



National Tay-Sachs & Allied Diseases Association (NTSAD)

Late Onset GM2 Gangliosidosis
(Tay-Sachs and Sandhoff)
Patient-Led Listening Session

January 15, 2021



Objective of Session

To provide an understanding of Late Onset GM2 Gangliosidosis (Tay-Sachs and Sandhoff), burden and symptom progression, heterogeneity of Late Onset GM2, and potential issues related to drug development.

Sue Kahn, Executive Director, NTSAD

Ms. Kahn opened the session with an introduction to NTSAD, the family community and how NTSAD support adults affected by Late Onset Tay-Sachs and Late Onset Sandhoff diseases (LOTSS).

Dr. Cynthia Tifft, Deputy Clinical Director, NHGRI (NIH)

Dr. Tifft provided a clinical description of LOTSS, including the biological pathway and the heterogeneity of both the symptomatic onset and progression of Late Onset Tay-Sachs and Sandhoff diseases, in comparison to the infantile and juvenile onset forms of these diseases. Dr. Tifft narrated two videos of an individual with LOTSS demonstrating how the disease deteriorates the anti-gravity muscles, i.e. the triceps and the quadriceps. It does not affect the biceps and hamstrings. She explained that LOTSS patients have normal IQ's, but there can be challenges when it comes to executive functioning. Speech is pressured, and there is dysarthria. The progression of the disease impacts the brain, specifically the cerebellum. Uneven surfaces are very difficult for LOTSS individuals to navigate.

She stressed the key challenge with LOTSS, in addition to it being rare diseases, is that the age of onset is variable as are the progression and symptomatic presentations. There are several advantages. There are natural history studies that show impact on gait, balance, and fine motor skills. There are animal models, i.e. mouse, cat, and sheep. There are biomarkers. There is an established LOTSS Think Tank with 20 investigators actively involved. There are patients who are incredibly motivated to find treatments and cures.

Members from the NTSAD Late Onset community, ranging in ages from 32 to 55, agreed to share their perspectives and experiences living with their diagnosis of Late Onset Tay-Sachs and Late Onset Sandhoff diseases.

Early Onset of Symptoms Before Diagnosis

All five patients who spoke about their symptoms could look back at points in time during their childhood and identify symptoms that caused them distress. From unexplainable symptoms, to being clumsy, to struggling with their speech, they expressed frustration with these confounding symptoms that interfered with their childhood, college experiences, and life plans.

- "I always wanted to be in the military and later become a police officer just like my father. I knew I would never attain that goal. Because of my symptoms, I would never pass basic training or the police academy."
- "[My daughter] is a Wellesley graduate and also has an MBA from Santa Clara University. She speaks three languages. However, she cannot work now and is on disability."
- "I used to play soccer and other sports. I had a tremor in my hands that appeared around 17-18 years of age. The neurologist prescribed medicine for the tremor. While I was in college, stairs became a problem. It took all of my energy to get up a flight of stairs, and the same was true for my twin sister."
- "I was always active, physical, and fast! Played all sports! I always had a speech impediment due to tongue movement. I had speech [therapy] through high school and nothing helped. In college, I became weaker and thought I was drinking too much, and partying too hard in my fraternity....and then I started falling down and not knowing why."

Journey to Diagnosis

Another common theme was the considerable length of time (ranging from 8 to 30 years) it took them to receive a confirmed diagnosis.

- "I'm 55 years old. I was diagnosed in 2014 [nearly 30 years since my diagnostic journey began] at the age 48 along with my sister, who is 10 years older."
- "I was seen by all the best people and places in New York. Two to three different neurologists and geneticists. My family and I all underwent blood test/genetic screening at the Mayo Clinic. As my family is not Jewish, the professionals (mistakenly) ruled out Tay-Sachs. They tested for the HEX A enzyme and found that both my twin sister and I had Late Onset Tay-Sachs. It took 8-10 years to get a diagnosis!"
- "[My daughter] was diagnosed correctly at 26, after about 15 years of being misdiagnosed. The initial diagnosis was anxiety disorder. Her speech impediment was blamed on me, because I was an immigrant mother, who was pushing her daughter too hard. The next, wrong diagnosis at 23 years was sporadic ataxia."

- “As my symptoms worsened, I sought out psychological testing and saw several neurologists. The first neurologist’s diagnosis was MS or Parkinson’s. She had no idea what was causing my physical imbalance and stiff legs. A neurosurgeon told me that I had an inoperable cyst on my cerebellum, but that it definitely wasn’t MS or Parkinson’s. I was finally referred to a geneticist at UCLA for testing and was diagnosed with Late Onset Tay-Sachs (LOTS). The LOTS diagnosis was shocking and devastating to us all.”

Range of Symptoms and Progression

The range of experiences, however, show the heterogeneity of LOTSS as was shown in Dr. Tiff’s presentation. While many can look back and identify points in time during their childhood where they may have struggled with speech, mobility, or even psychiatric struggles, the rate of progression varies from patient to patient.

- “Mentally, I have a hard time concentrating and making decisions, forgetfulness, and trouble finding the right words when speaking. I am also very grumpy at times. I don’t sleep well due to a R.E.M sleep disorder, which makes me kick and flail randomly throughout the night. I’ve even knocked my c-pap off the nightstand, punched the headboard, and unfortunately, even hit my wife.”
- “My LOTS symptoms impacted my life most significantly in the last decade. My physical symptoms included very stiff and weak legs, poor balance, which caused many falls, several broken bones, and a couple of surgeries. I couldn’t get up from a chair without arms for support and walking up and down stairs was nearly impossible. My mental health was all over the map. Sleeping was difficult, especially without a diagnosis and the correct cocktail of medications. Working with my clients became impossible, which increased my fear. I was living on my own at that time, but the stairs in my apartment building and working with clients in the field caused me to experience many falls. My parents and I decided that moving home would be in my best interest and enable me to focus on my health and getting a diagnosis. Moving home again was upsetting and increased my depression.”
- “[I] left New York to move closer to [my] parents four years ago. [The city] was too hard to navigate. I had to change my career due to the disease and symptoms. I had to move in with my parents because I’m afraid of falling and being alone (and unable to get up by myself.) I don’t like losing my independence and being unable to drive.”

Caregiver Perspectives

Two caregivers – one a spouse and one a mother – shared their concerns and fears for their loved ones as watch their loved ones' diseases progress.

- “As the wife of someone with a rare disease, I feel that [we] have to tell everyone about Tay-Sachs (and the difference between Infantile and Late Onset) because there isn't that much information out there. I have to explain to the hostess why a taller chair (like a barstool) is better than a booth. I notice things like if the ground is uneven, if there's a curb, where the handicap ramp is, are there any stairs? Is there a handrail in the bathroom? Sometimes I become [his] interpreter because sometimes people don't understand his speech. I worry for his future; he is preparing himself for a future in a wheelchair. I worry that more falls will happen and more surgeries.”
- “I am afraid to leave her at home alone. If she falls, she needs help to get up as she cannot do it by herself. I usually stay at home or have to hire help. What I worry about is not being able to take care of her if something were to happen to me. She has no other family, and she may end up in a nursing home.”

A Motivated Community

As Dr. Tiffit and one caregiver said – the Late Onset community is exceptionally motivated to participate in any study if the outcome would alleviate any one of their symptoms, and there would be an impact on future patients.

- “A treatment would mean the world to me, especially if it slowed down the progression of LOTS and its symptoms: mobility, balance, speech issues, memory, mental health challenges, bone health, muscle strength, and other bodily functions. I pray for a treatment that can halt, or even reverse the symptoms of LOTS, sooner rather than later, whether it's a medication, gene-replacement, or other treatment I can't begin to fathom.”
- “When we think about new drugs, we are not dreaming that she will be able to run or do mountain climbing. Our goals are for her to remain as independent as possible, be able to get out of bed by herself, to dress without help, go to the restroom herself, etc. If there is no treatment available soon, she will lose this independence completely. A year ago, she was stronger, could walk a little longer and a little faster, did not choke as often when she was eating.”
- “Participating in a drug trial helps future generations from not going through the same ordeal and potentially help me and my friends. I love my wife, and I want to do what I can for future generations. I had a good friend who had Late Onset Tay-Sachs die in his fifties. I don't want to die at fifty.”

- “My daughter and other LOTSS patients do not have time to lose. They need to be able to try different experimental drugs or combinations of drugs that have at least some chance to help them as soon as possible. We badly need your help to develop a more flexible and innovative approach to get drugs to our patients faster. We are willing to do whatever is necessary to make it happen. Thank you again from all of us.”

A Meaningful Impact

In response to a question, the patients shared what would be meaningful and impactful when it comes to a potential therapy:

- One patient said [it would] help with his speech. His spouse is more concerned about his falling and stability.
- One wants to get [up] and out of a chair. Swallow easily. Not choke.
- For another patient his tremors are so bad he has trouble eating.
- Another wants better mobility, and less memory lapses so he can do his job as a mental health clinician and have better concentration. He struggles to find words.

A question was asked of the patients—what concerns does the LOTSS community have regarding clinical trials?

- “I would do anything and fight anything to help science.”
- “We would eliminate the placebo control group. It is mentally, ethically difficult. Two years is a long time to not be receiving treatment, and the symptoms are all so different.”

In closing, Sue Kahn thanked Patient Affairs and all those attending from the FDA. She shared that this Listening Session for Late Onset Tay-Sachs and Sandhoff diseases was dedicated to a good friend and Late Onset Tay-Sachs patient, Scott Hunger, who died at 50 years of age from complications related to Late Onset Tay-Sachs.

Footnote

Since the NTSAD’s Listening Session with the FDA on January 15, 2021, one of the adults affected by Late Onset Tay-Sachs who spoke to the FDA fell in his home, breaking his hip and pelvis in two places. Unfortunately, this fall may have several repercussions – 1) it could set back his baseline of walking with assistance; 2) it may impact his ability to participate in an ongoing clinical trial; and 3) due to COVID, he cannot be in a rehabilitation center where he would get more intensive therapy to regain his strength.

Participants and Organizers

NTSAD consulted with Board members, Gerald Cox, MD, Jonathan Katz, and Jamie Ring to create the agenda. Diana Pangonis, NTSAD's Director of Family Services, identified and invited the patients who spoke during this FDA Listening Session. Bill Berry of Berry PR worked with patients prepare and share their remarks.

FDA Centers and Offices that attended Listening Session

Office of the Commissioner (OC) – 5 offices

- Office of Patient Affairs (organizer)
- Office of Clinical Policy & Programs
- Office of Combination Products
- Office of Orphan Products Development
- Oncology Center of Excellence

Center for Biologics Evaluation & Research (CBER) – 1 office

- Office of the Director

Center for Devices and Radiological Health (CDRH) – 2 offices/divisions

- Office of Strategic Partnerships and Technology Innovation/ Division of All Hazards Response, Science and Strategic Partnerships
- Office of Product Evaluation & Quality/Office of Health Technology I

Center for Drug Evaluation and Research (CDER) – 10 offices/divisions

- Office of the Center Director/Patient Focused Drug Development Staff
- Office of New Drugs/Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine/ Division of Rare Diseases and Medical Genetics (DRDMG)
- Office of New Drugs/Office of Neurology/Division of Neurology I
- Office of New Drugs/Office of Neurology/Division of Neurology II
- Office of New Drugs/Office of Immunology and Inflammation/Division of Dermatology and Dentistry
- Office of New Drugs, Office of Drug Evaluation Sciences, Division of Clinical Outcome Assessment

- Division of Translational & Precision Medicine
- Office of Translational Sciences/Office of Biostatistics/ Division of Biometrics I
- Office of Translational Sciences/Office of Biostatistics/ Division of Biometrics III
- Office of Translational Sciences/Office of Biostatistics/ Division of Biometrics IV

Non-FDA

- Reagan-Udall Foundation for the FDA

Patients represented

Four adults diagnosed with Late Onset Tay-Sachs disease

One adult diagnosed with Late Onset Sandhoff disease

One spouse of an adult diagnosed with Late Onset Tay-Sachs disease

One parent of an adult diagnosed with Late Onset Tay-Sachs disease

Disclaimer

Discussions in FDA Rare Disease Listening Sessions are informal. All opinions, recommendations, and proposals are unofficial and nonbinding on FDA and all other participants. This report reflects NTSAD's account of the perspectives of patients and caregivers who participated in the Rare Disease Listening Session with the FDA. To the extent possible, the terms used in this summary to describe specific manifestations of Late Onset GM2 Gangliosidosis, health effects and impacts, and treatment experiences, reflect those of the participants. This report is not meant to be representative of the views and experiences of the entire Late Onset GM2 Gangliosidosis patient population or any specific group of individuals or entities. There may be experiences that are not mentioned in this report