The Importance of Early Recognition of Tay–Sachs and Sandhoff Disease

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Case discovery

Jeanine Jarnes, PharmD: Thank you for joining us for this expert perspective's program. With this program, we will be discussing a group of diseases called the GM2-gangliosidoses. Specifically, we will focus on Tay-Sachs disease and Sandhoff disease.

Jeanine Jarnes, PharmD: A commonality of the group of diseases called GM2-gangliosidosis is that they all involve a deficiency of an enzyme called beta-hexosaminidase. This, in turn, leads to a toxic accumulation of the enzyme substrate, GM2-ganglioside.

Chester B. Whitley, MD, PhD: The most common GM2-gangliosidosis diseases are Tay-Sachs disease, with an estimated incidence of 1 out of 200,000 live births, and Sandhoff disease, with an estimated incidence of 1 out of 400,000 live births.

Jeanine Jarnes, PharmD: It is important to recognize that there are 4 different genes that are involved, each of which can cause defects leading to a beta-hexosaminidase deficiency.

Chester B. Whitley, MD, PhD: The defects that can occur in four different genes, in turn, result in four different diseases of beta-hexosaminidase deficiency.

Jeanine Jarnes, PharmD: For proper diagnosis, the activity of the enzymes involved, specifically beta-hexosaminidase A and beta-hexosaminidase B, must be measured by enzyme assay. These assays are commonly performed in white blood cells or plasma, but may also be measured in tissue, such as fibroblasts.

Chester B. Whitley, MD, PhD: In addition to enzyme activity, molecular diagnostics should be done to determine the specific allele mutations and genotype of the defective gene involved. Note, the specific ganglioside substrate that accumulates in a disease of hexosaminidase deficiency will vary somewhat, depending upon the disease variant. However, all forms of beta hexosaminidase deficiency involve an accumulation of GM2-ganglioside.

Jeanine Jarnes, PharmD: What are gangliosides? We know they accumulate to toxic levels in GM2-gangliosidosis diseases. Are gangliosides themselves toxic, or are they something that is necessary biologically? In fact, gangliosides are a critically important component of plasma membranes and of many intracellular membranes, such as the cell nucleus membrane, mitochondrial membranes, Golgi apparatus and lysosomal membranes.

Chester B. Whitley, MD, PhD: Gangliosides play a critical role in various forms of cell signaling, including immune function signaling, tyrosine kinase signaling, and cell-to-cell recognition. In addition, gangliosides contribute to modulation of numerous cellular responses, such as natural killer cell cytotoxicity, cell adhesion during inflammatory responses, insulin responses, epidermal growth factor response, and vascular endothelial growth factor response. Gangliosides are also critical for myelin-axon stability, growth, and repair.

Jeanine Jarnes, PharmD: The ganglioside distribution throughout the human body varies from tissue to tissue. Gangliosides are found most prominently in the nervous system, especially the central nervous system. It is important to recognize that the distribution is quite different in a healthy newborn baby when compared to the distribution in an adult. In a healthy newborn, most of the ganglioside in the brain is not GM1- or GM2-ganglioside; it's GM3-ganglioside. The ganglioside content changes during the first year of life to become predominantly GM1- and GM2-ganglioside.

In the GM2-gangliosidosis conditions, which are caused by a deficiency in beta-hexosaminidase enzyme, the GM2-ganglioside itself is not recycled properly, thereby accumulating to toxic levels within tissues throughout the body, the nervous system being most heavily affected.

Chester B. Whitley, MD, PhD: Let's turn our attention to the epidemiology, genetics, and inheritance patterns of GM2-gangliosidosis diseases.

Jeanine Jarnes, PharmD: The GM2-gangliosidoses are inherited through an autosomal recessive pattern. This means that for an individual to have a diagnosis of Tay-Sachs or Sandhoff disease, the individual must have a pathologic defect in both alleles that make up the gene that contributes to the defect. Such individuals are also described as "affected." In other words, the two mutations lead to a severe deficiency in beta-hexosaminidase enzyme. This, in turn, leads to the diagnosis. But if an individual has just one pathologic mutation, that one pathologic allele does not cause the disease. Then, this individual is a "carrier" of the defect. Importantly, such an individual will have sufficient beta-hexosaminidase activity

despite the one allele that is defective. They will have enough enzyme activity to prevent toxic accumulation of GM2-ganglioside.

Chester B. Whitley, MD, PhD: Carrier frequencies refer to the number of individuals who have a pathologic mutation in only one allele of one of the genes affecting beta-hexosaminidase activity. Carrier frequencies are based on estimations in the current literature. It's important to note that some populations have a higher frequency of carriers, such as Tay-Sachs disease or Sandhoff disease. The higher carrier frequency would naturally translate into a higher incidence of individuals who have a diagnosis of a GM2-ganglioside condition.

Sandhoff disease carrier status is higher amongst Ashkenazi Jewish individuals, Creoles of northern Argentina, Eastern Europeans, Lebanese and Metis Indians of Saskatchewan in Canada. Historically, Tay-Sachs disease has been considered by many scientists and medical professionals to be a disease that occurred almost exclusively in the Ashkenazi Jewish population. However, in the 1970s, screening of men and women of Ashkenazi Jewish heritage, typically through temples, to learn if they were carriers of Tay-Sachs disease, prior to having children, resulted in a significant reduction in the incidence of Tay-Sachs disease among Ashkenazi populations, although the carrier frequency is still notable in this population.

Jeanine Jarnes, PharmD: Let's discuss important key concepts from this module. There are 4 different genes that can have pathologic mutations that lead to a diagnosis of GM2-gangliosidosis. The gangliosides have a key function in the human body. They are not inherently harmful. GM2-gangliosidosis arises when the gangliosides are not recycled properly due to a deficiency of the enzyme needed to recycle them. The pattern of inheritance of Tay-Sachs disease, Sandhoff disease, and other gangliosidosis diseases is an autosomal recessive pattern. It's important for healthcare providers to communicate what this means for parents who know that they are carriers. Statistically, it's important that these parents understand that, with each pregnancy, there is a statistically 25% risk or 25% chance that the child will be affected, that is, have the diagnosis of a gangliosidosis condition.

Classic presentation of Tay-Sachs and Sandhoff disease: infantile, late-infantile, juvenile, and adult-onset forms

Jeanine Jarnes, PharmD: Thank you for joining us for this Expert Perspectives program. In this program module, we will be discussing a group of diseases called GM2-gangliosidoses. Specifically, we will focus on the classic presentation of these diseases at the time of diagnosis and their phenotype.

There are currently 4 recognized phenotypes of GM2-gangliosidosis conditions: infantile, late-infantile, juvenile, and late-onset (or adult). These 4 phenotypes can be distinguished most readily by the different ages of symptom presentation that in turn result in the patient, the patient's caregiver, or clinician beginning a process to seek a diagnosis. It is important to understand that in patients with a GM2-gangliosidosis condition, the progressive disease process is underway, even before the patient is born and even if prominent symptoms are not apparent. But often, at the time of birth, it is not apparent that the child has the condition. In most cases, there is no screening to learn if the newborn has a gangliosidosis condition, and the symptoms of the condition are not yet clearly visible. Thus, the child most often is thought to be perfectly healthy at birth. The age at which the symptoms of the disease become clearly apparent, again, varies with phenotype. The infantile phenotype has the most severe and earliest presentation of symptomatology.

It is also important to recognize that the phenotypes of rare diseases will become increasingly better-defined, if treatments become available for the disease. They will also become better-defined if newborn screening programs become available. This can enrich our natural history data banks, that is, the knowledge we have about diseases. In the future, should effective treatments for Sandhoff disease and Tay-Sachs disease become available and newborn screening becomes available, we anticipate learning more about the distinguishing phenotypes of these diseases.

Let's discuss the median age of diagnosis and the median age of the first symptom onset in the infantile phenotype. Note that the patient's symptom onset is usually significantly earlier than the actual diagnosis. In other words, there's a delay in diagnosis. In part, this is because it is a rare disease and the clinicians are not really sure where to look. In most cases, with the infantile phenotype, the first symptoms are noted by 6 months of age, if not slightly earlier, and the median age of diagnosis is approximately 15 months.

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Similarly, in the juvenile phenotype, the symptom onset is usually between 14 and 20 months of age, with the first symptom showing up approximately at 16 months of age, from a median statistical point of view. But the age of diagnosis is later at 22 months. For the juvenile GM2-gangliosidosis, the median age of onset is first noted at approximately 36 months of age, with a significant delay until the actual diagnosis is made at 86 months of age.

What are the initial symptoms that we see in these diseases? In the infantile phenotype-occurring right around six months of age in most patients if not earlier-the most prominent symptom is hypotonia with weakness. Oftentimes, the child is not able to hold his or her head up independently, and they're not able to sit independently. Another symptom that may develop includes an excessive startle reaction, and inevitably, a global developmental delay. Some patients may have a cherry red spot, noted on ophthalmologic exam.

A cherry red spot requires an ophthalmologic exam, which may be ordered if the clinician suspects the child has a lysosomal disease that will have this cherry red spot. The exam may also be ordered if the child is struggling with a lazy eye or has abnormal eye movements. The cherry red spot becomes visible due to ganglioside accumulation in the tissue around the fovea of the eye, as well as around the macula. The macula itself does not have cells and does not accumulate ganglioside. When this is viewed during examination, it looks like a prominent red spot on the retina.

It is important to note that the cherry red spot may not be present at birth, and it may develop later in childhood. It's not a yes or no question of whether the child has a cherry red spot. The question is, have they developed one, or should we check again and see if they develop one at a later time, if it initially does not show up on exam.

Pediatric developmental milestones are a standard way that general practice pediatricians evaluate how a child is developing. We have found through our natural history study at the University of Minnesota that, in addition to the validated and more complicated neurodevelopmental testing that can be done for children with a gangliosidosis condition, the pediatric milestones that are used in all pediatricians' clinics can actually signal to the pediatrician to check to see if the child might have Tay-Sachs disease, Sandhoff disease, or another disease that involves similar neurological impairment. The pediatrial developmental milestone chart typically shows standard pediatric milestones from age two months to five years of age. These parameters can be used to evaluate children and send them on for further screening. For example, can the patient sit independently? Most of the children I've seen with infantile Tay-Sachs, even at six or seven months of age cannot sit independently. However, what can happen is a child will use what is called a tripod position to support himself. This is important because when these pediatric milestones are being used to examine children as a signal that there's a neurological disease occurring, the parent or caregiver needs to properly understand the question, and the clinician needs to make sure that they do an actual physical exam to confirm.

The juvenile phenotype of GM2-gangliosidosis, particularly Tay-Sachs disease and Sandhoff disease, has a diagnostic odyssey that is different from the infantile phenotype. What are the most prominent symptoms that bring these children in to clinic and for which a diagnostic journey starts? It almost always involves two things: changes in the ability to ambulate and changes in speech. Note too, that other things can be going on with the child. If you talk to the parents of a child with Tay-Sachs or Sandhoff disease who has the juvenile phenotype, they will say, "yes, my child was very unique and they had all these other things." The one commonality that we have found in the natural history studies is that all the children with the juvenile disease experience a change in ambulation and a change in speech, prior to beginning the diagnostic journey.

In adult-onset or late-onset disease, the most common presenting symptoms also involve ambulation and sometimes speech, but most often ambulation. In particular, it is most often associated with weakness when the patient is climbing stairs or getting up from a sitting position. This is sometimes referred to as a limb-girdle weakness. The patient may report to clinic and say, "I'm getting clumsier. For some reason, I'm having falls. I've never fallen before, and now I'm having frequent falls." On rare occasions, these patients may have onset of new psychological conditions, and these have been found in some cases to be associated with the adult-onset Tay-Sachs disease.

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Disease Progression in Adult -Onset GM2-Gangliosidosis

Loss of anterior horn cell motor neurons		Cerebellar atrophy
Progression of weakness		Progressive dysarthria
Lower extremity weakness	Upper extremity weakness	Cerebellar dysarthria

• Increased difficulties in:
  • Balance and gait
  • Rising from sitting position
  • Jumping
  • Climbing stairs
• Increased falls
  • Inability to lock knees while in extension
• Eventual inability to ambulate independently requiring use of cane, walker, wheelchair
	Most prominent in triceps	Characterized by:
		• Stuttering
		• Explosive quality of speech
		• Spasmodic dysphonia ("breathy" or "strangled" voice quality)
		
		"Superimposed fast-paced speech"

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Regarding these changes seen in adults, it is understood at this time that there is a loss of anterior horn cell motor neurons that compromises the ability to ambulate. It may also cause the knees to lock when in extension, which is in part an explanation for increased falls. Also, cerebellar atrophy has been associated with the stuttering, explosive speech, changes in speech quality, and difficulty in speaking. These patients have a kind of unique pattern of speaking that develops over time. Initially, they may be talking a little more slowly and stuttering in their speech.

The disease progression in the adult patients varies, but the patients will all have progressive difficulties with ambulation and balance. Oftentimes, they develop tremors, dystonias, or acroparesthesias. Some patients suffer from anxiety, depression, and sometimes even more severe psychological illnesses, such as bipolar disease. It is common for these patients to have osteopenia or osteoporosis. This is likely associated in part with the decrease in their ability to exercise with weight-bearing movements and in their ambulation.

What about supportive care? There currently is no licensed therapy for these diseases, but most of these patients undergo a lot of supportive care and that does vary a bit from what country they live in.

Let's discuss the case of a patient with infantile Tay-Sachs disease. At six months of age, he had delayed development and profound hypotonia. By one year of age, he had progressive loss of fine and gross motor skills. By 18 months of age, he developed a severe seizure disorder, and he was experiencing excessive respiratory and salivary secretions that were resulting in recurrent aspiration pneumonias. He had swallowing difficulties that became increasingly more prominent, and a feeding tube had to be placed. By the third year of life, he had severe vision impairment, and he was most likely blind. It was a little bit unclear. He underwent numerous ophthalmologic exams, and it appeared that he might have little vision. However, he was primarily considered to be legally blind. He had urinary retention. He died at 4.5 years of age, secondary to aspiration pneumonia.

This second case is about a child with juvenile Tay-Sachs disease. She suffered from balance difficulties, muscle weakness at the early stages of her disease, worsening fine and gross motor skills, loss of walking ability, hypotonia, dysphasia, dysarthria, dysphagia, swallowing difficulties, and eventually, seizures and excessive respiratory and salivary secretions, again leading to aspiration pneumonias.

In these cases, these children need a lot of supportive care. For example, they will receive antiseizure medications. For secretions, they will oftentimes have manual chest percussion therapy, but in some cases, a more expensive device if their insurance will pay for it. In particular, this device is the high-frequency chest wall oscillation device that is also used by patients with cystic fibrosis to help clear secretion and mucous out of the lungs. We do this for 20 minutes, twice a day. They might need medications to control painful muscle spasms. The patient will also have a feeding tube placed or have the option to have a feeding tube placed. Also, these children often suffer from chronic constipation, neurogenic bladder, both of which involves medications and therapies.

Let's discuss important key concepts from this module. A biochemical and mutation analysis must be done to differentiate Tay-Sachs disease from Sandhoff disease. In addition, the best way to differentiate the phenotypes at this time is to look at when the first prominent and concerning symptoms became apparent. This usually works well for classifying patients or individuals as having infantile phenotype, late-infantile phenotype, juvenile phenotype, or late-onset phenotype.

Mild juvenile and adult-onset variants

Jeanine Jarnes, PharmD: We will be reviewing some case studies of juvenile- and adult-onset variants of GM2-gangliosidoses with this module. The first case involves a female with juvenile Tay-Sachs disease. At age 5 years, she began having balance difficulties and frequent falls. By age 6 years, she had a reduced vocabulary and difficulty saying words. She received a diagnosis of juvenile Tay-Sachs at age 6 years. By 6.5 years of age, she completely lost the ability to ambulate independently. By age 7, she lost the ability to speak altogether. By age 7.5 years, a feeding tube was placed due to swallowing difficulties. At 8 years of age, she had seizure onset with recurrent severe seizures. She died at 10.5 years of age, secondary to complications of aspiration pneumonia.

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Neurodevelopmental testing was done during this child's lifetime. She was involved in the natural history study at the University of Minnesota. A commonly used neurodevelopmental testing tool is the Bayley Scale of Infant and Toddler Development. Many countries have this tool, and that is why it is used most frequently. It also has been available for many decades and is considered to be a strong and robust tool. I want to point out here that no matter how we scored her on this test, whether we used the standardized, raw, or age-equivalent scores, her scores were extremely low. For example, when she was 8.5 years old, the age equivalent score indicated she was performing as if she was less than 16 days old.

This illustrates the difficulty with evaluating a child with Tay-Sachs disease or Sandhoff disease. She appeared to be cognitively aware of many things that were being told to her, but due to the neurological impairment, she could not adequately respond. Therefore, it was difficult to measure changes and to measure her correct status, using the Bayley Scale of Infant and Toddler Development, which includes domains such as cognition, receptive communication, expressive communication, fine motor skills, and gross motor skills. However, we did learn something important in the natural history study. The domains of receptive and expressive communication were the domains that consistently seem to be the domains that we can measure the longest and get the most meaningful measurements from, among all of our children with infantile and juvenile gangliosidosis conditions.

I want to share some cases of late-onset Tay-Sachs disease to help you understand what that might look like in a patient. The first case involves 2 adult male siblings. They were high academic achievers. They were both enrolled in college at the same time and at the same college. One was age 21 years and the other age 23 years. Quite unexpectedly, the older brother had a psychiatric breakdown and subsequent evaluations for nearly 2 years where no one could identify what was going on. Eventually, a brain MRI was done where it was noted that there was cerebellar atrophy. This led to genetic testing and with a diagnosis of adult-onset, or late-onset, Tay-Sachs disease.

His brother who was in college with him did not have any of these symptoms. The brother had reached the same age as the older brother when he had the first prominent symptoms that seemed to be associated with Tay-Sachs disease. The clinicians thought the younger brother might just be a carrier, and they wanted to test him to find out. He was also tested as having late-onset Tay-Sachs disease.

By the time the boys were in their 30s, they were both non-ambulatory, wheelchair-bound, and on feeding tubes. Their disease progressed quite rapidly within the next 10 years.

Let's discuss another case study. This is another case of late-onset Tay-Sachs disease that involves an adult female whose initial presentation was limb-girdle weakness. She was having trouble climbing stairs and getting up and out of chairs. She was a female police officer, active in her career for over 10 years. During routine physical fitness testing, she noticed that she was having trouble doing some of the required number of squats that she used to be able to do exceptionally well for her policewoman qualifications. She eventually sought out a medical evaluation, and she was initially misdiagnosed with multiple sclerosis. Approximately 5 years later, she was finally correctly diagnosed with late-onset Tay-Sachs disease.

Ten years after diagnosis, she had to be on disability. She had to retire from her job early. She needs assistance with ambulating. She usually has to use a scooter to ambulate, but if she is standing temporarily, she has to use a walker. Most recently, she has become very depressed about her condition and has opened up to say she's having suicidal ideologies. This is being addressed medically with her right now.

Let's discuss another case of late-onset Tay-Sachs disease. This also involves an adult female who, during childhood, seemed perfectly healthy. The one thing she noted during her history is that she tended to fall off her bicycle more frequently than her other girlfriends, but she wasn't sure if that was related. She started college. During her first year of college, at 19 years of age, she lived on the campus and suddenly began to have falls while she was walking from classroom to classroom on campus. She had never experienced trouble with falling down in the past, and she said her legs just gave out from underneath her.

She eventually sought medical evaluations. She also was initially misdiagnosed with multiple sclerosis and then amyotrophic lateral sclerosis. She was finally diagnosed with late-onset Tay-Sachs disease approximately 12 years after she sought medical attention.

Let's discuss common misdiagnoses and red flags. These cases illustrate a variety of initial presenting symptoms that may lead a caregiver, patient, or clinician to seek a medical diagnosis for someone who might have a GM2-gangliosidosis condition. It can be seen by these cases that it is not uncommon for an individual with a juvenile or a late-onset form of the disease, that is, the adult form, to be initially misdiagnosed.

Diagnosis differentials for the juvenile GM2-gangliosidosis condition include Canavan disease, ceroid lipofuscinoses, galactosialidosis, juvenile Niemann-Pick disease, Gaucher disease type III, juvenile GM1-gangliosidosis, and spinocerebellar ataxia.

Now, for the adult late-onset Tay-Sachs disease or Sandhoff disease, motor axonal neuropathy may lead to a diagnosis of Kennedy's disease or amyotrophic lateral sclerosis. Spinal muscular atrophy may lead to a diagnosis of Kugelberg-Welander disease or SMA type IV. These diseases that are classified as spinal muscular atrophy diseases are more axonal neuropathy, but patients have also been diagnosed with multiple sclerosis and Guillain-Barré syndrome.

Three key concepts come out of this discussion. One, the time of the onset of the first symptoms until an accurate diagnosis is made continues to be unusually long. Two, the consequence of this delay in diagnosis is that it delays initiation of appropriate, supportive medical care, as well as limits access to clinical trials and other potentially approved therapies as they evolve. Third, it's up to clinicians to recognize the early symptoms of GM2-gangliosidosis and initiate diagnostic testing immediately to ultimately advance the therapy for the patient.

Emerging treatments for TSD and SD

Chester B. Whitley, MD, PhD: Roscoe Brady at the National Institutes of Health was a pioneer in developing enzyme replacement therapy for many lysosomal conditions. In the late 1960s, Elizabeth Neufeld and other colleagues at NIH and globally were very excited about the observation that 1 cultured cell line from an individual seemed to cross-correct metabolism when it was co-cultivated with a different patient's cells. This cross-correction was eventually hypothesized to be due to a corrective factor that was transmitted from 1 cell through the tissue culture media to another cell. That cross-correction became a real key to developing enzyme replacement therapies.

It's based on the concept that enzymes are secreted from the lysosomes of 1 cell and can be picked up by an adjacent cell or even an enzyme that is transmitted through the bloodstream to an entirely different organ. Roscoe flew to Minneapolis with purified human hexosaminidase from urine for IV administration to an infant with Sandhoff disease. That first enzyme replacement therapy was done by him and colleagues at the University of Minnesota in 1970. We've been working on this concept for quite a long time. Now, 5 decades later, we're making progress. This article was initially titled, "Treatment of Tay-Sachs disease." Now, we know this was actually a patient with Sandhoff disease, a different form of hexosaminidase deficiency.

The challenges in treatment, particularly for the gangliosidoses, revolve around the concept of the blood-brain barrier. Treating the brain, the central nervous system, is very limited by large drugs and proteins. Also, we're dealing with small populations. When we have a good candidate therapy, we have to go from tissue culture to animals, and then we have very few patients to test this on. Finally, we don't have a good understanding of the natural history of the disease. We would hate to do controlled, double-blind, placebo studies where 1 group gets the drug and the other group doesn't. But despite the challenges of these concepts, they are being done, but we could do it better if we have a natural history study against which to compare the treated patient, therefore eliminating the use of placebos.

Let's talk about crossing the blood-brain barrier. Why would we even hope to give an enzyme in the blood and get it across the capillary endothelial cell where the blood-brain barrier is? We do know that some molecules which are very small, say 400 daltons or less, can get through the blood-brain barrier. Those molecules which are lipid-soluble also make it across the blood-brain barrier more readily. Also, if the substrate or the drug does not come out of the brain by active efflux, then we have a better chance of getting the drug into the brain and having it stay there. Those are aspects of the blood-brain barrier which have been faced in experimental studies.

Consider the size of a molecule as one of the characteristics that determines whether it will be transported across the blood-brain barrier. For example, beta-hexosaminidase A enzyme is a very large molecule, at least 150,000 daltons. This size of an enzyme replacement protein would not be able to cross the blood-brain barrier. This large size of beta-hexosaminidase is in marked contrast to smaller drug molecules, such as miglustat, venglustat, acetyl-leucine, and AZ-3102, which are all 400 daltons or smaller. They cross the blood-brain barrier relatively easier in comparison.

Other ways have been taken into consideration in delivering enzyme to the brain. One is through this kind of device here, typified by the Ommaya reservoir. You can see that there is some device that infuses the enzyme through a line. That line goes through the skull, the dura membranes, the parenchyma of the brain itself and into the cerebral spinal fluid. One lysosomal enzyme has been FDA-approved by this form of administration.

How about GM2? We have tried enzyme replacement therapies. Gene therapies are being explored. Small molecular pharmacologic chaperones are being studied. Hematopoietic stem cell has been investigated, as well as substrate reduction therapies, that is, not trying to get the enzyme in to digest it, but minimizing the amount of enzyme substrate that is made.

A clinical trial of AXO-AAV-GM2 is currently underway. Results are not available. It's being given by AAV vectors through 2 routes, one which is given to the thalamic part of the brain and another by intracisternal/intrathecal injection, 2 very innovative routes of administration to the central nervous system.

Gene therapy has an advantage because there's only 1 dose needed typically in most schema, and it's good for the entire lifetime of the patient, if things go as designed. If we're giving enzyme or AAV vectors, the cerebrospinal fluid is a good place for crossing the blood-brain barrier directly. Various forms of gene therapy have been given intranasally, directly into the parenchyma of the brain by a needle injected through the skull, into the intracerebral ventricular spaces, the ventricles and, more recently, through a little gap here in the back of the neck between the vertebral bodies and the skull through the intracisterna magna route. People have even explored in animals a subpial administration lower down in the cervical spine. A conventional lumbar spinal tap has been studied. Gene therapy has also been given intravenously, by a special alteration of the enzyme so that it is more prone to cross the blood-brain barrier.

Another kind of gene therapy we call gene-editing and work on in our own lab. We're pursuing something called the PS gene-editing system to treat gangliosidoses. We were able to use an AAV vector to insert a piece of DNA. This DNA carries key elements, such as the lysosomal enzyme, the cDNA which actually is promoter-less, and also the CRISPR Cas9 system. The CRISPR Cas9 system is targeted first by administration through an AAV and into the blood. Most of it moves through normal circulation, going to hepatocytes, that is, the liver cells, and then, with specific affinity for the AAV, a surface molecule goes to hepatocytes and through hepatocyte-specific promoters, all of which will be expressed only in the hepatocyte. There, CRISPR Cas9 inserts into intron-1 of the albumin gene. If there's successful insertion, then the liver's normal albumin production is converted to making that lysosomal enzyme. The liver becomes a factory, making the lysosomal enzyme in the body.

What's been very surprising, either giving normal lysosomal enzyme DNA sequence or even modified DNA sequence to cross the blood-brain barrier, we're able to see not only enzyme in the blood made by the hepatocytes, but we're actually able to see metabolic and histologic and behavioral evidence of brain therapy. Look forward to the PS gene-editing system as one that may go into clinical trials.

Hematopoietic stem cell transplant has become the model for many kinds of lysosomal disease therapies. It started in the 1980s when Jack Hobbs in London published that he could cure a mucopolysaccharidosis disease called Hurler syndrome. There was great question about that methodology simply because we know that a large enzyme is too big to go from the bone marrow through the blood and cross the blood-brain barrier. Larger studies were conducted. I have personal involvement with that. In 1983, we began a clinical trial to see if Dr. Hobbs was correct. It turns out he was correct. The transplanted stem cells in the marrow go from the peripheral blood into the brain, probably not through direct enzyme transplant, but through diapedesis using monocyte cells, into the central nervous system. Nevertheless, hematopoietic stem cell transplant has been tried for a number of patients with gangliosidoses, and we have not seen the great neurologic outcome that we did see with Hurler syndrome. While hematopoietic stem cell transplantation is the standard of care for Hurler syndrome, it has been proven not to be successful for Tay-Sachs disease, and that's very disappointing. Other investigational therapies have been considered. Dr. Jarnes will talk about pharmacologic chaperones.

Jeanine Jarnes, PharmD: There are a number of clinical trials that have evaluated the efficacy and safety of small molecule therapies. These include therapies that work as pharmacologic chaperones, as well as therapies that work as substrate reducing agents. One of the agents that is just entering clinical trials is AZ-3102. This works as a substrate reducing therapy and has a dual action both inside and outside the lysosomelysosome, which makes it a more novel product.

Drugs, such as venglustat and miglustat, are substrate reducing therapies. There's another investigational agent called IB1001. It's an enantiomer of N-Acetyl-L-Leucine that was originally available for 40 years over the counter. They have isolated the enantiomer and are thinking that it might help with cerebellar ataxia in patients with adult-onset Tay-Sachs disease and adult-onset Sandhoff disease.

Let's talk about pharmacologic chaperones. These are drugs that bind to the defective enzyme in a patient with a lysosomal disease, such as Tay-Sachs disease. In this case, we would want it to bind to beta-hexosaminidase. They bind to the enzyme to make it longer and more active. A longer duration of activity will ideally increase the amount of activity the enzyme has. The pharmacologic chaperones change the folding of the enzyme in the cell so that it can work more productively.

One pharmacologic chaperone includes an agent that was repurposed, that is, an anti-infective agent called pyrimethamine. Pyrimethamine has been available for many decades. It was found that pyrimethamine binds to beta-hexosaminidase and increases the activity of the enzyme in vitro.

This drug has been tried in patients with late-onset Tay-Sachs disease primarily. However, the observed increase in enzyme activity of the beta-hexosaminidase appears to be transient and does not change the course of the disease. At this time, this agent has been disappointing. Chaperones continue to be looked at. There is a pharmacologic chaperone that does have confirmed efficacy and is licensed for a different lysosomal disease. It is a valid concept that continues to be looked at.

What about substrate reducing therapy? Substrate reducing therapies bind within a metabolic pathway and inhibit a step of the pathway. What these therapies are doing is-in contrast to gene therapy where you're trying to introduce the enzyme that the patient is deficient in or intravenous enzyme where you're giving enzyme directly to the patient intravenously or even the pharmacologic chaperone where you are increasing the activity of the defective enzyme-these substrate reducing therapies do not affect the amount or activity of enzyme. Rather, they are reducing the amount of toxic substrate that is made. They have a completely different mechanism of action. The patient still has zero enzyme or very deficient enzyme, and that's why they have the disease. Because of that deficiency in enzyme, the substrate is accumulating to toxic levels. What these substrate reducing therapies do is they go into the metabolic pathway and bind at certain strategic locations. This results in a decrease in the amount of substrate formed.

In the case of Tay-Sachs disease and Sandhoff disease, 1 of the substrate reducing therapies that has been tried is miglustat. It's licensed for 2 different lysosomal diseases, Gaucher disease type 1 and Niemann-Pick disease type C, both of which are involved in the same metabolic pathway as Tay-Sachs and Sandhoff disease. This drug has been tested to see if it will reduce the amount of ganglioside that is produced from that pathway and thereby, decrease the disease burden.

Thus far, trials of this drug in infantile-, juvenile-, and late-onset phenotypes show that it's safe and, in most cases, well-tolerated, but we are not seeing a dramatic change in the course of the disease. It crosses the blood-brain barrier, so we are talking about small molecules here. The prior pharmacologic chaperone I just spoke about also crosses the blood-brain barrier.

There was a clinical trial called Syner-G that looked at miglustat with a ketogenic diet, that is, essentially no carbohydrates in the diet, in patients with infantile- and juvenile-onset gangliosidosis conditions, both GM1-gangliosidosis and GM2-gangliosidosis. The treatment group, albeit very small in number of patients, appeared to survive for a longer period. All the patients that were in this treatment group eventually died from the disease and, in many cases, their duration of life was similar to what we would see in untreated patient. We were not able to draw any conclusion there, but the concept may be applicable in future applications.

Other small molecules being investigated include acetyl-leucine, mentioned earlier, that was historically an over-the-counter agent used for dizziness and ataxia. It may help patients with Sandhoff disease and Tay-Sachs disease with their ambulation difficulties. This drug is just recently in clinical trials. We do not have a summary yet of the outcomes.

There's another drug called AZ-3102 which is getting ready to enter clinical trials. I mentioned this one earlier also. Again, it crosses the blood-brain barrier, so that's good. It was shown in a Sandhoff mouse model to improve survival and behavioral activity assessments. It also showed a reduction in tremor in the Niemann-Pick disease type C mouse model. Further, it has a unique mechanism of action. It is a substrate reducing agent, but it inhibits 2 processes, one within the lysosome and one outside the lysosome. The manufacturer hypothesizes that this might make it a more promising agent when compared to agents such as miglustat. It also has no dietary restrictions that we encounter with miglustat.

Lastly, there is a drug called venglustat. This is a substrate reducing therapy. This drug is the furthest along in clinical trials, and a larger number of patients have tried it. It is well-tolerated. There have been no safety concerns, and it crosses the blood-brain barrier. It has no dietary restrictions associated with it. This is potentially the most promising agent that we know of currently, due to the amount of data we have on it. We need to watch the research on this drug as it enters into new trials to see if it might be a good candidate for our patients with Tay-Sachs disease and Sandhoff disease. Currently, it has already been tried in patients with adult, or late-onset, Tay-Sachs disease, as well as in some other groups of children that have gangliosidosis conditions. This trial is called the AMETHIST trial. The data from a phase 3 trial is being evaluated. It is a multinational, randomized, double-blind, placebo-controlled trial in patients with GM2-gangliosidosis.

Chester B. Whitley, MD, PhD: From this discussion, there are a few key concepts. Over the past 50 years, potential therapeutic agents have advanced clinical trials for treatment of patients with Tay-Sachs disease and Sandhoff disease. Despite more than 5 decades of work, there is, however, no approved or generally accepted treatment for these conditions. Primarily because of the central nervous system involvement, the gangliosidoses are a very difficult challenge regarding treatment. Nevertheless, diligence and recent innovations are offering promise for safe and effective treatments in the future. Thus, it's important to identify and sustain such patients, offer palliative and symptomatic care, and involve them in natural history studies that enable the development of these effective systemic treatments.

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