Resources for those Newly Diagnosed with ALSP, a mutation of the CSF1R gene.

Provided by:

Table of Contents

Your newly diagnosed guide offers resources, information, and guidance for living well with ALSP.

Newly Diagnosed

A diagnosis of ALSP is life changing and creates many questions. Knowing what to Expect and connecting with others living with the disease can lessen the fear of the unknown and will help you and your family prepare for the future. Understanding your diagnosis is an ongoing process, but there are steps you can take to move forward and live your best life for as long as possible.

Stay Connected

- ✓ Visit https://www.sistershopefoundation.org; created for those diagnosed with ALSP, their caregivers, family members, physicians and others interested in gaining knowledge and staying up to date on the newest information available for ALSP.

- ✓ Social Media;
  Facebook: @SistersHopeFoundationALSP
  Twitter: @SistersHopeALSP
  YouTube: Sisters Hope Foundation
  TikTok: TikTok.com/sistershopefoundation
  LinkedIn: https://linkedin.com/company/sisters-hope-foundation and
  https://www. linkedin.com/in/heidiLedwards
  Instagram: sistershopefoundationalsp
  Pinterest: Pinterest.com/SistersHopeFoundation

- ✓ Support Groups; Available virtually each month via Zoom or our online community available on Facebook @SistersHopeALSP, Family and Caregivers Support Group for HDLS/POLD and ALSP (https://www.facebook.com/groups/196377142318807)

- ✓ Contact Sisters' Hope Foundation to learn more about programs available for people living with ALSP. Email: info@sistershopefoundation.org

Who We Are?

Sisters' Hope Foundation is the first and only global organization supporting those affected by ALSP.

The mission of Sisters' Hope Foundation is to support and empower families impacted by Hereditary Diffuse Leukoencephalopathy with Spheroids (HDLS) also known as Adult-Onset Leukoencephalopathy with Axonal Spheroids and Pigmented Glia (ALSP) caused by a mutation on the CSF1R gene by:

- educating the public to increase awareness around this rare disease
- advocating for further research and funding to improve treatment options
- connecting patients and families with this diagnosis to build community and support
- providing financial assistance and resources to those in need

Through Sisters' Hope Foundation, we envision a world where those affected by HDLS/ALSP have support and knowledge, leading to a better quality of life and one day, the first survivor of HDLS/ALSP.

Introduction to ALSP

Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) is a rare, progressive neurological disease that causes brain tissue known as white matter to waste away (leukodystrophy), forming lesions in certain brain areas due to disease-causing variants in the CSF1R (colony-stimulating factor-1 receptor) gene. ALSP is one type of leukodystrophy disorder, estimated by some studies to account for 10 to 25% of adult-onset leukodystrophies. Lesions of this white matter lead to major changes in personality, thinking (cognition), and muscle function, eventually causing people with this disorder to develop dementia and later decline into a vegetative state. Aside from the presence of a specific gene variant, the brains of people with ALSP show characteristic microscopic changes and patterns of atrophy on brain imaging that distinguish ALSP patients from those with other neurological conditions. Symptoms of ALSP overlap with frontotemporal dementia and other disorders associated with dementia such as Alzheimer disease as well as other neurological disorders such as Parkinson's disease, multiple sclerosis, schizophrenia and several others, making diagnosis difficult unless genetic testing is done. Symptoms can vary considerably from one person with ALSP to the next (even in the same family). Currently, brain biopsy is not necessary for diagnosis because genetic testing is available.

ALSP was previously known as two separate disorders: hereditary diffuse leukoencephalopathy with spheroids (HDLS) and pigmentary orthochromatic leukodystrophy (POLD). Once both disorders were linked to CSF1R gene variants, they became known as ALSP.

Synonyms of Adult-Onset Leukoencephalopathy with Axonal Spheroids and Pigmented Glia

- ✓ hereditary diffuse leukoencephalopathy with spheroids (HDLS)
- ✓ leukoencephalopathy, diffuse hereditary, with spheroids
- ✓ adult-onset leukodystrophy with neuroaxonal spheroids
- ✓ autosomal dominant leukoencephalopathy with neuroaxonal spheroids
- ✓ neuroaxonal leukodystrophy
- ✓ pigmentary orthochromatic leukodystrophy (POLD)
- ✓ CSF1R-related leukoencephalopathy
- ✓ ALSP

I have ALSP – Patient Story (Serena, Carrier of CSF1R gene mutation)

Living my Best Life everyday – Hope from a Carrier

My story begins with my younger brother's diagnosis of HDLS/ALSP when he was 54. His most noticeable symptom was seizures. Family that lived nearby eventually took him to the Mayo Clinic in Rochester, MN when other changes became apparent. No diagnosis was given during that trip. A relative saw an unopened letter on his kitchen table and questioned him about it. The relative received permission from him to open it and learned of his diagnosis. Not long after I learned of the letter's contents. When I called my brother to visit with him about the contents of the letter, he was very hazy as to what his diagnosis was. That was when I started researching what HDLS/ALSP meant for my brother and the rest of our family. Four to five years ago there was very little information available about HDLS/ALSP for patients and their families that was not research findings phrased in medical terminology. What little I found gave me a sense of impending doom. What an awful disease. Not only would it take your body, but it would also take your mind. After onset, life expectancy on the average was seven years. No treatment. No cure. No way to prevent it. Worse yet, it was autosomal dominant. The children of a parent that had the mutated CSF1R gene had a 50/50 chance of passing it on. Yikes! I started reading research papers/findings. I learned more about the disease. The more I read, the less Greek the terminology seemed. What at first seemed incomprehensible became understandable. If I came across a term I didn't know, I looked it up. I concluded that if I had a difficult time finding information, so would others in my family's shoes.

Prior to my brother's diagnosis, two of our first cousins had become nursing home residents. Each entered a nursing home at 64 years of age for differing reasons. Our cousin, who I will refer to as J, had the diagnosis of frontal lobe dementia thought to have been caused by excessive exposure to pesticides. Which made perfect sense as he was a farmer. It was after my brother's diagnosis that my cousin's family began to wonder if J had HDLS/ALSP. They planned to have him tested. His blood test indicated that he too had the mutated CSF1R gene. With J's diagnosis it was now known that the disease was being passed down the paternal side of our families. J's dad and our dad were brothers. J's diagnosis also verified that my brother's gene wasn't a new mutation.

Families cope with the news that there may be a genetic disease in the family in various ways. When families live in a small, rural community it is especially interesting. Some family members will openly discuss the disease. With others it becomes a family secret. Not to be acknowledged or spoken of. The grown children and grandchildren are not informed. Other family members are kept in the dark. The disease does not exist. If the topic of the disease is brought up…. deny that the disease has affected you and yours. I get why this happens. Family members who are young need not be traumatized. Nosy neighbors and community members don't need to know all your business. No one wants to carry the stigma of a genetic disease. I saw it happen both ways with my relatives. Some openly discussed the disease. Others denied that their family member/s had HDLS/ALSP. Right or wrong, I chose to openly speak of the mutated gene and of the disease associated with it. My adult children learned early on that their uncle had a genetic disease and that I had a 50/50 chance of also having the gene and the disease.

A few years down the road various health concerns caused me to wonder if I too had the disease. My husband and I priced long term care insurance and term life insurance. We discussed what would happen if I had the gene. We discussed what assisted care options were available to us where we lived. Serious conversations for a couple married only a few years. Even though I had suspicions, I hesitated when it came to verifying one way or another as to whether I had the mutated CSF1R gene. Finally, I asked my physician to plan for me to be tested. Initially, he was hesitant. It was not until I provided him with more specifics about my brother's diagnosis was, he willing to refer me to a genetic counselor. A disease as rare as ALSP means you become an educator when you meet with your healthcare provider. Interaction with a genetic counselor is interesting to say the least. I could tell that she was trying to determine if I could mentally cope with the knowledge of knowing the test results if they came back positive. At the end of our online virtual consultation, she approved my being tested. A test kit arrived at the medical clinic near me. Blood was drawn and sent back to the lab where the kit was ordered from. It seems like it took months for my results to arrive at the genetic counselor's office. Our conversation was brief. The result of the test was positive for the mutated CSF1R gene. No matter how prepared you think you are prepared to hear the worst, the worst still is a hard hit. I am going to be honest; I had hoped that the test result would come back negative. I coped, but my coping was to make end of life plans. I confided in J's sister about my results. I told her that I intended to contact Mayo in Rochester which is the hospital where my brother receives care. She suggested Florida Mayo as she had read that it was the Mayo Clinic researching the disease. I started searching and came up with the name of the neurologist /researcher at the Florida Mayo who was researching HDLS/ALSP. Between my cousin and I we contacted Dr. Wszolek and his assistant. My cousin helped her family make arrangements for her siblings' brains to be donated to Mayo. Yes, you heard correctly the term siblings. Around the time I was tested, J's sister who went into the nursing home at 64 was tested. She too, was found to have HDLS/ALSP.

I called Florida Mayo to make an appointment with Dr. Wszolek. I don't recall all the details but with some effort I was able to make the trip to Florida Mayo as part of a research project in June of 2021. Expect the following when you go through an assessment to determine if you have the disease. Blood is drawn, urine is taken (I was handed a jug to fill over a 24-hour period), a spinal puncture is done, an MRI (possibly with contrast) and a CT scan done, a mental assessment is given by a psychiatrist (I think it was the Montreal Dementia test), The neurologist also administered a physical exam and spent time visiting with me. I should mention that by the time I arrived at Mayo in June I had processed and had come to terms with my mortality. I had made my peace with what my future held. If anything, my belief in God had been strengthened.

It was around this time that I reached out to the Sisters' Hope Foundation. Heidi quickly responded. It helped to have support from another family who had knowledge of the gene and the disease. It was a comfort to communicate with someone whose family knew intimately the same disease.

The results of the tests came back as a surprise to me and my husband. They were, I think, also a surprise to Dr. Wszolek. Dr. Wszolek informed me that I was only the second person he knew of that had the gene, but not the disease. There was no sign in my brain of the disease. July 2021 Dr. Wszolek visited my hometown where my brother and many of my cousins live. He spent time at the local nursing home where my two cousins reside. He ran some tests on them. Later that afternoon Dr. Wszolek met with myself, my brother, our children, our cousins, their children, and grandchildren. Interestingly, nursing home staff from the nursing home where my cousins resided also attended Dr. Wszolek's presentation regarding the mutated CSF1R gene and the disease ALSP/HDLS. November 2021 cousin J died at the age of 72. His obituary stated that he died of a genetic disease.

In January of this year, I returned to Florida Mayo as part of another research project. It is a two-year natural history study. Once again, the test results were good. Dr. Wszolek and his colleague, Dr. Tipton, both stated that I may never develop the disease. At this point I am referred to as an asymptomatic carrier of the CSF1R gene. My brother is now also part of the natural history study of CSF1R gene and HDLS/ALSP. My brother still can live on his own. He has family and friends nearby that assist him as needed. One of the advantages of living in a tight knit rural community. My brother and I both believe that doing something is better than doing nothing. Perhaps through us, more can be learned as to how this genetic disease can be treated. My brother and I both have adult children. My brother also has grandchildren. We have a reason to assist where we can further the research and development of a successful treatment of ALSP. Prior to my examination at Mayo, I presumed my life with the CSF1R gene meant that I soon would become mentally and physically incapacitated with a life expectancy of approximately seven years. I have the gene, but apparently not the disease. I am considered an asymptomatic carrier which is not typical for someone of my age (63). Dr. Wszolek finds my disease resistant state an intriguing puzzle. What has protected me from developing the disease? My son posed an interesting question, could there be others out there with the gene who haven't been tested to learn if they have the gene? If my brother hadn't been found to have the disease, I would not have taken the genetic test. Maybe, it means others are out there living with the gene, and who may never develop the disease.

I know firsthand that when you or your family member is found to have the CSF1R mutated gene and/or ALSP that there will be despair. I have a few words of hope for those who are new to the mutated CSF1R gene and ALSP/HDLS. This is a fairly new disease where research and treatment are concerned. What is amazing is that there is research into this seemingly rare disease. That alone is hopeful. Do not lose faith that a treatment will be developed. If the present treatment/s that are currently in various stages of development are successful, then the future of those with the CSF1R gene, and the disease, adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) suddenly becomes so much brighter. I have been reminded that tomorrow is not promised to any of us. Take each day as a gift. Live your life fully while you are able.

To read more patient, family and caregiver stories please visit; https://www.sistershopefoundation.com/patient-family-caregiver-stories/.

Causes

ALSP is caused by an abnormal CSF1R gene variant that codes for the protein colony-stimulating factor-1 receptor found on many cell membranes, including those in the central nervous system, or CNS (consisting of the brain and spinal cord). This receptor plays a role in cell growth and cell specialization where cells take on specific functions in the body. Without a normally functioning CSF-1 receptor, structural changes to the nerve cell, or neuron, eventually occur. Axons, the portions of neurons that transmit signals to the next neuron, are covered in a myelin sheath, or the white matter that is destroyed in ALSP and other leukodystrophies. In ALSP, the formation of swellings known as spheroids within axons causes immune cells known as macrophages to destroy myelin sheathing, further damaging nerve cell function. Microglia, another type of macrophage immune cell of the CNS that's responsible for maintaining brain tissue, are highly dependent on the CSF-1 receptor. When the receptor is inhibited, microglia become underactive and are destroyed. Macrophages and microglia take on a pigmented appearance in brain biopsies of ALSP patients.

ALSP is an autosomal dominant genetic condition, meaning only a single copy of the disease-causing CSF1R gene variant is necessary to cause ALSP. The altered gene can be inherited from either parent or can be the result of a new mutation in the affected individual, known as a de novo mutation where the mutation has never before been present in the family. The latter case is referred to as a sporadic, rather than an inherited, case of ALSP. In autosomal dominant conditions, there's a 50% chance the affected individual will pass the altered gene to their child, with the risk of inheritance being the same for males and females.

Affected Populations

The estimated number of people thought to have ALSP in the United States is 10,000 with similar estimates in Europe and Japan. Average age of diagnosis is 43 years old, but symptoms have been reported to occur in patients as young as 18, and 95% of ALSP patients start having symptoms before age 60. Both men and women are equally affected but symptoms usually appear earlier in women, at age 40 versus 47 for men. Life expectancy ranges from 2 to over 30 years, with an average life expectancy of 8 years after symptom onset.

Patient Story (Mason, 19-years old, asymptomatic)

Love, Loss, and the Power of Knowledge from a Young Carrier of the CSF1R gene mutation

One of the realities of growing up and becoming an adult is the day when children are faced with the need of their parent who may be in failing health or require some type of health-related care, and the child's commitment to caring for that parent. Roslyn Carter is a former First Lady of the United States and founder of the Roslyn Carter Institute of Caregiving and has a famous quote on caregiving: "There are only four kinds of people in the world. Those who have been caregivers. Those who are currently caregivers. Those who will be caregivers, and those who will need a caregiver." Of course, most of us kids feel that we won't be put into a position of having to care for our parents and accepting those responsibilities until late in our lives; maybe when we have started our own families and have a more stable life. In my case, this responsibility came at a much earlier age than most.

When I was 16, my mom began to have difficulties with her speech. It was very minor, and I didn't really notice it at first. When I did, it didn't alarm me, and I thought that maybe she was just tired from work. At that time, it never occurred to me that there could be something medically wrong with her. She started misplacing words or mispronouncing words that began with an "s" or a "c". My mom and I had a great relationship, and we would often make fun of each other in a harmless way, especially when one of us had a slip of the tongue, but this seemed different because it was occurring more often than in the past. When I asked her about it, she would just chalk it up to being tired from work or the effects of her asthma, and at the time I accepted and didn't pressure her any further. After a few months passed her word slip ups not only happened more often, but they seemed to be getting worse and she was having a hard time with her speech in general. During this time, she would mumble through entire sentences and not enunciate any words at all; it was clearly different than it had been even a few months before. She did not think anything was wrong and continued to blame work fatigue or asthma as the cause. Everything else in her life seemed normal: she was still working, driving, and taking care of herself and me. I agreed with her until my Aunt Heidi, who is also my mother's twin sister, asked me if I noticed anything different about my mother's behavior, particularly her speech. I shared my observations with my aunt, and I suddenly became more concerned because someone else noticed these changes. We finally got Mom to agree to a check-up and took her to the hospital. She was given an MRI and CT which resulted in the observance of some abnormalities that they were unable to accurately identify but knew that under normal circumstances should not be observed. Although the doctors were not forthcoming with specific information, given our family's history, my aunt and I had a guess of what might be wrong. My grandmother, great aunt, great uncle, and my mother's older sister and my Aunt Heather all were diagnosed and died from complications from adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP). Both Aunt Heidi and I were sure my mother was showing the beginning signs of this disease. A few months later, she was diagnosed with ALSP after receiving the results of her genetic test. Two months later, she had a seizure at work. It was a focal seizure that only affected the left side of her body. While in the hospital with her seizures she was given an anti-seizure medicine and sent home a few days later. This entire incident made me very anxious because I felt this was the next step in her battle with ALSP and I knew from watching my grandmother's journey with the disease that our lives were about to change in a big way. It began to be clear that my mother's disease was progressing quickly, and she would need some type of caregiver assistance. As her only child I knew it would become my responsibility.

This was all happening at the time when COVID-19 became widespread and was starting to shut everything down, which meant I was home from school full-time. I was still responsible for my schoolwork, but my mother's needs became a priority, and I chose to spend time away from schoolwork caring for her. Most of my work was doing domestic chores like cleaning, cooking, doing the dishes, walking the dog, and taking my mother on errands. Due to the seizures her license was revoked. Caring for my mom was all new to me and at times I questioned whether I could do everything to help her while I also focused on school. I realized that I had no other choice. she needed help, I was available, able and an only child, end of story!

As soon as things appeared to be settling into a manageable routine for the two of us; everything blew up. My mother had completed all her initial testing, including an MRI and memory and cognitive tests at University of Pennsylvania. They informed us of a bone marrow transplant program at the University of Minnesota Medical Center available to my mother and my Aunt Heather. Heather had been diagnosed with ALSP before my mom and was in the final stages of her battle with the illness. The bone marrow transplant was not a cure and had some risk involved, but as a family we felt it was worth Heather entering into the program. One month into the transplant program, Heather had a heart attack which put her in the ICU and during which her body rejected the bone marrow. Based on Heather's difficulty with the transplant I felt strongly about my mom not being involved. Sometimes being a caregiver means having hard discussions with the people you love and want to protect. I told my mom that if she entered the bone marrow program it is likely that she would suffer the same fate as her sister and after spending four months alone in Minnesota she would likely die away from home. The alternative would be to go back home and be

around family and friends for her final days. My mom decided to come home. While living back home, Mom had good days and bad. The good days were spent with those that loved and cared for her doing things she enjoyed like going to the beach, being outside, and sitting on the couch and watching lots of TV. The worst day happened when Aunt Heather passed away while still at the University of Minnesota Medical Center; ironically this would have been the same day that my mom was to begin the bone marrow transplant program.

Part of what made my mom's last days more enjoyable was when one of Aunt Heidi's neighbors, April, joined us as a caregiver. She was great, had a ton of energy and compassion, and helped me out a bunch. And while my mom seemed to respond in a positive fashion to this new situation, this was perhaps the hardest time for me. COVID lockdown inside a small space, cold weather which kept us inside, my mom's progressive disease, isolation from my friends, and the ongoing pressures all caregivers experienced were a huge emotional burden for me. I had nobody to talk with or activities to help alleviate the emotional strain.

The progression of the disease became obvious when the day after my Aunt Heidi launched the Sisters' Hope Foundation to help support ALSP patients and their families, my mom became quite sick in the aftermath of the event. The next day April and I noticed that Mom had slept in later than usual. After spending the week in the hospital, my mom returned home on hospice care.

One of the things that was a departure from all the stress of caring for my mom was my upcoming graduation from high school; an event she desperately wanted to attend. All my mom wanted to do was see her only son graduate from high school. She lived for this moment, knowing she succeeded in raising her only child and set him up for his future. She was able to attend my high school graduation, with assistance. It was not without its challenges but ended up being a good time and wonderful memory for me. She was excited, but I wasn't sure if she would make it as her condition continued to worsen, including more frequent seizures and the addition of home hospice to her care. She made it to my graduation and for that I was extremely grateful, but bittersweet at the circumstances. It's interesting as I think back about that particular chapter in our lives and how we both began to detach ourselves from different aspects of our lives. Mom from her present physical being which had changed so drastically in the space of a couple of years and me letting go of the person she had become. I couldn't think of her in the present and kept remembering her past self. A few weeks after attending my high school graduation my mom passed away on July 20, 2021.

I took my mom's death hard, especially how she died and watching her slip away the way she did. It also came at a time in my life where she and I had become good friends and we would have had so much more to share had she lived. One of the hard lessons I learned throughout this experience was the ongoing affect ALSP had on our entire family and how I might also become symptomatic one day. One of the people who was a huge help to me in the final days of my mom's life and the weeks after she died, was my Aunt Heidi. She and I talked a lot and one of the things we discussed was whether or not I would want to know if I carried the mutation. From what we know about ALSP, it could be 20 or 30 years before I become symptomatic. I felt strongly that I needed to know for sure. I decided to get tested to see if I carried the CSF1R mutation which causes ALSP. The process was surprisingly quite simple: I received an at-home test where I swabbed the inside of my mouth and sent it to a lab in California. During the approximate two weeks while I waited for the results, everyone was encouraging and telling me that I would test negative, but somehow, I knew, deep down, that I carried the mutation. It was just a suspicion and gut feeling. I knew from family's experience that if you tested negative, the lab would share that information with a simple phone call. Those who tested positive received a message to schedule a Zoom call to review the results. My fear and inclination came true when I received an invitation for a Zoom call with the genetic counselor.

I have decided to just live my life as best I can, which means continuing my plans to attend and graduate from college – something my mom and I both shared. I also decided to enroll in an ALSP Natural History Research Study at the Mayo Clinic in Jacksonville, Florida, close to my father's home. I had an MRI and some bloodwork which I will repeat every six months. The goal of this study is to compile data of people who have tested positive and use that information for future research and hopefully drug development programs. Taking part in the Natural History Study also allows doctors to monitor me for any disease related changes. If and when this occurs, we will be able to take immediate action. I am the first person in my family to receive a positive CSF1R genetic test and have no symptoms. I have lost five family members to this disease, and they have taught me that knowing my genetic status is no longer a death sentence. I am now in control of my future. A future where as soon as the doctors observe changes in my exam and MRI, I have an option available, and hopefully more options in the future.

It's important that patients and caregivers share their stories with one another. Connecting with others who are going through what my family experienced is sometimes the knowledge they need and knowing there are others in the same situation is comforting. My mom lived life to the fullest, she loved me with every ounce of her being and she would want me to advocate every day for early detection of this disease, so I have a fighting chance of living a long and fulfilled life.

Early:

Early symptoms of ALSP often include mild psychological or cognitive changes, but, while rare, can present as disturbances in motor function, such as difficulty walking, falling, and slowness of movements. Eventually, as damage in the brain becomes more extensive, psychological, cognitive and motor symptoms exist together. Initial symptoms and rate of disease progression vary quite a bit from one individual to the next, including those within the same family when the condition is inherited.

Psychiatric changes:

Psychiatric features of ALSP include changes in personality and the development of anxiety, depression, lack of interest in things (apathy), irritability, distractibility, socially inappropriate behaviors (disinhibition) and cravings for certain types of food (for example eating only ice cream). Cognitive features include the development of dementia, with a general decline in mental functioning, including memory loss, word-finding and language difficulties (aphasia), difficulty planning voluntary muscle movements (apraxia), poor attention, poor judgment and problem solving and reduced impulse control.

Pyramidal:

Brain degeneration in ALSP also affects what is known as the pyramidal system in the brain. These are nerve tracts that travel from the cerebral cortex (responsible for control of voluntary movements) to the brainstem or the spinal cord. Damage to these tracts in ALSP causes overactive reflexes (hyperreflexia); increased muscle tone, meaning muscles stay stiff and contracted at rest (hypertonicity); muscle spasms with increased movement (spasticity); weakness of one side of the body (hemiparesis) or in all four limbs (quadriparesis); reduced coordination; changes in vision; difficulty walking; difficulty swallowing; slurred speech; and heightened emotional responses, meaning patients may cry or laugh at inappropriate times (pseudobulbar palsy).

Parkinson's like symptoms:

Symptoms similar to Parkinson's disease, such as increased muscle stiffness (rigidity), tremors, a slowing of movement (bradykinesia), a shuffling gait and a reduction or loss of facial expression (hypomimic face or masked facies) can occur in ALSP as well. In ALSP, these symptoms are referred to as Parkinsonism and are not helped by increasing dopamine levels with medications like levodopa, which would ordinarily improve symptoms in Parkinson's disease.

Sensory:

Changes to sensory nerves can also occur, making it more difficult for patients to sense pain, touch, vibration and changes in body position. Frequently, the patients cannot recognize the right or left side of the body.

Seizures:

Less commonly, seizures can accompany ALSP, occurring in approximately 30% of patients with the diagnosis. The seizures usually occur at the onset of the illness.

Late stage:

As the disease worsens, patients enter a state where they can no longer walk or speak and need total care with all daily living functions. They also lose control of bladder and bowel sphincter functions (double incontinent). Most patients with ALSP die from pneumonia.

Related Disorders

Many symptoms of ALSP overlap with other neurological disorders, including other types of leukodystrophies. Genetic testing is required for accurate diagnosis. Based on symptoms, ALSP is most similar to the following disorders:

Frontotemporal dementias (FTDs) are a group of neurodegenerative disorders associated with shrinking of the frontal and temporal anterior lobes of the brain. Symptoms include marked changes in social behavior and personality, and/or problems with language. People with behavior changes may have disinhibition (with socially inappropriate behavior), apathy and loss of empathy, hyperorality (eating excessive amounts of food or attempting to consume inedible things), agitation, compulsive behavior, and various other changes. Examples of problems with language include difficulty speaking or understanding speech. Some people with FTD also develop a motor syndrome such as Parkinsonism or motor neuron disease (which may be associated with various additional symptoms). (For more information on this condition search for “frontotemporal degeneration” in the Rare Disease Database.)

Multiple sclerosis (MS) is a chronic neuroimmunology (both the nervous system and the immunological system are involved) disorder of the central nervous system involving the brain, spinal cord and optic nerves. By means of a mechanism not clearly understood, the protective fatty, insulating substance called myelin sheath that covers the nerve is destroyed. The inflammatory attacks that produce the characteristic scarring (plaques or patches) of the myelin sheath occurs unpredictability, vary in intensity, and at many sites thus the name, multiple sclerosis. During the course of the disease, patients may have attacks (relapses or exacerbations), gradually worsen (progression), or stabilize. The randomness of the location of damage can result in a wide range of neurological symptoms, which may vary from person to person. (For more information on this condition search for “multiple sclerosis” in the Rare Disease Database.)

Parkinson’s disease is a slowly progressive neurologic condition characterized by involuntary trembling (resting tremor), muscular stiffness or inflexibility (rigidity), slowness of movement (bradykinesia) and difficulty carrying out voluntary movements (akinesia). Degenerative changes occur in areas deep within the brain (substantia nigra and other pigmented regions of the brain), causing a decrease in dopamine levels in the brain. Dopamine is a neurotransmitter, which is a chemical that sends a signal from one nerve cell to another in the brain.

Diagnosis

Diagnosis of ALSP is made by a neurologist. ALSP is diagnosed through genetic testing that identifies a CSF1R gene variant associated with the disease. However, family history, clinical signs and brain imaging results are integral in raising suspicions enough to order genetic testing. When symptoms affecting cognition and movements or when seizures combined with either cognitive or motor symptoms are present before or by age 60, suspicion for ALSP should be raised. Cognitive testing by psychiatrists, neurologists or psychologists can identify behaviors that confirm frontal lobe dysfunction (e.g., reduced inhibition), especially when subtle, that is associated with ALSP.

Specific patterns of brain deterioration on MRI and CT scans can further raise suspicion. These include the existence of lesions of white matter on both sides of the cerebrum (the largest, most exterior part of the brain that controls more complex functions) that in earlier stages of ALSP are less symmetric but become more symmetric and extensive as the disease progresses. White matter lesions in ALSP are most common in the frontal and parietal brain lobes of the cerebrum and the white matter around the lateral ventricles (periventricular deep white matter), making the ventricles appear enlarged in imaging. Also apparent in brain scans is thinning of the corpus callosum (a bundle of white matter, or myelinated, nerve fibers that connect the right and left halves of the brain so that they can communicate with one another) and small calcifications (from calcium deposits) in the white matter around the frontal and parietal brain lobes.

Detection of high levels of neurofilament light chain, a protein that serves as an indicator of axonal damage, has been found in the blood and cerebrospinal fluid of ALSP patients and may aid clinicians in formulating their diagnosis.

Standard Therapies:

There are currently no FDA-approved treatments for ALSP. Researchers are further investigating underlying disease mechanisms and symptom progression to develop more effective treatment options. Current treatment options do not reverse brain damage but instead are meant to manage symptoms. For patients with ALSP who have seizures, anti-epileptic medications are useful for controlling seizures. Antibiotics may be prescribed to help control infections, such as pneumonia or urinary tract infections that may arise as patients grow progressively weaker. Muscle relaxers may be recommended to target spasticity. Anti-depressants are often prescribed to treat psychological symptoms of ALSP but are not especially effective. Anti-psychotic medications may be used to control aggression in ALSP, but side effects are generally not well-tolerated. Nutritional supplements and physical therapy are often recommended to slow overall decline and maintain the most optimal overall health possible.

Investigational Therapies:

As of the beginning of 2022, bone marrow transplantation is the first and only available potential treatment to modify the ALSP disease course. Results vary between each patient, but in some cases, bone marrow transplants have slowed the progression of motor and cognitive symptoms of the disease. Bone marrow transplants are thought to be beneficial for some individuals with ALSP by providing new immune cells from donors with normal CSF-1 receptors to develop into and increase levels of microglia in the brain.

Observational Studies:

Vigil Neuroscience is conducting a Natural History Study. More information can be found at https://www.clinicaltrials.gov/ct2/show/NCT05020743?term=NCT05020743&draw=2&rank=1 or by contacting trials@vigilneuro.com.

The Myelin Disorders Biorepository Project (MDBP) seeks to collect and analyze clinical data and biological samples from leukodystrophy patients worldwide to support ongoing and future research projects. For more information please visit: **https://clinicaltrials.gov/ct2/show/NCT03047369?cond=POLD&draw=4&rank=9**

Clinical Trials:

Current clinical trials are posted on the Internet at https://www.clinicaltrials.gov.

Information about clinical trials being conducted at the NIH Clinical Center in Bethesda, MD, contact the NIH Patient Recruitment Office: Toll-free: (800) 411-1222, TTY: (866) 411-1010, email: prpl@cc.nih.gov.

Information about clinical trials sponsored by private sources, visit https://www.centerwatch.com.

European clinical trials can be found at: https://www.clinicaltrialsregister.eu/.

Genetic Testing

Genetic testing has potential benefits whether the results are positive or negative for a gene mutation. Test results can provide a sense of relief from uncertainty and help people make informed decisions about managing their health care.

A negative result can eliminate the need for unnecessary checkups and screening tests in some cases. A positive result can direct a person toward available prevention, monitoring, and treatment options.

When ALSP is diagnosed early you may have the option of investigational treatments, observational studies and clinical trials. The ALSP community no longer has to worry about carrying a genetic disease with no treatment options available. See Treatments, Trials and Research.

Your Neurologist will be able to provide you with available testing options or to learn more about genetic testing visit www.invitae.com.

Please Note: Genetic counseling is recommended to help patients and families understand the genetics and progression of ALSP and to provide psychosocial support.

Medical Expense & Medical Travel Reimbursement Program

Sisters Hope Foundation provides financial assistance to ALSP patients for medical and medical travel expenses directly related to ALSP. The program is on an as needed basis and provides financial assistance with co-pays, deductibles and services not covered or services denied by your insurance company.

We can help pay for:

- Treatment-related co-pays, deductibles, and services not covered or denied by your insurance company.
- Prescription medication related to prescribed treatment and over the counter medication.
- Medical equipment including cane, walker and/or wheelchair. Incontinence products.
- Travel expenses directly related to a clinical neurology appointment within your "home" country or within a reasonable distance of your "home" country. May include; airfare, hotel, rental car or rideshare, food and drinks.

Program Eligibility Criteria:

To be eligible for Financial Assistance, you must

- Be a United States citizen or permanent resident of the U.S. or U.S. territory. Exceptions may apply and will be approved on an as needed basis.
- Have medical insurance and provide proof of insurance.
- Have an ALSP diagnosis (CSF1R mutation) confirmed by a genetic test. Must provide proof of CSF1R mutation.

Note: These programs are for patients and their families who reside in the United States, but exceptions will be reviewed. SHF's ability to help outside of the US is limited. However, we will review and consider all requests.

Exclusions:

- Due to the extremely high cost of certain medical procedures including bone marrow transplant, SHF is not able to offer financial assistance when insurance denies coverage for this procedure.
- Medical insurance premiums are not an eligible expense for reimbursement.

How to Apply:

STEP 1:

Email heidi@sistershopefoundation.org and provide the following information:

- Proof of ALSP diagnosis provided by genetic testing.
- Proof of Medical Insurance, as well as Medicare/Medicaid.
- Name of treating physician.
- Include Direct Payment to Medical Provider or Reimbursement for Payments Made (See STEP 2 BELOW)

STEP 2:

Direct Payment to Medical Provider:

- Copy of unpaid invoice, bill that includes the exact treatment or service.
- Copy of Explanation of Benefits (EOB) from your medical insurance company.

Reimbursement for Payments Made:

- Provide proof of payment (receipt, bank statement, credit card statement, cleared check)
- Copy of unpaid invoice, bill that includes the exact treatment or service.
- Copy of Explanation of Benefits (EOB) from your medical insurance company.

This information will not be shared and is for verification purposes only.

Decisions:

You will be notified via email when a financial determination has been made. The financial assistance program is made possible by sponsors and donations to SHF. Financial assistance is not guaranteed and are available on a first come, first served basis.

Benefits and Taxable Income:

As a charity, SHF is exempt from federal income tax and individuals who receive assistance from a charity to meet their personal needs do not generally have to pay federal income tax on the value of the assistance they receive. It should not affect your ability to receive financial assistance from the government or affect your income taxes. Any questions or concerns should be discussed with a tax professional.

FAQ's:

What is a Co-Pay? A fixed amount you pay for a health care service that is covered by your insurance and after you've paid your deductible. Copays vary for different services like drugs, lab tests, and visits to specialists within the same plan.

What are some expenses that are necessary for an ALSP patient and may be eligible for reimbursement? CT and MRI scans, Labs and Tests; Treatment-Related Co-Pays, Deductibles, Co-Insurance, Prescription Drugs and some Over-The-Counter Medications, Incontinence Products, Cane, Walker and/or Wheelchair travel to a Neurologist considered to be a specialist for ALSP.

Please Note:

You have complete freedom to choose doctors, providers, suppliers, insurance companies and treatment-related medications.

As a non-profit organization, we rely on the generosity of our sponsors. Program continuation is dependent on the availability of funds and the program could be modified or discontinued at any time if funding is limited or no longer available.

Plan for your Future

"The future is not guaranteed to any of us especially those suffering from a rare, neurodegenerative disease. Even when treatment options are available, complications may arise. Planning and preparing for the future can alleviate undue stress which is important for you and your loved one." Heidi, President & Founder, Sisters' Hope Foundation

Follow our social media pages and sign up for the SHF newsletter so you can be informed of guest speakers and presentations discussing this topic.

Get Involved

Some individuals living with ALSP have found that by getting involved and raising awareness about the disease, they can strengthen their sense of purpose and connection to others. You have a unique opportunity to contribute to the ALSP cause by turning your experience into inspiration for others. Sisters' Hope Foundation offers ways to join the fight and help raise awareness and funds.

1. Advocate
2. Become a leader, chair a committee, volunteer at an event
3. Fundraising – support our events and host your own fundraising event.

References and ALSP Publications

Hereditary diffuse leukoencephalopathy with spheroids - About the Disease - Genetic and Rare Diseases Information Center (nih.gov)

Tipton PW, Kenney-Jung D, Rush BK, et al. Treatment of CSF1R-Related Leukoencephalopathy: Breaking New Ground. Mov Disord. 2021 Jul 30. https://pubmed.ncbi.nlm.nih.gov/34329526/

Gelfand J, Greenfield A, Barkovich M, et al. Allogeneic HSCT for adult-onset leukoencephalopathy with spheroids and pigmented glia, Brain. 2020 Feb; 143(2): 503-511 https://academic.oup.com/brain/article/143/2/503/5678694?login=true

Han, J., Sarlus, H., Wszolek, Z. K., Karrenbauer, V. D., & Harris, R. A. Microglial replacement therapy: a potential therapeutic strategy for incurable CSF1R-related leukoencephalopathy. Acta neuropathologica communications. 2020; 8(1), 217. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7720517/

Konno T, Yoshida K, Mizuta I, et al. Diagnostic criteria for adult-onset leukoencephalopathy with axonal spheroids and pigmented glia due to CSF1R mutation. Eur J Neurol. 2018 Jan; 25(1): 142–147. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5741468/

Konno, T., Kasanuki, K., Ikeuchi, T., Dickson, D. W., & Wszolek, Z.K. CSF1R-related leukoencephalopathy: A major player in primary microgliopathies. Neurology. 2018; 91(24), 1092–1104. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6329328/

Lynch D, Jaunmuktane Z, Sheerin U, et al. Hereditary leukoencephalopathy with axonal spheroids: a spectrum of phenotypes from CNS vasculitis to parkinsonism in an adult onset leukodystrophy series. Journal of Neurology, Neurosurgery & Psychiatry. 2016; 87:512-519. https://jnnp.bmj.com/content/87/5/512.info

Sundal C, Wszolek ZK. CSF1R-Related Adult-Onset Leukoencephalopathy with Axonal Spheroids and Pigmented Glia. 2012 Aug 30 [Updated 2017 Oct 5]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021.\ https://www.ncbi.nlm.nih.gov/books/NBK100239/

Genetic and Rare Diseases Information Center. Hereditary diffuse leukoencephalopathy with spheroids. Last updated: 3/27/2013. https://rarediseases.info.nih.gov/diseases/10981/adult-onset-leukoencephalopathy-with-axonal-spheroids-and-pigmented-glia

Sisters' Hope Foundation. What is ALSP? https://sistershopefoundation.com/what-is-alsp/