges started as early as during the assessment to determine accommodations for individuals for SSADHD. One caregiver in our preliminary focus groups found that their child's speech apraxia diagnosis made it difficult to assess cognitive and intellectual function during standardized testing, which subsequently made it difficult to determine appropriate placement and necessary resources and accommodations for their child.

One caregiver described their experience in trying to obtain school-based accommodations:

"At five years old, [our child] entered kindergarten, and from the very first day, we could tell that he wasn't very welcome. Our home school had never had a nonverbal child attend there, and they weren't open to making modifications or accommodations to support him…. We requested a translator be present for him throughout the school day and after school events, and our request was denied because those services were only provided to children that were deaf."

In this case, the caregiver had to pursue legal action to obtain the appropriate accommodations:

> ***"We went through over a year and a half of legal proceedings to get [our child] a proper placement. We had to go through the Department of Justice, and the federal government became involved before we were able to get the correct services for [our child]."***



Even after legal intervention, obstacles for school accommodations continued to appear as the individual with SSADHD got older and was ready to transition into a new school setting. These continued obstacles delayed educational progress for the individual with SSADHD.

> ***"As we move into middle school, we are not going to have sign language support again, so [our child is] actually going to repeat 5th grade at the school. It's not that he's not ready for middle school, I just need another year to prepare myself before we can fight again to get him proper services in middle school."***

In another case, a caregiver reported that appropriate accommodations for their child with SSADHD were not available in their local area:

> ***"We literally exhausted all resources in our area. Then, we found an amazing school…that specializes in children that have speech and language disorders, but it was two hours away from our home."***

IMPACTS ON EMPLOYMENT AND TRANSITION INTO ADULTHOOD

As individuals with SSADHD transitioned into adulthood, the impacts of SSADHD on academic performance shifted to impacts on gainful employment, as well as volunteering opportunities.

Inability to focus, as well as difficulties with reading and writing were all described as obstacles to obtaining and maintaining employment. As a result, employment would often be on a short-term and inconsistent basis. One parent shared their thoughts:

> ***"My [children] have had small jobs here and there, but their jobs are limited because they can only pay attention to so much."***

Moreover, according to caregivers, many employers underestimated the potential ability of individuals with SSADHD in a workplace environment. Two caregivers stated that they were only approached about unskilled and low-wage occupations, such as cleaning positions, for their adult children with SSADHD.

The COVID-19 pandemic appeared to exacerbate the circumstances surrounding employment for individuals with SSADHD. During our preliminary focus groups and patient interviews, most caregivers with adult children with SSADHD shared that their children were not employed during the pandemic.

Beyond the impacts on completing employment or volunteering-associated tasks, some behavioral/psychological symptoms in individuals SSADHD often resulted in difficult interactions in the work environment, detracting from their ability to work, and resulting in eventual termination of employment. One parent shared their adult child's volunteering experience:

> ***"We once had [our child] volunteer with a support person at our community's local food pantry. After working one shift, we were told that he was too loud and disruptive; [our child] often speaks his thoughts aloud (and loudly) and repeats the same question over and over even after being responded to."***

It should be noted that although employment or volunteering opportunities were available for some individuals with SSADHD, for many families, the transition into adulthood and out of the education system resulted in a loss of services, resources, and social interactions once individuals with SSADHD. One caregiver referred to the time following high school graduation as a ***"significant void"*** for their adult child with SSADHD.

EXECUTIVE FUNCTIONING, DECISION-MAKING AND TASK COMPLETION

Due to the inability to be understood by others, caregivers shared circumstances where they were required to translate what their child was articulating to others. Family members, including caregivers and siblings of individuals with SSADHD shared during the meeting that they needed to interpret what their child/sibling was saying to family and friends. During the patient interviews, all individuals with SSADHD required their parents to assist them in not only understanding the questions that were asked, but also for the interviewer in understanding their responses.

The impact of SSADHD created significant challenges with executive functioning, problem solving and cognition in patients. To that point, one caregiver stated that ***"executive functioning is an overriding umbrella that impacts everything else."***

Many caregivers of individuals with SSADHD discussed challenges with overall cognitive functioning. Two caregivers during the meeting reported that their child was not aware of the time of the day, the day of the week, and other basic information:

> ***"They have very little idea of the day of the week, sometimes even the time, which is mostly reminded by rituals (such as lunch) that mark the progress of the day…like not knowing what town you live in; they barely understand what town they live in…. It takes constant reminding over and over for them to understand just what tomorrow will be. And [my child] will ask a thousand times."***

One impact of the decreased cognitive ability and awareness was that the individuals with SSADHD were often unaware of their challenges. One caregiver referred to their child as being ***"blissfully unaware"*** of their condition, so that they would not be able to perceive the social and other related impacts of their disorder. During our preliminary interviews, when the individuals with SSADHD were asked what their biggest challenges were, many stated that there were no challenges or difficulties that they experienced. Some individuals would look at their parents for assistance in answering questions during the preliminary interviews. One patient shared that their ***"brain didn't work"*** during the interview. Another patient during the meeting shared the following, with assistance from his caregiver:

> ***"My potential is to solve these problems, but my body doesn't let it happen."***

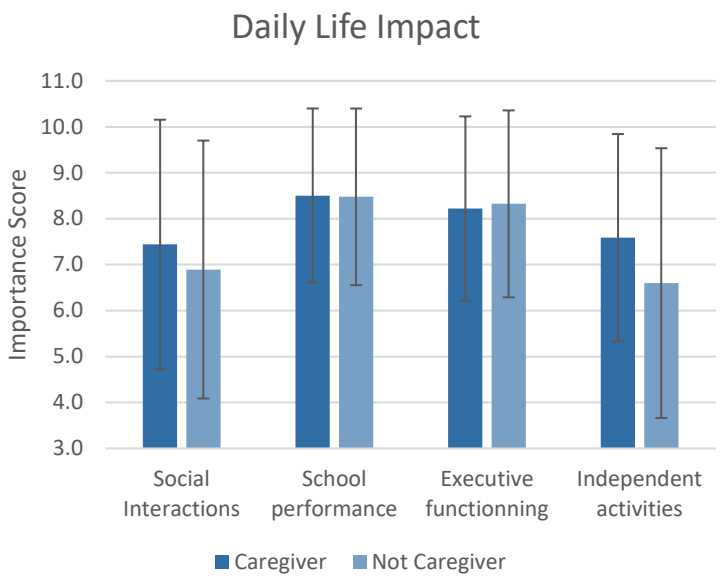
The challenges with cognitive ability created challenges for executive functioning in individuals with SSADHD, resulting in an inability to complete tasks. One caregiver stated that their child with SSADHD referred to their brain as being ***"frozen"***, making it difficult to complete responsibilities and tasks. One caregiver shared regarding their child:

> ***"When they problem solve, it seems to take them halfway…. But they often stop; they go halfway with it, they can't follow through, they say, 'it's just not working.'"***

Challenges with bringing tasks to completion was a common theme discussed during the meeting as well as the focus groups. Even simple tasks of everyday living presented challenges for individuals with SSADHD. One caregiver shared during the meeting:

> ***"I mean, he knows what to do, but he can't do it—something blocks him, and he can't do the other thing. For example, he was on the elevator last week. He knows what to do to go down, but he didn't press the button to go down. The light was [off], and he stayed there, he did nothing."***

During our preliminary focus groups, some caregivers also shared that their child would often ***"freeze"*** when presented with a task and therefore would not be able to complete the task. During both the focus groups and the meeting, caregivers shared that activities of daily living, such as personal hygiene, taking medications, and transportation posed many challenges and often required constant reminders from caregivers in order for the individuals to complete them.



Although not discussed as extensively, two caregivers implied that the behavioral/psychological symptoms of SSADHD also affected their child's ability to complete tasks. They shared the following:

"[OCD] really sets him apart from other people, but he can't do some things because of that."

"In this way, he's actually never really absorbed by any activity. He keeps asking what will happen now, what will happen in 10 minutes, what will happen after lunch."

INDEPENDENT ACTIVITY

According to our live polling, SSADHD had significant impacts on the independent activity of individuals with SSADHD, likely due to impacts from all symptom categories. Multiple caregivers reported that their child was unable to be left alone at any time. This necessity primarily appeared to be related to instrumental activities of daily living, sleep patterns, seizures, and threats to physical and social safety.

MOBILITY

Although some caregivers shared that their child with SSADHD was able to walk, the process of moving from one place to another for patients still required some dependence on the caregiver. One caregiver shared their experience about their 6-year-old child with SSADHD getting into a car.

> ***"[Our child] also cannot climb in and out of a car or into her car seat. She can walk up to the car, but as she gets bigger obviously, we have to lift her. Once she's in the car, she's fine, but it's that step into the car and then up into the car seat."***

One caregiver shared during the preliminary focus group that although their child had the ability to walk, they were primarily wheelchair-bound due to the risk of drop (atonic) seizures. This significantly affected their independence, as shared by their caregiver during the meeting:

> ***"The other issue is the fact that [our child has] lost his independence. He'll never walk alone again—simple as that. He is mobile, he can walk .... but if he's out of his wheelchair I hold him to make sure he doesn't fall."***

FEEDING

Impacts on feeding, chewing and swallowing were all described by individuals with SSADHD and caregivers due to both hypotonia and limited fine motor skills. These challenges were present from infancy into adulthood. One caregiver stated that their child with SSADHD had a ***"severe eating problem"*** as a baby and was unable to drink from a bottle. Another caregiver shared their experiences with feeding their child who presented with a weak sucking reflex as an infant.

> ***"It would take [our child] forever to drink…. I remember saying, 'I feel like when I finish feeding him, it's time to eat again.' …it would take him hours. And for the longest time it was because of his suck. His sucking was so weak."***

As individuals with SSADHD grew older, difficulties with sucking and feeding reflexes transitioned into difficulties with chewing and swallowing food, which posed serious risks of choking and aspiration. One individual with SSADHD (with assistance from their caregiver) shared the following during the meeting:

> ***"I don't eat. I was tube fed for many years, and now I only drink Boost. I cannot chew at all, really…I worry about aspirating."***

Multiple caregivers described their child with SSADHD being unable to chew food, requiring assistance from the caregiver or another person, or modification of foods. One caregiver reported that their child with SSADHD could ***"only drink through a straw".*** One caregiver described the various food modifications that were necessary for their child as they grew older.

> ***"...We thickened [our child's] liquids until age seven"***

> ***"[Our child] can't eat anything beyond what a toddler would eat in terms of it needing to be soft"***

Caregivers during the meeting shared their perspectives on their child's difficulties with chewing, especially in relation to the risk for choking:

> ***"[Our child] has always had problems chewing. When she entered kindergarten, she was also in mainstream school for a year and a half and she needed a teaching assistant to help her because she wasn't chewing her food. Sometimes when she was eating something, it would get stuck in her throat."***

> ***"[Our child] will almost forget to chew his food, and a lot of times he has choked either because he overstuffs his mouth, or he doesn't chew. Even at 13 years old, I have to cut his food up very small."***

With respect to independent feeding as individuals with SSADHD, many caregivers discussed difficulties with their child actually putting food into their mouths. One caregiver described self-feeding as a "***very messy process"***, and two caregivers during the meeting shared that their child often had ***"food all over their face while eating"***. This was described even by caregivers of adult children with SSADHD. One caregiver shared the experience of her 26-year-old son with SSADHD:

> ***"[Our child] can make his own peanut butter and jelly sandwich, but then there is jelly and peanut butter everywhere…when he gets done eating, half of the food is on his face."***

One caregiver mentioned that their 13-year-old child's difficulties with self-feeding resulted in being ***"messy when she eats, and nobody wants to sit around her"*** during mealtimes in settings such as in school.

Another parent described difficulties with handling eating utensils, stating that their "***13-year-old child with SSADHD was only able to feed themselves with a spoon, and was unable to use a knife".***

DRESSING

Due to the impacts of SSADHD on fine motor skills, many caregivers described difficulties in their children with dressing themselves independently, requiring intervention from the caregiver as well modified clothing to aid in more independent dressing. This was described in our preliminary focus groups, where caregivers described difficulties with buttons and tying articles of clothing in individuals with SSADHD. Several caregivers also shared their experiences with their children during the meeting:

> ***"My [child] is 13 and he still is not able to dress himself."***

> ***"[Our 19-year-old child] needs a lot of help getting things over her head and she cannot put a bra on by herself."***

> ***"We can start her and sometimes she can get her arm through a hole, but most of the time she needs help."***

"... [our 13-year-old child's] clothing options are very limited…to what you would put a toddler in."

"...Zippers don't happen. He's 12. Buttons don't happen, so we get elastic pants. Shoelaces don't happen, so we have Velcro"

"[Our 25-year-old child] put his shoes on the wrong feet…his shirt on backwards or his pants on backwards"

PERSONAL HYGIENE

Some caregivers discussed the impacts of SSADHD on specific personal hygiene habits, particularly with respect to bathing and brushing teeth. One caregiver mentioned that her "***13-year-old child with SSADHD still needs to be bathed"***, and several caregivers mentioned that they needed to brush their child's teeth for them. In many cases, the difficulties with brushing teeth, although likely attributable to problems with fine motor skills, were compounded by sensory overstimulation caused by the sensation of brushing teeth. One caregiver stated the following:

"He's not able to brush his teeth, and, even when I do it for him, it's like a sensory issue in his mouth; he won't open his mouth or he resists and doesn't want me to be in his mouth brushing his teeth."

Although not discussed at length during the meeting, one caregiver alluded to the development of oral health problems as a result of their child's inability to independently brush their teeth.

INABILITY TO SLEEP INDEPENDENTLY

Some caregivers noted that their children with SSADHD were unwilling to sleep in their own room or their own bed. This was reported in individuals with SSADHD even past preteen and teenage years. Several caregivers shared these experiences during the meeting:

"We had to get a tent bed because [our child] will not stay in her own bed…"

"[Our child has] been very resistant to moving into her own room because of all the various symptoms that I've explained...every time we try to transition her into her home bedroom, she just sits outside our door, cries for hours, and knocks and calls out."

Beyond the unwillingness to sleep independently, many caregivers felt compelled to have their child sleep in their own bedroom, in order to be present for potential seizures that occurred in the night or injuries associated with sleep disturbances and related behaviors.

SAFETY

PHYSICAL SAFETY

Multiple caregivers discussed concerns for the physical safety of their child with SSADHD, referring to prevention of physical harm. Balance issues, walking challenges, seizures, and sleep disturbances introduced problems with physical safety in patients with SSADHD. One adult with SSADHD, using assistance from their caregiver, shared their experience during the meeting, stating:

"It is life-altering. It affects my walking—well, my few steps, and my balance."

One caregiver discussed that the falls associated with their child's drop **"*seizures resulted in fractured teeth and a broken collarbone*".** Despite surgery to address the fractured teeth, the drop seizures resulted in significant impacts on both walking AND feeding. This caregiver also shared that their child ***"gave up eating"*** and is ***"now very tactile and defensive when it comes around his teeth"***.

One caregiver reported that their child's sleepwalking contributed to the risk of their falling and injuring themselves:

> ***"One night, I heard a big bang, and I woke up to see what happened. I found [our child] laying on the floor; from upstairs, she rolled all the way down the stairs, and she was laying on the floor. I believe she was sleepwalking and fell down."***

One caregiver reported that the chronic fatigue caused disorientation and confusion in their child with SSADHD, which increased the risk of physical injury:

> ***"[My child] does not sleep, and he thinks that when he gets up that he can walk— he's not capable of doing that—-so, that fatigue really blurs everything."***

Sometimes, patients with SSADHD require hospitalization due to the impacts of their symptoms. Several caregivers during the meeting shared that their child had been previously hospitalized due to seizure activity. Additionally, another caregiver during a preliminary interview reported that their child was hospitalized and subsequently required intubation due to a status epilepticus event triggered by aspiration pneumonia. While most hospitalizations were intended to control seizure activity, one caregiver reported that their child had been hospitalized for surgery to repair dental injuries that were sustained during seizure activity.

Many caregivers also referred back to the lack of awareness that individuals with SSADHD had with respect to understanding how to stay safe and respond to threats to physical safety. Parents described working with their child with SSADHD, even as adults, to recognize the significance of safety alerts, such as fire alarms. One parent stated:

> ***"He really doesn't know how to respond to whatever that may be— to shelter in place or those basic things that most people know."***

SOCIAL SAFETY

In addition to physical safety concerns, caregivers shared concerns regarding social safety, such as encounters with strangers that could lead to aggression, rejection, being taken advantage of, or even abduction of individuals with SSADHD. Respondents in our preliminary caregiver survey shared that their child with SSADHD has ***"no sense of danger"*** when asked about some of the biggest impacts on daily life. One caregiver during the meeting referred to their adult child's awareness of their own individual safety as ***"non-existent"***. Specific issues surrounding social safety were discussed among caregivers of both adult and younger individuals with SSADHD. Many of these concerns stemmed from patients approaching unknown individuals or ***"strangers"*** without caution. Caregivers stated the following regarding social safety in their child:

> ***"He's not afraid of someone he's not met."***

> ***"[Our child] kept escaping from the room where we were staying and approaching strangers. That has been a big thing with her as of lately. We have new neighbors, and she will run across the yard and walk right into their house…. Safety is a big issue for us. She will take off from our yard, she will approach strangers and ask them to hold their hands. It's scary. I'm afraid that she will go off with someone. She is fearless"***

The concerns that caregivers shared with respect to social safety also included how others perceived and responded to individuals with SSADHD in social situations, especially for adults with SSADHD. One caregiver shared their experience about their adult child:

> ***"He was once over in an elementary school playground and the police were called on him because they didn't know what he was doing there."***

Multiple caregivers expressed concerns over their children's inability to communicate and the potential implications that it had on their safety. One caregiver shared a specific instance at an airport:

> ***"One time we were traveling, and at the airport, [our adult child] disappeared. We knew he could not tell anyone who he is, who his parents are, and we were looking everywhere. Somehow, he went on an escalator to a different floor. We found him about a half an hour later. So, there are safety concerns."***

SOCIAL INTERACTIONS

SSADHD had a significant impact on social interactions. Caregivers in our live polling reported that some of the greatest impacts of intellectual disability and speech/communication impairment in SSADHD were on social interactions. One caregiver shared about their adult child's experience with social interactions with respect to their intellectual disability:

> ***"This…. pertains to everyone else; the people they meet on the street, how they interact with all of them. Their cognition affects how people interact with them—how they accept them or don't accept them, and how they relate to them."***

Caregivers described several situations in which their child's social interactions were impacted by their speech and communication difficulties, whether they were everyday interactions or establishing and maintaining friendships.

SOCIAL ISOLATION

One individual with SSADHD, with assistance from their caregiver, shared that they had ***"no friends"*** when discussing the social impact of intellectual disability. One caregiver reflected on the fact that their adult child's ***"tribe is small"***, again referring to their child having a limited number of friends to support him.

Multiple caregivers and family members shared about the isolation that their children with SSADHD experienced regularly:

> ***"It is hard for other kids to play with [my sibling] because they can't understand him. "***
>
> ***"One time, we went out with the other kids for a walk. [Our son] started talking, and the other kids listened to him and said, 'What is he saying?' They don't understand him."***
>
> ***"A lot of people don't understand him and can't have a conversation"***
>
> ***"Making friends [is] excruciatingly hard for him because of his language difficulties; it can be very isolating"***

The impact on social interactions appeared to become more pronounced as the individual with SSADHD become older and could not interact typically with their peers. In our preliminary focus groups, a caregiver shared that although their child was 10 years old, ***"...intellectually, [they are] two and a half, three years old."*** The caregivers also shared that their child engaged in parallel play with their peers as opposed to more age-appropriate direct peer play.

These cognitive delays resulted in circumstances where individuals would repeat statements over multiple times to others, speak out of turn in social situations, not have the proper social cues to understand when and when not to be physically affectionate, such as giving hugs, and being self-centered when interacting with others. One caregiver shared the following about their adult son:

> ***"His communication with others is largely based on his needs and interests…. so, he has not developed friendships in the way [one] naturally would. "***

This was also observed in the preliminary patient interviews, where individuals with SSADHD were very conversational during the interview, and would ask questions, but more commonly would share information on topics of interest for them.

The behavioral/psychological symptoms also had a considerable impact on social interactions in individuals with SSADHD, in a variety of ways. Symptoms of depression and anxiety reduced their desire to interact with others or be in large social situations. Physical and verbal manifestations of OCD behaviors, as well as the aggressive behaviors, reduced

the desire of other people to interact with individuals with SSADHD. During our preliminary focus groups, one caregiver mentioned that their child's sensory stimulation behaviors such as banging their head or clapping also had an impact on social relationships with their peers. One caregiver shared the following**:**

> ***"[Our child] has basically no friends. Sometimes, neighbor kids tolerate him, but he doesn't really get involved into play."***

One caregiver noted that her child's verbal stimming affected his ability to be social with his peers:

> ***"It causes a lot of social issues, children don't ask [my child] to play, or they don't want to be with him. He gets a lot of strange looks. I once got pictures sent back to me from one of the camps with Gen Ed children, and [my child] was off to the side and all the other kids were together; I know it's [my child's] stimming that's keeping him from being able to participate with them."***

For some families, the challenges with social interactions in individuals with SSADHD, led to outcomes such as warnings to caregivers about removal from social situations due to disruptive behavior. One caregiver shared:

> ***"We do get contacted by [our adult community program] on occasion regarding concerns over [our child's] behavior. It can be … taxing for staff and disruptive to other clients. I recognize that [our child] could be asked to stop attending, which would make his world and his engagement with others all the smaller"***

Similarly, behaviors related to intellectual disability in individuals with SSADHD at social events also impacted whether or not these individuals were invited back to future social events. One caregiver shared their experience regarding birthday parties for their 12-year-old child with SSADHD:

> ***"...they don't know what's appropriate. For example, if they are invited to a birthday party and they're standing next to the person that's cutting the cake, they will just put their hand into the cake—they won't even think…. soon, they're almost blacklisted because [our] child is [perceived as] too high maintenance to bring them into certain social environments. And it doesn't matter how empathetic the parents might be. So, you might get one invite, but then after that it's gone."***

LIMITED PARTICIPATION IN RECREATIONAL ACTIVITIES

The physical limitations and mobility issues associated with SSADHD appeared to affect social interactions in various ways, according to caregivers at the meeting. Several caregivers mentioned that their child's physical limitations made it difficult to participate in any social activities that required physical strength, coordination and balance, such as youth sports, riding a bike or playing in the park. One caregiver during our preliminary focus groups mentioned that delays in gross motor coordination negatively affected their child's ability to keep up with other children at the playground. Multiple caregivers during the meeting also shared their perspectives on this topic:

> ***"...physical abilities limits activities [our child] is involved in and makes it hard to make friends with children her age"***

> ***"... [our child] can't keep up with other children…he starts to get left behind"***

Similarly, one individual with SSADHD, with assistance from his caregiver, shared his experiences during the meeting regarding participation in specific social and recreational activities related to their seizure disorder.

> ***"Also, around me, people will not let me participate in certain activities because I am at risk for seizures. That is hard because it is school, it is social, it is sports—even wheelchair sports are hard to do."***

Additionally, the inability to focus made it difficult to pay attention to rules in recreational activities or understanding social cues and norms.

> ***"[Our child] cannot really follow games or rules. He cannot concentrate on anything."***

During our preliminary focus groups, one caregiver mentioned that sleep attacks during the day resulted in less social interaction and participation in school-based activities. One caregiver during the meeting described the following:

> ***"[Our child] would often fall asleep on the ground or in the playground—kids would be walking around her. It didn't faze her."***

MISUNDERSTANDINGS WITH OTHERS

One caregiver described how their child's speech and communication patterns made it so that they were ***"unable to effectively communicate with unfamiliar listeners"*** As a result, the individual with SSADHD was subject to ridicule and contempt from others. The caregiver described two situations where she was shopping with her child with SSADHD:

> ***"Once, we were at a store. As I was putting things on the conveyor belt, my son kept telling me no, and pointing to the end. He was communicating that there was no room on the conveyor belt at the beginning, and he was going to wait for there to be room on the end. The person working the cash register heard this exchange and told him to quit being a little brat…. Another time, he told a different cashier, 'Thank you,' for handing him the receipt, but his thank you was in sign [language] and kind of looked like he was blowing a kiss, and he was made fun of by a grown adult in the middle of a store."***

INABILITY TO SELF-ADVOCATE IN UNDESIRABLE SITUATIONS/MISTREATMENT

Caregivers also described difficulties for their child in addressing and communicating information about problems, conflicts and ill treatment outside of the home due to speech challenges. One caregiver described the mistreatment her child with SSADHD was experiencing in school, which they were previously unaware of because of their child's inability to communicate this information. This allowed the problem to go on for an extended period of time without being noticed:

> ***"This year at school, [our child] was excluded by a specific teacher due to his food allergies and speech problems. He couldn't effectively communicate what happened, only that it made him sad. He also couldn't come home and tell us that he was being given old candy corn for birthday treats, when the other students were having cupcakes. This sadness and mistreatment went on for months unnoticed."***

In a more extreme situation, this caregiver also reported that her child's inability to communicate made it difficult to understand the circumstances of an allergic reaction that their child experienced during school, requiring them to call emergency medical services to intervene:

> ***"[Our child] also didn't have the words to come home and tell us the day that he was given M&M's and had an anaphylactic attack at school; we weren't sure what happened, so we called 9-1-1. We couldn't get a straight story."***

SEXUAL HEALTH

One topic related to social interactions during the meeting was how to address sexuality with individuals with SSADHD who had reached puberty. One caregiver described having to teach their adolescent child about how to behave with respect to their sexuality. Another caregiver shared their experience with their adult child:

> ***"We are also trying to help him with his sexuality. He has the interests of a 30 yr. old but no appropriate outlets. We never realized we'd have to teach [our child] things that come normally to his developmentally appropriate peers. It can be uncomfortable for his support staff- but we're working on it. He can be inappropriate in public by asking questions. There are many awkward and uncomfortable situations and interests that we are currently trying to address."***

Despite these challenges with social interactions, individuals with SSADHD placed heavy importance on their relationships with others. During our preliminary patient interviews, both adults and adolescents with SSADHD shared that they enjoyed seeing people and meeting new people in various settings, such as work, church and at school. One adolescent with SSADHD shared that she was sad about the impact that the COVID-19 pandemic had on her ability to spend time with her friends.

EMOTIONAL IMPACT

The challenges in daily life due to SSADHD resulted in significant emotional impacts in patients. These included expressions of fear and anxiety, frustration, distress, resignation, and sadness. In some cases, these expressions manifested in harmful behavior to the patient or others around them. With respect to seizures, many patients showed a change in mood and behavior after experiencing a seizure. One caregiver described their child's mood following a drop seizure.

> ***"What's the most frustrating part of the seizures is [our child] could be in his wheelchair looking at a cartoon or something and happy, very content, no increased hyperactivity or any of that. And the next thing he drops. It's just devastating to look at him. I mean, try to recover from that. He sleeps, comes around again, gets in a good form, and then another drop."***

The most common emotional impact related to seizures in SSADHD was fear, as reported by caregivers and individuals in both the preliminary focus groups and during the meeting. One individual, with assistance from his caregiver, shared the following during the meeting:

> ***"I don't remember the seizures; I remember the aftermath. It is terrifying. I worry that I will seize. It is not possible to stop it."***

Caregivers during the meeting and the focus groups shared that fear may stem from the awareness of the onset of the prior to seizure or from the prospect of having another seizure. One caregiver stated during the meeting:

> ***"It's disruptive for [our child]; he gets very anxious after he's had [a seizure]. I could tell [our child] was very anxious and looking for reassurance from me— 'Am I okay again, mom? Is this going to be, okay?'"***

This anxiety was also related to intellectual disability in SSADHD. During the patient interviews, one adult individual with SSADHD, with assistance from their caregiver, shared that they would often feel apprehension in their ability to complete tasks, and experience anxiety. These feelings would often result in the individual with SSADHD requiring constant reassurance and external validation.

Frustration was a common experience in individuals with SSADHD, primarily related to intellectual disability and speech/communication impairment. Caregivers shared the following:

> ***"They cannot speak, they cannot express their feelings, and that has frustrated them."***

> ***"[Our child] began to get frustrated that he could not communicate easily."***

> ***"He got really, really frustrated because he couldn't express himself."***

> ***"I think their brains freeze in this process and that is unbelievably frustrating for them…. they're so slow to do it and you can see it through their incredible frustration."***

Additionally, a caregiver during a preliminary interview shared that the involuntary movements associated with the choreoathetosis and the dystonia were frustrating and upsetting for their child with SSADHD.

In some cases, the frustration experienced by individuals with SSADHD would result in physical acts of aggression. One caregiver during this focus group described their child stomping and clapping to indicate their frustration. Speech and communication challenges in SSADHD led to various impacts on mood and behavior, as described by several caregivers. One caregiver described destruction to property related to their child's frustration:

> ***"He had challenges with behavioral issues as a result of not being able to express himself…. we have holes in the walls to demonstrate that."***

In one case, the inability to communicate resulted in the biting of other people:

> ***"There were months that went by where he would just bite; if he was hungry—bite, if he was thirsty—bite, if wanting to play—bite… it was a terribly hard time for us."***

Another caregiver shared that their child also engaged in ***"injurious behavior"*** to both himself and his caregivers, requiring additional intervention, such as having to wear a helmet for protection against the self-harming behavior.

IMPACTS OF SSADHD ON CAREGIVERS AND OTHER FAMILY MEMBERS

The meeting discussion, focus groups, and interviews all found that SSADHD did not just have major impacts on patients, but the entire family providing care. Caregivers reported on the variety of impacts related to all symptom categories that they experienced, as well as impacts on the rest of the immediate family.

INCREASED BURDEN OF TASKS

During the meeting, caregivers reflected on how SSADHD exponentially increased their own daily tasks and responsibilities, often due to the impact SSADHD has on the independent activity of individuals with SSADHD. Caregivers shared that the greater the impact on independent activity in SSADHD, the greater the burden of tasks for caregivers. Throughout all stages of life, caregivers were often solely responsible for managing all of their child's activities of daily living, including dressing, personal hygiene, transportation, medication administration, financial dependance, guardianship, and many other tasks. Part of this management included teaching and reminding their child how to perform basic tasks repeatedly, as well as monitoring time management to ensure timely task completion.

Moreover, risks associated with some of the physical symptoms of SSADHD required caregivers to take extra precautions to avoid any potential issues. For example, one caregiver stated that she needed to stand by her child with SSADHD at the playground when they were on climbing equipment to ensure that their child did not climb too high and risk a fall or injury.

This impact of symptoms on independent activity also created increased tasks for siblings of individuals with SSADHD. One caregiver shared that her typically-developing child (younger than their child with SSADHD) was often responsible for their sibling with SSADHD if the caregiver was not available. A sibling of an individual with SSADHD also discussed the direct impact that behavioral/psychological symptoms of SSADHD had on their ability to conduct everyday tasks:

> ***"It affects me as well because I would have to leave my classes or leave work because the teacher would call my parents and they weren't available at the time, so I would go and walk into the room because she's fighting the teachers."***

Multiple caregivers also stated that they needed to be near their child with SSADHD constantly to help them communicate with other people. This was evidenced in our patient interviews, where caregivers needed to be present to help translate speech to the interviewer. The responsibilities of translation even fell upon young siblings of individuals with SSADHD. One sibling of a patient shared their experience:

> ***"Talking is hard for [my sibling], but I can understand him best; I interpret what he is saying for my parents, family and friends."***

In addition to direct translation, caregivers spent a considerable amount of time developing means to facilitate communication for their child with SSADHD. One caregiver shared that they spent ***"hours and hours each night researching"*** options to aid in communication.

This impact on the task burden for caregivers and siblings was regarded as ***"extremely tiring"*** by one caregiver, especially with the prospect that these responsibilities were ***"ongoing"*** and never-ending. Another caregiver stated that there were many ***"sleepless nights"*** as a result of managing their child's symptoms, including sleep disturbances. Caregivers described being woken up regularly or not getting enough quality sleep to be able to complete daily responsibilities efficiently. This may have stemmed from either their child with SSADHD requiring their attention through sleeping hours or the caregiver feeling obligated to stay awake due to concerns regarding the safety of the individual with SSADHD.

Job responsibilities were often affected by lack of sleep-in caregivers of individuals with SSADHD. Certain symptoms, such as seizures and behavioral/psychological symptoms were also disruptive to work and other everyday activities for the caregiver. As a result, many caregivers needed to leave or reduce their time working to manage their caregiver responsibilities. One caregiver shared that they left their position as an attorney so that they could focus on their child. This often created a significant financial impact on families, compounded by the need for acquiring appropriate school-based resources and accommodations for their child with SSADHD. One caregiver shared their financial burden related to SSADHD:

> ***"We pay the equivalent of a college tuition for [our child] to go to his grade school because that's where he receives his therapy."***

Even in families where the individual with SSADHD lived outside of the caregivers' homes, caregivers discussed their considerable burden of tasks. One caregiver shared the following during the meeting:

> ***"Our [child], 30, lives in an apartment with 24 hr. support. I just stopped doing his laundry, but still prepare his dinners which take up most of my weekends. I still do his grocery shopping- even though he has staff to do these things… Staff always calls me with questions, problems usually with his repeated storytelling which interrupts his daily activities. It's nice having him on his own, but it still requires a lot on our part. Staff expects us to have all the answers. Whenever staff calls out or there isn't coverage, he comes and stays with us, which has been several times a week since COVID."***

INCREASED RISK OF PHYSICAL HARM OR STRAIN

The behavioral symptoms in SSADHD sometimes presented with the risk of physical harm to anyone providing care for these individuals. This included both caregivers and siblings; one caregiver stated that their child with SSADHD has become aggressive with their sibling, in addition to teachers and other individuals providing instructions.

Additionally, one caregiver noted that as her child grew older, it became increasingly difficult for her to carry him during sleep attacks, causing physical strain.

EMOTIONAL IMPACT

Caregivers reported a considerable emotional impact as a result of SSADHD. Many caregivers described fear and worry as a large part of their emotional experience related to their child's experience with SSADHD. These include anticipatory fear related to seizure activity, overall safety, negative social interactions with others, and the transition of care into adulthood for their child with SSADHD. Additionally, there is an inherent concern that the parents share, as to who will care for my SSADHD affected child when I am no longer living. With respect to safety, caregivers alluded to physical injury, choking hazards, and possible abduction as concerns with their child's welfare.

Caregivers described their concern with seizure activity:

> ***"We live in fear. We fear that the advances that we achieve with her from time to time—we can lose them in just a few minutes. We are terrified some of these seizures will happen when we are far away, and someone can't administer [rescue medication] to stop it. We are terrified of losing her."***

> ***"We're very fortunate that we don't have seizures yet, but the anxiety level that we experience in our house—especially to go wake them up in the morning—thinking that something might have happened in the night, that they might have died, is extremely high…. I feel that, for even the families that***

haven't experienced seizures yet, we know there's a high likelihood that it's coming, and I would say it's our greatest fear with SSADHD."

With respect to intellectual disability, two caregivers expressed anger over others underestimating the abilities of their child with SSADHD, especially when it was related to job placement.

Many caregivers also described feeling confused or frustrated related to behavioral or psychological symptoms, as well as speech and communication challenges in their children with SSADHD. This frustration was often followed by feelings of guilt One caregiver expressed trauma, grief, and feeling conflicted with respect to their child's violent behavior towards them:

"So, the impact of that is really hard when you're a parent because you love your kid and you want them to be close to you, but if someone is physically attacking you, it feels like an attack."

Caregivers and other family members also expressed grief and sadness related to their child's speech and communication difficulties and their related impacts, such as not being able to effectively communicate and connect with others outside of the family. The sibling of an individual with SSADHD also expressed their sadness related to their sibling's inability to communicate with others the way that she was able:

"It is hard for other kids to play with him because they can't understand him. I worry that he'll be made fun of or be left out. He understands and hears everything and just wants to do all the normal things like me. "

IMPACT ON CARE OF/RELATIONSHIPS WITH OTHER FAMILY MEMBERS AND FRIENDS

SSADHD also affected other members of the immediate family, especially siblings. In addition to siblings of patients with SSADHD often needing to be caregivers themselves, even at a young age, one caregiver mentioned that management of their child's disorder caused her to miss out on important events of her other child 's life:

"My [typically developing child] has soccer tournaments sometimes, and I have to miss the games because [our child with SSADHD] has to take his rest time."

In some cases, caregivers alluded to sleep disturbances and other symptoms in SSADHD having a negative impact on their marital relationship. Another caregiver stated that their child's sleep schedule limited their ability to socialize and maintain relationships outside of the household.

In one case, a caregiver described the significant impact SSADHD had on various members of the immediate family. Impacts included effects on the marital relationship, disruption to siblings of individuals with SSADHD, and ultimately, a complete relocation for the family. These were mainly as a result of seeking out appropriate educational and developmental accommodations for speech and communication challenges:

"We found an amazing school that specializes in children that have speech and language disorders, but it was two hours away from our home. We took him for an evaluation anyway; he was accepted, and we enrolled him. My husband and I lived separately during the week, only seeing each other on the weekends, and shuffling our now 10-year-old daughter—seven at the time—back and forth between [the other city] and home. We pulled her out of her little private school and enrolled her in a [closer] school, then eventually decided to homeschool her just to make everything work. In the last few months, we've decided to completely relocate our family, sell our house, and move halfway between home where my husband and I grew up and graduated—where our families still are—and [where my child's school is]."

IMPACT ON RECREATION AND TRAVEL

Multiple caregivers reported that family trips, vacations and holidays were limited due to SSADHD. Caregivers stated regarding the planning of vacations as ***"challenging times"*** or ***"debilitating"***. One caregiver shared that since their child started having seizures, they have never gone on a family vacation, as aspects of the vacation may be triggers for seizures.

For those families that were able to travel, SSADHD symptoms limited or disrupted recreational activities. Multiple caregivers reported that they would miss activities during family vacations due to seizure risk, behavioral/psychological symptoms, fatigue or sleep attacks. One caregiver noted that due to the specific equipment required in order for their child to sleep, air travel was not possible. These difficulties made it so that this family was unable to attend the EL-PFDD meeting in person:

> ***"The main reason why my wife and daughter aren't here today is because of that fact. We… were denied through our insurance, as well as through appeal, a travel bed, three times. We've had to modify things from Walmart—whatever we can do. And so, trying to travel with a twin-size mattress in a tent bed, modified, that doesn't exactly fly on a plane, if we're not going somewhere for an entire week, it's really challenging."***

Multiple families of individuals with SSADHD shared difficulties resulting from speech and communications challenges when traveling through an airport. caregiver described their adult child with SSADHD getting lost at the airport, and not being found until considerably later due to the inability to communicate where they were. Another caregiver described challenges when going through the security checkpoint:

> ***"We also experienced great difficulty at security in two different airports last year because he couldn't articulate his name to where they could understand him."***

CONCLUSIONS ON SYMPTOM IMPACTS

The symptoms of SSADHD can affect individuals from childhood into adulthood. Between seizure activity, behavioral/psychological symptoms, sleep disturbances, movement and mobility challenges, decreased cognition, memory retention and focus, the impacts of SSADHD can result in significant physical injury, reduced decision-making ability and decreased executive functioning. Collectively, this affects the ability to engage in independent activity, including activities of daily living, academic and work-related performance, social interactions, and the ability to stay safe during independent activities. Many individuals have been hospitalized due to the impacts of SSADHD. Despite the decreased cognition, individuals with SSADHD still have demonstrated anticipatory fear related to symptoms such as seizures and movement disorders, as well as frustration and anxiety at what they are unable to do compared to their peers.

Caregivers of individuals with SSADHD report an increased burden of tasks, lack of respite, a disruption in daily activities and work, earning potential, impacts on family relationships as well as family circumstances. Caregivers often feel overwhelmed and concerned for their child's welfare as they get older. Caregivers also experience grief and sadness, triggered by the challenges their children face, especially with respect to maintaining friendships, social interactions, living independently, and meaningful purpose for their life. Since SSADHD is ultra-rare, there is very little information available outlining the support and resources needed for each patient and caregivers often spend a significant amount of time securing the services their children need.

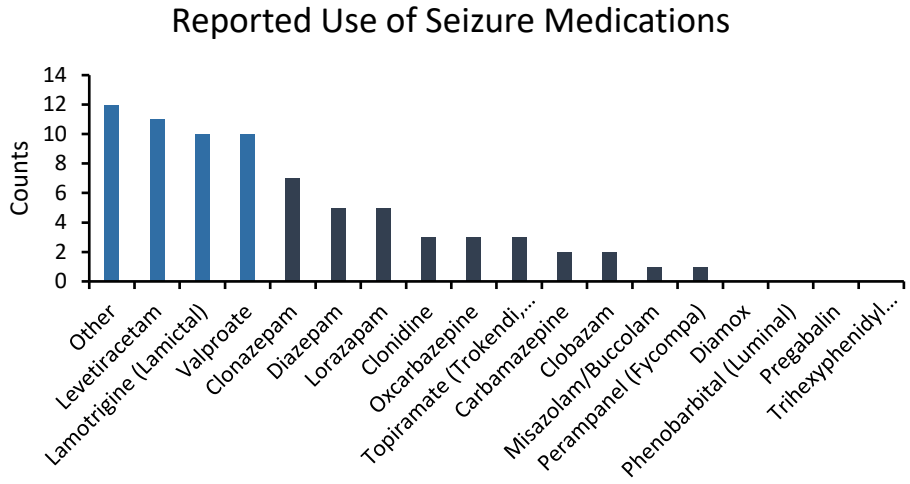
CURRENT TREATMENTS FOR SSADHD

It is widely accepted that the neurometabolic consequences of SSADHD (increased GABA and GHB, decreased GABA receptor expression) are key determinants of clinical severity and disease burden, and disease burden is extreme both for individuals with SSADHD and caregivers (Bose, 2021). It follows that developing treatments with curative potential are warranted to address considerable and urgent medical needs.

PHARMACOLOGICAL TREATMENTS

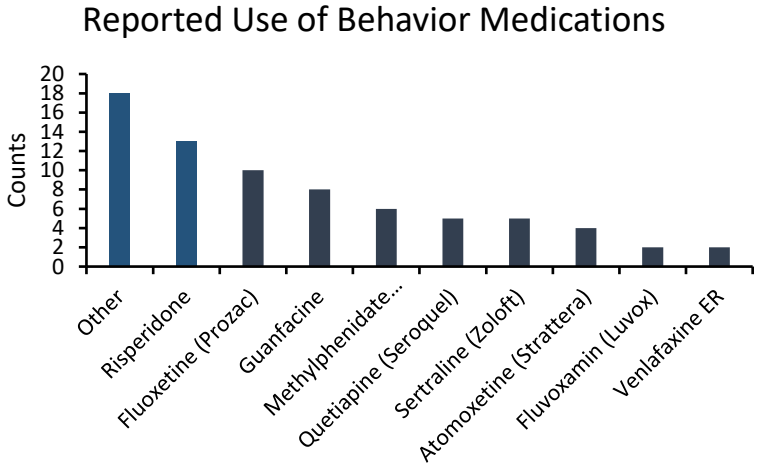
SEIZURES

Our preliminary caregiver survey found that 44% of respondents reported that their child with SSADHD was taking seizure medications. These medications included both daily antiepileptic medications as well as rescue medications. The most commonly used daily antiepileptic medication included Keppra (levetiracetam) and Lamictal (lamotrigine). The most common seizure rescue medication used was Ativan (lorazepam), but Diastat (diazepam) and Buccolam (midazolam) were also reported to be used as rescue medication for seizures.



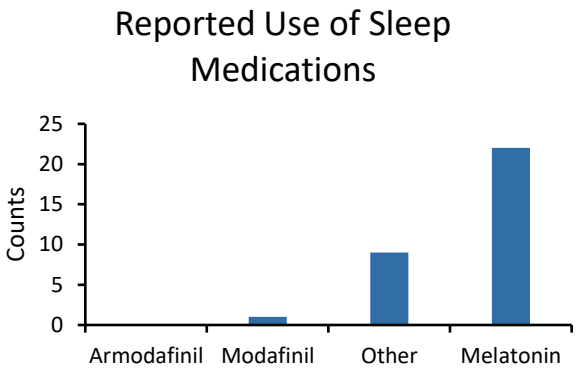
BEHAVIORAL/PSYCHOLOGICAL SYMPTOMS

According to our survey, 53% of individuals with SSADHD were on medications to treat behavioral and psychological symptoms. The most commonly used medications were risperidone (Risperdal), followed by fluoxetine (Prozac), and guanfacine (Tenex). Other medications used include methylphenidate (Ritalin), quetiapine (Seroquel), sertraline (Zoloft), atomoxetine (Strattera), fluvoxamine (Luvox), venlafaxine ER, Adderall, aripiprazole, brexipiprazole (RXULTI), clonidine, dexymethlphenidate (Focalin), escitalopram (Cipralex), herbal remedies, homeopathy, hydroxyzine, (ATARAX), lisdexamfetamine (Vyvanse), olanzapine (Zyprexa), pramipexole (Mirapex). During the discussion, caregivers discussed the use of these medications to treat symptoms of anxiety, hyperactivity and impulsiveness, and inattentiveness.



SLEEP DISTURBANCES

Our survey found that 44% of individuals with SSADHD were on medications to treat sleep disorders, with most treatments aimed at increasing the ability to fall and/or stay asleep. The most predominantly used medication was melatonin (33% of individuals with SSADHD). Other medications for insomnia and restlessness included Alprazolam, Clonidine, Clobazam, Delorazepam, Lorazepam, Olanzapine, Seroquel, Trazodone, and Zopiclone. One caregiver during the meeting also stated that their child with SSADHD took Abilify (aripriprazole) before bedtime to help with sleep. Additionally, modafinil was prescribed in some individuals with SSADHD as a stimulant to promote wakefulness and prevent sleep attacks during the day.



MOVEMENT DISORDERS

In our survey, some caregivers did report that their child with SSADHD did receive treatment for choreoathetosis and dystonia, although the specific medications were not indicated. However, our preliminary caregiver interviews found that one patient was taking Clonazepam, Trihexyphenidyl and Oxcarbazepine to treat their dystonia.

EFFECTIVENESS OF CURRENT PHARMACOLOGICAL TREATMENTS

In general, current available medications to treat the symptoms of SSADHD have had mixed success. In most cases that were described, rescue medications for seizures were effective in stopping the seizures in those moments once they were administered but were reliant on when seizures were recognized and the swiftness in delivery. Daily medications for seizures were less effective, with some patients completely resistant to all seizure medications, and some having breakthrough seizures. One caregiver shared that the drop (atonic) seizures in particular were difficult to treat:

> ***"He's been resistant to medication the whole time. He's recently started cannabis medication and he's tried epidiolex, etc. You name it he's been on it—there's been no effect. That's why we're looking for a different route."***

Regarding behavioral/psychological symptoms, two caregivers stated that they had tried multiple medications, with no significant effect in improving their child's symptoms. Other caregivers discussed risperidone and fluoxetine with limited effectiveness, where risperidone did somewhat improve some symptoms, but not all, and fluoxetine only being effective part of the time. Melatonin also yielded inconsistent effectiveness in the treatment of insomnia and restlessness, often resulting in the need for a higher dose. One caregiver shared their experience:

> ***"Usually, if it's before three o'clock in the morning, we give [our child] another dose of melatonin just to sort of see if that helps settle her back down—sometimes it works and sometimes it doesn't."***

Some caregivers reported having to use multiple medications to fully control symptoms related to sleep disturbances:

> ***"[My child] currently takes clonidine and melatonin and Abilify before bedtime, and without those medications, he would stay up all night."***

One caregiver discussed the effectiveness of modafinil which appeared to help ***"a little bit"*** to keep their child awake. Interestingly, one caregiver shared during the live polling that the behavioral medication that her adult child with SSADHD was taking for their attention deficit symptoms improved their ability to stay awake. They shared the following:

> ***"[Our adult child] started taking Ritalin/Concerta in 2nd grade for attention but coincidentally helped regulate his sleep. He used to fall asleep in the middle of the day if inactive. That stopped. When he doesn't take it, he is a bit sloppy and drowsy."***

SIDE EFFECTS OF CURRENT PHARMACOLOGICAL TREATMENTS

A major concern shared by caregivers were the side effects of current medications. Caregivers described hair loss with some seizure medications, lethargy for both seizure and behavioral/psychological medications, and, in one case, increased violent behavior with medication intended to treat behavioral/psychological symptoms. One caregiver shared their concerns with current medications for SSADHD:

> ***"Most of these drugs have a lot of side effects and sometimes we wonder if we are doing more wrong than well."***

REHABILITATIVE THERAPIES

Our survey results showed that 15% of respondents had children with SSADHD who received individual services or went to special schools geared towards individuals with intellectual disabilities. Related, several respondents also reported that their adult child with SSADHD was receiving services or continuing education. One caregiver discussed trying applied behavioral analysis (ABA) therapy with their child with SSADHD to manage oppositional or defiant behavior, as well as inattentiveness and hyperactivity. Three caregivers discussed speech therapy to address speech and communication difficulties in their child with SSADHD. Speech therapy started as early as toddler age and continued through adulthood. One 19-year-old adult with SSADHD shared that during their speech therapy session, the therapists would ***"help articulate sounds and words"***, and that there was a group for the speech therapy session, where the group would practice speaking with one another to help achieve various speech therapy goals. Caregivers also alluded to physical and occupational therapy for gross and fine motor skills, as well as feeding.

The various therapies improved some of the impacts of SSADHD, including academic performance and some physical symptoms. Both physical and occupational therapy appeared to be useful for mobility and self-feeding in patients with SSADHD.

Family members expressed frustration with the length of time therapies took to yield results. Therapies were often very rigorous and time-consuming, as shared by several caregivers:

> ***"[My child] started right away in occupational speech and physical therapy, along with music and equine therapy. [My child] had therapy both privately and through early intervention… He had therapy five days a week for several hours a day."***

> ***"We tried everything…speech therapy—both private and given by the state through early intervention—videos made by speech pathologists that were supposed to promote speech, reading book after book to him, etc…."***

> ***"We enrolled him in the local university's graduate student speech and language program twice a week, in addition to speech in our local school district and a private therapist."***

Furthermore, the time spent in therapy itself had negative impacts on peer social interactions in individuals with SSADHD. A caregiver shared the following:

> ***"Our kids are very geared towards dealing with adults, but not their peers. And our time—80 percent of our time is spent in some sort of medical or therapy intervention, which leaves very little time for fun or for social activities. "***

One caregiver discussed how ABA therapy had negative emotional impacts on their child with SSADHD:

> ***"We've tried ABA therapy, and she has made a lot of progress with that type of therapy, but I can't really say that it has been the best thing for her…We've recently stopped the ABA since she started kindergarten and I've noticed that when she sees their staff she completely shuts down. So, I feel as though that (ABA therapy) has caused some trauma."***

OTHER TREATMENT/ASSISTANCE RESOURCES

Several caregivers reported that their child with SSADHD used assistive devices and similar tools to help manage the impact of their symptoms. One caregiver stated that when their child with SSADHD was younger, they would use a multitude of physical equipment supports and trainers, such as orthotics, braces and gait trainers to assist in their mobility efforts.

Sign language and electronic devices for speech support were often an integral component of the ability to communicate with others in individuals with SSADHD. Acquisition of sign language provided a meaningful outlet for communication for individuals with SSADHD, as shared by one caregiver:

> ***"So, I started learning sign language and I started teaching [my child] sign language. He loved it, and so he started off with [signing] 'more' and he progressed to [signing] 'more milk' and then he progressed to [signing] 'more chocolate milk' and then he progressed to [signing] 'I want more chocolate milk, slightly warmed please.' So, [my child] finally had words."***

In one case, one caregiver shared that once their child started using sign language, behaviors related to frustration due to the inability to communicate subsided:

> ***"We were trying everything; teaching him sign language, showing him baby sign language videos…and then one day, his little hypotonic hands were able to sign 'more' and 'eat,' and the biting stopped."***

Electronic tools included telegraph devices, Language Acquisition through Motor Planning (LAMP) program devices, and various speech-assistance applications, such as Proloquo, on electronic tablets and computers. One nonverbal patient with SSADHD shared the following at the meeting, via their electronic device:

> ***"I am 11 years old, and I use both my iPad and sign language to communicate."***

The caregiver of this individual shared how using relevant applications on their electronic device was more useful than sign language with respect to general communication with others:

> ***"Once his signing was underway, we introduced Proloquo on his iPad to give him even more vocabulary. The iPad is much more granular, and it lets him speak with people that don't understand sign language."***

One of the biggest challenges related to sign language use, aside from individual difficulties due to low muscle tone and fine motor skill impairment, was that if other individuals did not understand sign language, then patients with SSADHD would continue to have communication difficulties. One caregiver shared that their child thrived in their school environment because it was a specialized school for the deaf where the staff and students were able to understand and use sign language. However, as their child grew older, this support was not as consistent and had an impact on the academic progress of her child with SSADHD.

Moreover, although use of electronic devices was extremely useful for communication, the coordination of using these devices during specific activities proved to be challenging, according to one caregiver:

> ***"It's really hard to take a speech device to play soccer, which he likes to play, or to do taekwondo and play on the playground."***

Another caregiver discussed the fragility of the electronic devices as a significant limitation:

> ***"[My child's] communication on the iPad is so fragile. At the end this school year, they were updating his iPad and the school erased the entire iPad memory since kindergarten. So, I equate it to somebody that's had a brain injury and lost all their language. [My child has] lost discussions that he had with his grandparents—funny little phrases, all of these things. His grandparents have passed, so we're never going to be able to rebuild that part of it, and it was a huge loss to our family."***

In addition to assistive devices and sign language, our preliminary caregiver survey found that 34% of individuals with SSADHD were using various dietary supplements to address specific symptoms in SSADHD. Nearly a third of these responded reported that their child was taking up to 3 dietary supplements a day. These supplements included a general multivitamin supplement, taurine, B-vitamins, vitamin D, fish oil, coenzyme Q10, vitamin C, and magnesium. Although dietary supplements were not discussed at length during the meeting, one caregiver stated that they did use magnesium flakes in their child's bath to promote relaxation and restfulness before bedtime.

CONCLUSIONS

Currently, there is no cure for SSADHD, and treatments are exclusively symptomatic (reviewed in Didiasova, 2020). Pharmacologic treatment is generally aimed at ameliorating symptoms of the disease, primarily seizures and psychiatric sequelae. Currently employed symptomatic interventions primarily target seizures, behavioral symptoms (ADHD, OCD, anxiety), and sleep disturbances, but individuals with SSADHD are also taking numerous dietary supplements the efficacy of which in treating disease-related symptoms remains unconfirmed. The antiepileptic vigabatrin is sometimes used, but it is a last-recourse drug for refractory seizures because of a significant risk for ocular toxicity. The use of valproic acid, another antiepileptic drug, is also limited because of the potential for inhibition of residual SSADH activity. There is a significant need for more effective treatments for SSADHD to address the symptom impacts and improve the quality of life for individuals with SSADHD.

TREATMENTS AND CLINICAL TRIAL CONSIDERATIONS FOR SSADHD

PREVIOUS THERAPY RESEARCH

A number of investigational targeted therapeutics have been considered in SSADHD. Pre-clinical studies with NCS-382, bumetanide, ganaxolone, farnesol, and torin-2 were conducted, but the clinical potential of these compounds remains unconfirmed. An open label study of taurine was conducted, but the results were inconclusive. A phase II placebo controlled double-blind crossover study was conducted using SGS-742, a GABAb receptor antagonist (R01 NS082286). Nineteen patients enrolled in the SGS-742 trial and sixteen completed the study. The trial did not reach statistical significance on the primary endpoint of neuropsychological improvement. (Schreiber, 2021; NCT02019667).

CURRENT THERAPY RESEARCH

Enzyme replacement therapy (ERT) is currently in preclinical development with Green Cross BioPharma. Gibson and colleagues (Vogel, 2018) treated KO mice with recombinant SSADH and showed significant improvement in survival and decrease in brain GHB levels. They are promising findings, although ERT would only correct circulating enzyme levels, the patient group is looking forward to ERT demonstrating its potential in controlled clinical trials.

Successful adenoviral (AV)-mediated gene therapy was reported in the KO mouse model with increased survival rates. It is important to note here that correction of the gene defect in the liver led to drastic decrease of brain GHB (Gupta, 2004), AV-mediated therapy is in preclinical development with Galibra. Adeno-associated viruses (AAV; Lee, 2020) or lentiviral vectors appear to be better suited for gene therapy. However, such vectors await preclinical confirmation of their potential to successfully deliver the *ALDH5A1* gene and rescue the SSADHD phenotype.

This also suggests that *ALDH5A1*-mRNA therapy, the subject of ongoing preclinical investigations, with delivery vehicles such as lipid nanoparticles that predominantly target the liver may provide significant metabolic improvement in the brain as well.

A natural history study began in 2019 and is currently ongoing. The study is designed to address the knowledge gaps and give SSADHD its warranted place on the Recommended Uniform Newborn Screening Panel. These gaps include a comprehensive description of the natural course of the disease, the availability of an objective measure of clinical severity score that can be used to monitor disease progression or therapeutic efficacy, and an understanding of the prognostic value of neurophysiological and biochemical markers of the disease. The specific aims include: 1) to determine the natural course of the clinical presentation of SSADHD; 2) to determine the natural course of neurophysiological and biochemical indices known to be altered in SSADHD; 3) to identify neurophysiological and biochemical predictors of clinical severity. The study will provide the clinical, biochemical and molecular information needed to better predict the natural course of the disease including fulminating, early onset presentation and sudden unexpected death caused by epilepsy, and better monitor the success of future therapeutic trials. There are currently 61 patients and 42 healthy controls patients enrolled in the study.

PATIENT PERSPECTIVES ON CLINICAL TRIAL PARTICIPATION

In our preliminary caregiver survey, we found that 59% of survey respondents (38 caregivers) reported that their child with SSADHD had participated in at least one clinical trial for SSADHD. Of those 38 respondents, the majority of them (83%) indicated that their child was enrolled in the ongoing Natural History Study for SSADHD. Other studies that patients had participated in were the SGS-742 clinical trial, the PET Imaging of GABA Receptors Study, the Taurine clinical trial, and the Brain Excitability Study. Although most had reported participation in one of these studies, a small percentage of respondents (6%) indicated that their child had participated in 2 of these. These results as well as the discussions in our focus groups emphasized the value that the SSADHD community puts in clinical trial participation, as shared by one caregiver during the meeting:

> ***"We got introduced to this SGS-742 trial, and it was a lot of hope for us. We were interested in what that was going to bring, what it would mean for [our child], and for all the other patients that are affected by SSADH deficiency."***

Watch the Clinical Trial Panel

However, specific experiences with the clinical trials process left considerable impacts on patients and caregivers, which has shaped needs for future clinical trial participation. In our preliminary caregiver survey, respondents reported (in order of importance) that study goals, serious risks, interactions with the clinical research team, types of assessments during the study, amount of travel required, route of treatment administration, and timing of scheduled clinic visits were the most important aspects in considering enrollment in a clinical trial for SSADHD. During the meeting, caregiver and patients' interactions/communication with clinical staff, as well as logistical arrangements for clinical trial participation were all factors that determined the success of the clinical trial experience for patients with SSADHD and their families.

INTERACTIONS WITH RESEARCH TEAM AND STAFF

Caregiver and patient interactions with the research team set the tone for overall experience in the clinical trials. Caregivers valued empathy, responsiveness, and clarity and frequency in their communications with the clinical research team and staff. In both the meeting discussion and the focus groups, caregivers demonstrated the differences between positive and negative interactions with the clinical team by discussion of their experiences with the current Natural History Study (positive) and the other previous studies (negative).

With respect to empathy, one participant in our preliminary focus groups stated that the research team for the Natural History Study was more ***"patient-focused"*** whereas the research team for the previous studies were more ***"procedure-focused"***, referring to the previous research staff as being more focused on the administering the protocol of the study rather than take account of the patient experience during the study. Caregivers reported previous research team members referring to patients as ***"terrible"*** or berating their caregivers when patients were tired or exhibiting

behavioral symptoms of SSADHD. These interactions influence caregivers' willingness to continue participation in that study:

> ***"It was a tough situation [in the previous studies], and at that point, we'd already had so many other issues with them that we just decided that this wasn't going to be the right fit for us at the time."***

In contrast, multiple caregivers were extremely satisfied with the interactions with the clinical research team for the Natural History Study. Caregivers shared their experiences:

> ***"[The Natural History Study] is filled with people who care about you, care about your child, understand that your child is different."***

> ***"But [the Natural History Study team], I cannot say enough about—from the person that opened the door and let us in the facility to the doctors, the nurses, everybody; they were amazing, and it was all such a great experience for us."***

Moreover, these positive experiences also influenced caregivers' willingness to continue participation in this study:

> ***"I feel like the doctors at [the Natural History Study] are in it with us, and they're saying, 'yeah, me too,' even though they don't have children with SSADH. The way that they treated us, I felt like they were in it with me. So, I just wanted to say how much I appreciate that, and that it's a big reason why we continue to do the study, go every other year to [the study], and do the poop samples at home, which is not fun."***

Caregivers expressed that they needed clear information about the details of the clinical trial; this was a requirement before they would continue participation. To that end, one caregiver reported that they were ***"misinformed"*** about study purpose from the clinical research team in the previous studies and another caregiver stated that their interactions with the previous research team were ***"ambiguous"*** with respect to study purpose and impact:

> ***"I think the other aspect of the trial that was challenging was the ambiguity around what the expectations were. If you read the protocol study, which was three or four pages long, there were things in there that mentioned the benefits to the patient, including performance, memory, language skills and different things like that, but then during the trial, we talked to different providers and clinicians, and they made it sound more like it was just a safety study."***

Related, one caregiver in the focus group felt that they needed feedback on how the trial was going during participation, stating that in previous clinical trials, they found themselves wondering ***"why are we still doing this?".*** Individual patient reports and if a patient was on placebo or drug were never reported back to the families, even after several inquiries with the previous research staff.

Specifically, caregivers in the focus groups and in the meeting, discussion reported that they need information on the specific aims of the clinical trial, details about the study design and procedures, expected outcomes, safety profile of the therapeutic, side effects and risks, any contraindications to current treatment regimens, and most importantly, protocol considerations to ensure safety of patients throughout the clinical trial.

LOGISTICS AND SCHEDULING

Caregivers discuss some of the challenges with the arrangement of clinical trial participation. Distance to the clinical trial site was an important factor for caregivers, especially those that resided in countries outside of the United States. The level of disability and severity of symptoms in the individual with SSADHD often determined how far they could travel for clinical trial participation. Additionally, missing school (as well as work for caregivers) was also an important factor in determining participation.

Once enrolled in a clinical trial, caregivers reflected on the ease of participation, which affected the willingness to continue participation. Caregivers discussed their experience at a previous clinical trial:

"The organizational side of going to the [previous trial] was a giant nightmare. There were times we had the flight booked from the wrong airport—even the wrong state's airport, nowhere close to where we lived. We would get there, and we didn't know the schedule or where we were supposed to be."

"As a family, it was our first experience of clinical trials, and it was really shambolic. We got to find out about corners of the hospital that looked like no one had ever visited because they were sending us to the wrong area of the hospital at the wrong time."

"I remember carrying home the box of medications the first time. We were all sitting there looking at the calendar and thinking about how we're going to get all these delivered and jotting down notes. As we went through it, the challenges with getting it scheduled, receiving everything, and getting the return visits set up were difficult, especially with everything else going on."

In one case, a caregiver during the preliminary focus group mentioned that scheduling of appointments during the previous clinical trial did not take into account their child's fatigue and need for down time, which subsequently made clinical procedures and data collection extremely difficult.

This was not the case in the current Natural History Study, where caregivers were generally pleased with the logistical experiences:

"[The Natural History Study] is filled with people who care about you, care about your child, understand that your child is different, and [the clinical coordinator] is so organized that there is no wasted time. You go from one test to the next test, and it just runs so smoothly."

MODE OF TREATMENT ADMINISTRATION FOR CLINICAL TRIALS

Although not discussed at length during the meeting, the mode of therapeutic delivery during the clinical trial was an important topic during our preliminary caregiver focus groups. When participants were asked about what mode of administration would be acceptable for treatment of individuals with SSADHD in a clinical trial, two participants stated that their family member with SSADHD has only taken pills or tablets as medication, one stated that their family member with SSADHD will only be able to receive medication in liquid form due to their gastrostomy tube. Related, one participant stated that a pill, even crushed up, would not be an effective mode of administration, and that a liquid administration would be preferable if treatment needed to be consumed through the gastrostomy tube. Another participant mentioned that their child with SSADHD would not be open to medication that involved an injection but would be comfortable with a nasal spray administration for medication. Aversion to needles and shots was a common theme in our interviews when patients were asked about experiences in a clinical setting.

Some participants mentioned that willingness to participate in clinical trials as well as being open to more invasive modes of treatment administration was dependent on the age of individual with SSADHD. Older individuals might be less likely to agree to a more invasive mode of treatment administration than younger patients.

There were concerns that were shared about the reversibility of the treatment, particularly in the case of an adverse event, especially with a gene therapy.

Another participant felt that they would need to engage their child with SSADHD in the decision-making process before committing to a clinical trial and a specific treatment mode.

One participant suggested that older individuals with SSADHD may already be accustomed to their condition so they would weigh the benefits from a new treatment more heavily with possible risks.

Even with the concerns, many participants expressed that their family would be willing to go to ***"great lengths "*** and that ***"nothing was off the table"*** with respect to treatment if there was a good chance of improvement in health and abilities.

CLINICAL TRIAL OUTCOME MEASURES IN SSADHD

When caregivers of individuals with SSADHD were asked if they had the opportunity to enroll their child in a clinical trial to study a new treatment for SSADHD in our preliminary caregiver survey, 47% of survey respondents said yes. When they were ask to rate how willing they would be (on a scale of 1 to 10, 1= not willing at all, 10 = very willing) to enroll their child in a clinical trial evaluating specific symptoms, results showed an average score of 8.5 out of 10 for a new treatment addressing cognition, 7.4 out of 10 for a new treatment addressing behavioral/psychological symptoms, 7.0 out of 10 for a new treatment addressing seizures, and 6.3 out of 10 for a new treatment addressing other symptoms, including speech, sleep disturbances, and physical symptoms. This is with the understanding that all patients don't experience all of the symptoms.

SPEECH/COMMUNICATION

Caregivers were asked to rate how important it was to improve speech and communication in daily life for individuals with SSADHD. On a scale of 1 to 10 (1 being not important, 10 being very important), survey respondents rated this with an average score of 8.4 out of 10, the highest scores of all the symptoms of SSADHD that caregivers were asked to rate for this question. When caregivers were asked for indications of improvement during our preliminary focus groups, improved enunciation, improved pacing in speech (including taking less time to find appropriate words AND also slowing actual speech down), finishing words, and better overall articulation were identified as appropriate measurable outcomes related to speech and communication. More broadly, some caregivers during the focus group suggested that more ***"meaningful verbal communication"*** with others was a desirable outcome related to both speech and intellectual disabilities.

INTELLECTUAL DISABILITY

Considering the lack of treatment options specifically targeting intellectual disability (in SSADHD), it was challenging for caregivers to identify specific outcomes to measure overall improvement in intellectual ability. Our preliminary focus groups found that caregivers did not believe that IQ testing or related standardized testing were suitable metrics for intellectual disability, primarily due to other symptoms confounding the results. As reduced overall independent behavior seemed to be the major impact of intellectual disability in SSADHD, many caregivers in our preliminary focus groups alluded to signs of ***"increased independence"*** or ***"being able to do things [by themselves]"*** as initial indicators of improved intellectual ability. One caregiver in our preliminary focus groups, owing to the perceived frustration that they sensed from their child due to their intellectual disability, reported that if their child showed ***"less bursts of anger,"*** that would be an indication of improvement in intellectual ability.

In our preliminary survey, caregivers were asked to rate how important it was to improve decision making and focus (as related to intellectual disability) in daily life for individuals with SSADHD. On a scale of 1 to 10 (1 being not important, 10 being very important), survey respondents rated this with an average score of 7.8 out of 10, one of the highest scores of all the symptoms of SSADHD that caregivers were asked to rate. When caregivers were asked for indications of improvement in these outcomes during our preliminary focus groups, they shared that less time to make decisions, less requiring of other people's input to make decisions, less redirection required from caregivers or teachers and less time to bring a task to completion would be strong indicators of improvement of intellectual ability. Specific tasks were dependent on age, but caregivers referred to completing a movie, building a Lego set or coloring a picture.

Caregivers were asked to rate the importance of improving school performance, grades, and work performance in our preliminary survey. Respondents rated the importance of improving these outcomes with an average score of 7.5 out of 10. With respect to school-based skills, caregivers participating in the preliminary focus groups suggested that outcomes such as improved reading comprehension, reading level and reading words per minute, and other school-based metrics and assessments for math would be good indications of improvement in their family member with SSADHD, as well as improved ability to work with money.

BEHAVIORAL/PSYCHOLOGICAL SYMPTOMS

When caregivers were asked to rate how important it was to improve behavioral/psychological symptoms in daily life for individuals with SSADHD, survey respondents rated this with an average score of 7.3 out of 10. In terms of specific outcomes with respect to behavioral and psychological symptoms, one caregiver during our preliminary focus groups

stated that ***"less ticks"*** such as ***"less touching of random things"*** associated with OCD symptoms would be a good indicator for improvement. Given that many OCD rituals often preclude or delay everyday tasks, an increase in bringing tasks to completion was also suggested as an indirect indicator of improvement according to a caregiver.

For the inattentiveness and lack of focus, similar to outcomes related to intellectual disability, quicker decision-making and better executive functioning would indicate improvement in SSADHD. This may also be an indicator of improvement with respect to anxiety, as quicker decision-making and executive functioning would imply a reduced need for constant validation and reassurance. Although not explicitly shared during the discussion, there was an implication that less ***'freezing'*** episodes in times of anxiety may also be a good indicator of improvement.

For oppositional and defiant behaviors, caregivers shared that less angry facial expressions and less bursts of anger may be indicative of improvement. Although not explicitly stated, conversations surrounding oppositional and defiant behaviors suggested that being more agreeable to complete tasks would also be an indicator of improvement in SSADHD.

SLEEP DISTURBANCES

In our preliminary survey, when caregivers were asked to rate how important it was to improve specific sleep disturbances in SSADHD, results showed an average rating score of 6.9 out of 10. For insomnia and restlessness, caregivers during our preliminary focus groups reported that the increased desire to sleep and sleeping more soundly through the night (less waking and movement when sleeping) would be indicators of improvement in their child with SSADHD. For sleep attacks and chronic daytime fatigue, one caregiver in our preliminary focus group mentioned that less instances of falling asleep suddenly, and less reliance on daytime naps would be an indicator of improvement in their child with SSADHD.

SEIZURE DISORDER

In our preliminary survey, caregivers were asked to rate how important it was to decrease seizure activity in individuals with SSADHD. On a scale of 1 to 10 (1 being not important, 10 being very important), survey respondents rated this with an average score of 6.5 out of 10. In our preliminary focus group with caregivers of individuals with SSADHD that presented with seizures, participants indicated that a reduction in seizure activity or a diminished mood and behavior changes following seizures would be a meaningful change following treatment. However, this would only be meaningful if the change were not accompanied with negative side effects, such as mood changes or a reduction in respiration.

PHYSICAL SYMPTOMS

In our preliminary survey, caregivers were asked to rate how important it was to improve specific physical impacts of SSADHD, such as head and neck control, walking, feeding, dressing, writing and cutting with scissors. Of these activities, caregivers rated writing and cutting with scissors as the most important (average rating score of 7.8 out of 10) in terms of what needed improvement in individuals with SSADHD. This was followed by dressing (6.2 out of 10) and feeding (5.2 out of 10). Walking as well as head and neck control were rated as the least important of these symptoms, likely due to the fact that most individuals with SSADHD had adequate head and neck control and could walk to some degree. When caregivers were asked to rate their willingness to enroll their child with SSADHD in a clinical trial evaluating the safety and efficacy of a new treatment (on a scale of 1 to 10), respondents rated their willingness to consider clinical trial enrollment at an average score of 6.3 out of 10 for treatment of multiple symptoms, including physical limitations and symptoms of movement disorders, such as choreoathetosis, dystonia, and exertional dyskinesia.

Our preliminary focus groups with caregivers revealed several indicators for improvement with respect to physical symptoms of SSADHD. For gross motor skills, caregivers shared that less falling and injuries would be indicators for improvement. One caregiver specifically mentioned ***"not stubbing toes or running into doors"*** would suggest improvement. Additionally, less sedentary behavior would also be indicative of improvement of gross motor skills. For younger individuals with SSADHD or those more severely affected, one caregiver suggested that earlier achievement of physical development milestones, such as head and neck control and sitting up may be appropriate outcomes.

For fine motor skills, caregivers mentioned improved use of scissors, cutting food, increased grip strength and effort in reaching for objects, handwriting, being able to close buttons and tie shoes, putting on clothes correctly, and typing as suitable outcomes for improvement.

For individuals with SSADHD that experience movement disorders, caregivers shared that less spasms or ***"explosion"*** movements would be a sign of improvement in SSADHD.

CONCLUSIONS

The various symptoms of SSADHD manifest in a multitude of ways, and can affect patients from infancy into adulthood. These symptom categories discussed at length in this report, including speech and communication difficulties, intellectual disability, behavioral/psychological symptoms, seizure disorders, sleep disturbances and physical/mobility symptoms are by no means comprehensive and likely only represent a small portion of the individual manifestations of SSADHD. Nevertheless, the impacts of the symptoms described in this report are broad with respect to day-to-day living for individuals with SSADHD, with the primary impacts of SSADHD being on independent function, social interactions, academic and work performance, safety, and emotional wellbeing. Moreover, each of the symptom categories impact these aspects of daily life in different ways. For example, seizures and mobility issues affect the physical requirements of various independent activities, while intellectual disability affects the executive functioning and decision-making ability to carry out these independent activities. As a result, these symptoms together amass a cumulative impact on daily life in individuals with SSADHD, considerably more than any effect these symptoms would have alone. Taken together, the symptoms and lived experiences of individuals with SSADHD are both far-reaching and formidable, resulting in a tremendous impact on overall quality of life.

Currently, there are no treatments specific for SSADHD, and existing treatment plans address only individual symptoms. Some treatment options will address multiple symptom categories, such as some behavioral symptoms and certain symptoms of sleep disturbances. However, most available current treatments are at best, inconsistently effective, and have many side effects. Treatment of individual symptoms in SSADHD also often requires administration of multiple medications, even within symptom categories. In some cases, treatment of one symptom category may exacerbate the symptoms of another category. There is an urgent need for more effective, safer, and less burdensome treatment plans and management of SSADHD symptoms.

New therapies for SSADHD are an active area of scientific research. Given the multi-system, multi-symptom nature of SSADHD, a thorough evaluation of clinical trial design will be required to ensure that new therapeutics are achieving meaningful outcomes in patients with SSADHD. Although both patients and caregivers have indicated some difficulty and inconvenience associated with specific forms of treatment administration, such as injections, nearly all families participating in the meeting and the preliminary focus groups indicated that all treatment modalities would be considered provided that the benefits of therapeutics on given outcomes would outweigh the risks.

With respect to specific patient outcomes in clinical trials, families shared specific details of what they would like to improve including improved executive functioning, increased completion of tasks related to activities of daily living, improved fine/gross motor activity, improved sleep patterns, reduced behavioral symptoms, and reduced seizure activity and uncontrolled physical movements.

Overall, families of individuals with SSADHD report that there are various symptom categories that need to be improved upon with future therapeutics, and have indicated willingness to participate in clinical trials if the treatments resulted in any of these identified outcomes. The feedback provided during this meeting and the preliminary focus groups, interviews, and survey has served as an important foundation to develop meaningful outcomes to measure in clinical trials for SSADHD.

SAMPLE BENEFIT-RISK ANALYSIS FRAMEWORK FOR PATIENTS WITH SSADHD

Dimension	Evidence and Uncertainties	Conclusions and Reasons

Analysis of Condition	Patients are mostly or completely dependent on their caregivers for their daily life functions. Patients continuously deal with very difficult symptoms in their daily lives including:
	• Speech and Communication Impairment
	  • Apraxia
	  • Dysarthria
	  • Delayed language development
	• Intellectual disability
	• Behavioral and Psychological Symptoms
	  • ADHD
	  • OCD
	  • ODD
	  • Anxiety
	  • Depression
	• Sleep Disturbances
	  • Restlessness and insomnia
	  • Sleep attacks and fatigue
	• Seizures
	  • Myoclonic
	  • Tonic-clonic
	  • Atonic (drop)
	  • Absence
	• Physical Symptoms and Mobility Issues
	  • Infantile hypotonia
	  • Delay of gross motor skills
	  • Difficulty with fine motor coordination
	  • Movement disorders
		• SSADHD is an inherited disorder of GABA metabolism with significant complexities and highly unmet needs:
		• No newborn screening
		• Clinical heterogeneous symptom presentation across the population
		• Long diagnostic odyssey for many patients
		• Diagnosis based on clinical presentation is challenging considering variability of symptoms
		• Diagnostic methods are often cost-prohibitive
		• SSADHD often not included in appropriate genetic screening panels
		• Misdiagnosis is common, and often leads to ineffective or potentially harmful treatments
		• Likely many undiagnosed patients, which affects access to treatment and resources.
		• Treatments are based exclusively on symptoms that can vary in individuals
		• Current available treatments are not consistently effective
		• Current available treatments for specific symptom categories only are effective against a subset of symptoms
		• Current available treatments have multiple side effects that may exacerbate other symptoms or reduce the effectiveness of other treatments
		• Current rehabilitative therapies are time-consuming and expensive
		• Resources for speech can be effective, but limited in scope

	Impacts on education:
	• Writing difficulties
	• Decreased memory retention
	• Decreased overall focus
	• Chronic fatigue
	• Lack of appropriate accommodations
	• Frequent absences
	Impacts on daily living:
	• Independent activity
	  • Hygiene
	  • Feeding
	  • Dressing
	• Executive functioning
		• The diverse symptoms of SSADHD have global impacts on daily function, independent activity, which affect overall quality of life
		• SSADHD also bears a significant caregiver impact, which can affect care for the patient

	Impacts on social, emotional, or economic status:
	• Difficulty maintaining employment
	• Difficulty making friends and maintaining relationships
	• Feelings of fear, frustration, sadness
	• Impacts on caregiver and family
	  • Financial
	  • Recreation
	  • Need for relocation
	  • Emotional	

Current Diagnosis/Treatment Options	**Current state of diagnosis** • Biochemical analysis urine/blood GHB levels • Genetic analysis of ALDH5A1 pathogenic variants • Based on appearance of symptoms • Variable times to diagnosis • Infant to post-mortem	**Needs for diagnosis** • National newborn screening for SSADHD • Inclusion of SSADHD in more genetic screening panels related to symptoms • Wider availability of exome and whole genome sequencing • Greater understanding of *ALDH5A1* VUS

	Current state of disease management
	• No treatment specific for SSADHD
	• Mainly symptomatic treatment
	• Some adverse side effects
	• Pharmacological treatments
	  • Antiepileptic/anticonvulsant drugs
	  • Rescue medications for seizures
	  • Psychotropic drugs
	  • Sleep aids
	  • Stimulant drugs
	  • Dietary supplements
	• Rehabilitative therapies
	  • Speech
	  • Feeding
	  • Occupational
	  • Physical
	  • ABA
	  • Equine
	  • Music
	• Assistive resources
	  • Sign language
	  • Speech assistive devices
	  • Orthotics/braces
	  • Gait trainers
	  • Wheelchairs
		Treatment Criteria
		New treatments should refrain from using IQ and standardized testing as outcome measures and should focus on these unmet needs:
		• Increased enunciation
		• Improvements in speech pacing
		• Improvements in word and sentence formation
		• Increased ability to understand communications and be understood
		• Increased executive functioning
		• Improved reading and math skills
		• Decreased outbursts and related behavioral symptoms
		• Decreased OCD symptoms
		• Increased time of sleeping through the night
		• Decreased sleep attacks and fatigue during the day
		• Decreased seizure activity
		• Decreased mood swings and changes
		• Increased mobility
		• Decreased falls and injuries due to falling
		• Increased independent activities of daily living
		  • Feeding
		  • Dressing
		  • Personal hygiene
		New treatments should have minimal side effects and be covered by insurance to avoid financial barriers to access.

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