Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/lysosomal-storage-disorders-recognizing-and-addressing-a-group-of-rare-conditions/16047/

Released: 09/28/2023
Valid until: 12/12/2023
Time needed to complete: 60 Minutes

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Lysosomal Storage Disorders: Recognizing and Addressing a Group of Rare Conditions

Announcer Open:
Welcome to CME on ReachMD. This activity, titled *"Lysosomal Storage Disorders: Recognizing and Addressing a Group of Rare Conditions"* is provided by Partners for Advancing Clinical Education (PACE) in partnership with Smart Patients and is supported by an educational grant from Sanofi.

Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Nurse Viall:
Hello and welcome to the Practicing Clinicians' Exchange CE/CME e-course on Lysosomal Storage Disorders: Recognizing and Addressing a Group of Rare Conditions. This program is supported by an educational grant from Sanofi. I am Sarah Viall, I am a Nurse Practitioner at OHSU in Portland, Oregon, and I'm pleased to be joined by Dr. Neal Weinreb, a Voluntary Associate Professor in Human Genetic at the University of Miami School of Medicine in Miami, Florida.

Welcome, Dr. Weinreb.

Dr. Weinreb:
It's a pleasure to be here, Sarah.

Nurse Viall:
Here are our disclosures. After completing this activity our learners should be better able to identify signs, symptoms, and biomarkers associated with lysosomal storage disorders, or LSDs, incorporate appropriate diagnostic testing and other considerations for referral of patients suspected of having LSDs, and describe principles of management and available options as part of patient counselling. Before we begin, I want to point out that throughout this program there are going to be multiple-choice questions, some of which are the same as the pretest questions you just completed. These questions will count as your post-test for CME credit, and they also help us determine the value of this educational activity.

And now, here is Dr. Weinreb to get us started with an overview of LSDs.

Dr. Weinreb:
Thank you again, Sarah. The lysosomal storage diseases are very rare disorders. Some of them are ultra-rare, but altogether they actually are fairly common in the general population. The estimated incidences somewhere between 1 and 5,000 to 7,500 live births. These diseases are prodiem and they affect multiple organs and systems, visceral, ocular and neurologic scale and that list could certainly be extended.

I think, as diseases, they are quite heterogeneous. What they have in common is that they are all inherited and progressive over the course of variable lifespan, and they share tendencies to manifest as neurologic diseases early in life, although there are some exceptions. Again, as a general rule, symptoms that present during childhood suggest a more severe phenotype of the disease.

So, let's just briefly mention what a lysosome is. The lysosomes are organelles, which are vital for breaking down and recycling cellular

material for new synthesis and new use. In the lysosomal storage diseases, certain toxic substrates tend to build up inside the lysosomes. In most cases, this storage is due to deficiencies in lysosomal enzymes, which prevent the breakdown of the more complex substances, which are then metabolized to the substrates, which are stored. There are some storage diseases in which there are transport enzymes involved, which fail to remove the substrates once they are broken down. One other point to remember on this slide is that the lysosomal storage diseases don't operate in a vacuum, and even on a cellular level, part of their pathology is related to the effect of either storage, or lysosomal dysfunction on other cellular organelles including for example, endoplasmic reticulum, mitochondria, Golgi apparatus, and even sometimes the nucleus. And as a result of this interplay, lysosomal storage diseases often do share some pathophysiologic pathways with several adult-onset neurodegenerative disorders such as Parkinson's disease and Alzheimer's disease, and for that reason, understanding the LSDs is also opening a window, in many cases, to starting to be able to understand these many much more common degenerative diseases that we see in the population.

We classify lysosomal storage diseases generally by the nature of the accumulated substrate. So, for example, sphingolipidosis refers to accumulation of sphingolipids, oligosaccharidosis to oligosaccharides such as glycogen, and mucopolysaccharidosis refers to diseases in which there's storage of substances called glycosaminoglycans which are commonly found in all cells, but most commonly in connective tissue. They sometimes can be classified according to the underlying disease mechanism or according to the nature of the defective enzyme, as I mentioned, most are catalytic. There are some LSDs which involve transport enzymes. And then, there are subgroups which are further divided by age, acuity of onset, and it's worth remembering that with the exception of mucopolysaccharides, that storage disorder Hunter syndrome, and the sphingolipid storage disorder Fabry disease, also which are inherited as X-linked recessive disorders. All the others are autosomal recessive hereditary disorders.

There are certain LSDs which are particularly prevalent within the family of the LSDs. Some of them are found in specific ethnic populations, most are pan ethnic in nature. So, examples are, Gaucher disease, which exists in 2 major forms, what we call non-neuronopathic disease meaning the central nervous system is not usually affected early in life, although there is evidence now that patients with this disease may have an increased risk for developing Parkinsonism as they become elder adults. Symptoms associated with this disease in the type 1 form are systemic enlargement of the liver, spleen, bruising usually associated with decreased platelet counts, as you can see that's hematologic involvement, bone involvement. We go over this again in a little bit more detail later, so I'm not going to extend myself here.

The type 2 and type 3 diseases are neuronopathic. There's early involvement of the central nervous system. With the type 2 infants, usually failing to survive longer than 3 on average, maybe 4 years with supportive therapy. They do have blood abnormalities and enlargement of the liver and spleen, but they have major neurological symptoms as well as certain types of skin abnormalities. The type 3 disease is less acute, it sometimes can present in childhood. It can be a very serious disease in children and adolescents. There are classic eye muscle movement abnormalities associated with this disease, which help to define its presence and separate it from type 1 disease. There's a variable amount of neurodegeneration and cognitive impairment, and surprisingly some individuals may have no abnormalities beyond the eye muscle movement abnormalities, and such individuals can sometimes live now well into adulthood, or even late adulthood. There are characteristic muscle spasms, myoclonus, and unlike the type 1 disease where lung infiltration and lymphadenopathy are very unusual, this is found in patients with type 3 disease. And there are overlaps, like any classification one has to be aware that there can be some overlaps between type 1 and type 3 discerning them may be sometimes different, and even more significantly between the type 2 and the type 3 where there's sort of intermediate phenotype. I think the important message to remember about this is that when we talk about treatment, that treatment decisions probably should not be automatically made on the basis of classification.

Another, and perhaps the most prevalent of the lysosomal storage diseases, is Fabry disease, which again, I will discuss in further detail later on, but I think that one of the points to remember here, as I mentioned, this is a X-linked hereditary disease. Sometimes in earlier education we've been taught that women who are in families with X-linked heredity are carriers of the disease and asymptomatic. We now know that that is not true, and that's particularly not true in Fabry disease where both males as well as females can be symptomatic and affected, and actually can have reduced life expectancy. Usually, the onset in women is later than in male children and in men, but again, I've seen a patient with – a woman with Fabry disease who already had renal failure by the time she was 20 years old. There are, again, some common symptoms which I think we will review later on.

Another disorder is called acid sphingomyelinase deficiency. This again comes in 3 categories, only 2 of which are actually linked in a biochemical fashion, and that's type A and type B. These are associated with accumulation of a sphingolipid called sphingomyelin. The type A disease is again, a very aggressive and devastating disorder with both enlargements in the liver and severe neurological symptoms, including a cherry red spot, which some of you with genetic background may identify with Tay-Sachs disease or gangliosidosis, which are another of the LSDs which we are not going to have time to discuss here, and even the neurological course is very reminiscent of Tay-Sachs disease.

Of these diseases, only the type A, the very aggressive type is typically found in Ashkenazi Jews, whereas the type B disease, which presents with a generally later onset with enlargement to the liver, learning disabilities, psychiatric problems, lung involvement, and a tendency to develop atherosclerosis, increased LDL, and coronary artery disease through concurrent storage of cholesterol. This disease can be found throughout the populations and it's very variable as well. Its onset can at some times be confused with type 1 Gaucher disease. Type C is called type C Niemann-Pick disease. A different enzyme is involved, actually a transport enzyme, and here the presentation is primarily neurological symptoms such as you see on this slide.

Among others, there's a disorder called metachromatic leukodystrophy, which usually presents in infancy, but is sometimes seen only in childhood and adolescence. Again, it develops its neurological manifestations are the primary ones due to accumulation of a sphingolipid called a sulfatide, and specific enzyme deficiency, and an enzyme called arylsulfatase. There are a whole variety of mucopolysaccharide storage disorders. I mentioned the type 1, which is, again, the second that is inherited and X-linked fashion. I think they're up to type 7 already and type 3 has 4 subcategories. You can see that this classification of LSDs is quite complicated. The Hallmark of this contrasts some of the others is major skeletal and joint deformities as well as facial abnormalities, osteoarthritis, growth delay and short stature, and again, unfortunately, usually a shortened lifespan, although, again, therapy is starting to be available.

And finally on this slide, one type of glycogen storage disease called Pompe disease is due to a lysosomal storage disorder with a deficiency in alpha-glucosidase, an enzyme which cuts off carbohydrates from the very long carbohydrate chains of glycogen. Again, there are 2 major forms of this disease, the infantile form, a very aggressive associated with cardiomyopathy as well as rapid muscle weakness and without treatment it can be rapidly fatal. Fortunately, there is a very effective treatment currently available. And then there's a late-onset form which does not present until much later in life, but with slowly progressive muscle weakness and respiratory insufficiency due to that muscle weakness of respiratory muscles. Again, there are many different glycogen storage diseases with some of the similar symptoms, different hereditary patterns, and this will lead to some degree of confusion.

Nurse Viall:
Here's a post-test question. Which of the following is consistent with all LSDs. Number 1, they arise spontaneously and are progressive. Number 2, they all have their onset in early childhood. Number 3, they are inherited and progressive. Or number 4, they are inherited but they do not progress once a patient has reached adulthood. The answer is number 3 – they are inherited and progressive.

And now I'll turn it back over to Dr. Weinreb.

Dr. Weinreb:
Because these disorders are progressive, it would make sense that the outcomes are better when diagnosis occurs early in life and with treatment, if applicable, can be started early before irreversible organ damage. One of the real problems with early diagnosis is that many clinicians are unfamiliar with LSDs, many have never actually encountered a patient with such a disorder in their professional careers, and the manifestations are so heterogeneous as we sort of touched on before. So, it's not unusual that patients can go for years without an accurate diagnosis and consequently, without appropriate treatment being started, and sometimes patients can be misdiagnosed with other disorders, which leads to inappropriate referrals, unnecessary tests, and sometimes even incorrect therapy. And when untreated, the LSDs can cause irreversible damage such as chronic bone pain, growth failure, organ failure, mental deterioration, and even premature death.

Nurse Viall:
Now I want to introduce our patient, Gary. He is a 28-year-old single white man who works for an advertising firm, and he has been having increasingly frequent symptoms since childhood, which include burning tingling pain in his feet and hands, tinnitus, fatigue, heat intolerance, decreased sweating, abdominal cramping and bowel irregularity. He thought his GI symptoms were inconsequential at first, but they have persisted as did his other symptoms. And when he was a child, he remembers his complaints were often downplayed. He's consulted several clinicians, he's undergone numerous tests, symptomatic treatment attempts, and has had no symptoms resolution, so he is very frustrated.

Of all the symptoms Gary reported, which combination is most suggestive of a specific LSD? Number 1, acroparesthesias, heat intolerance, and hypo hidrosis. Number 2, fatigue and GI problems. Number 3, heat intolerance and tinnitus. And number 4, tinnitus. And in this case, it's number 1, acroparesthesias, heat intolerance, and hypo hidrosis.

Dr. Weinreb:
So, at this point I think it would be useful to review some of the common signs and symptoms of LSDs, although as you'll remember, there is such a heterogeneity that nothing here is necessarily specific for any single disorder. So, the majority of LSDs do have some neurologic manifestations, which can range anywhere from intellectual impairment to psychiatric problems. And then, some specific manifestations such as epilepsy, myoclonus, hypotonia, dysphagia, sometimes spasticity, and even peripheral neuropathy. On the other hand, the non-neurologic symptoms include abnormal facial features, bone and joint abnormalities including carpal tunnel syndrome,

vision and hearing impairment, heart problems, pulmonary problems, GI problems, hematologic problems including anemia, thrombocytopenia, and sometimes skin abnormalities.

So, just let's look at 2 of the more common LSDs, Gauche disease. In the patient we're presenting here is the one that does not have neurologic involvement. But you'll note that the major manifestations here include enlargement of the liver and spleen, and abnormalities involving the blood counts and subsequent anemia, low platelet counts sometimes associated with bleeding. And then, a large number of manifestations related to skeletal abnormalities, which include tendency to develop fractures, joint collapse due to necrosis of bone or osteonecrosis, even more commonly, osteopenia or decreased bone mineral density with fragility of the bone, which is what leads to the fractures, and an infiltration of the bone marrow, which has an effect on the actual skeletal integrity itself, as well as on the manufacture of blood cells, consequently contributing to the abnormalities there.

So, now let's, in contrast, turn to a different disease, Fabry disease. Well, you see that many of the manifestations are quite different. In Fabry disease, early on, particularly in what we call a classic male patient with Fabry disease, some of the manifestations that can be seen relatively early in life, even in childhood and in adolescence, include a specific type of skin rash called angiokeratomas, hearing loss, tinnitus, and with regards to the eye, there's a classic abnormality of the cornea, which can be detected by ophthalmologists and curiously is not usually associated with visual abnormalities. But sometimes ophthalmologists are actually the ones who make the diagnosis. Some patients do have lung involvement. More commonly and later in life, cardiac involvement, which can include heart failure, tendency to develop very troublesome arrhythmias. Some patients, even early in life, may develop strokes, but otherwise also have white matter involvement which can be seen on MRIs. Some patients classically do have neuropathic pain due to involvement of the peripheral nervous system. And perhaps the most familiar later-onset manifestation is kidney failure due to abnormalities of the blood vessels within the kidneys.

Nurse Viall:
Back to our patient, Gary. Gary reports he has no siblings. He was told that his maternal grandmother had some symptoms similar to his and died in her 40s with a diagnosis of heart disease. Gary is very concerned that the same fate will befall him, and he has not been told that any family member ever received a diagnosis of an LSD.

Back to Dr. Weinreb.

Dr. Weinreb:
Family history is very important no matter what type of medicine one is practicing, and unfortunately, it tends to be neglected. But with regards to hereditary disorders, it's absolutely critical as it may give you a tipoff that a lysosomal storage disease is likely to be present.

Now, sometimes in the presence of puzzling signs and symptoms and in the absence of a conclusive diagnosis of an acquired disease, this would again be a reason to think about a potential hereditary disease, not only in children but also in adults because again, I think some clinicians generally think of hereditary disorders as primarily effecting children rather than later on in life in adults. The diagnosis can be confounded by this heterogeneity of symptoms and should one have clinical suspicion, it's probably reasonable to order prompt testing, especially since much of the testing can be done with blood samples rather than through invasive diagnostic procedures. And once an index case is identified, it certainly very, very wise to look for involvement of siblings and possibly other relatives as well, and offer evaluation as well as genetic counseling, which is extremely important regarding future reproductive options for individuals who are going to live into age when they can have children.

The choice of tests ordered depends on which LSD is suspected, and when there are overlapping signs and symptoms, sometimes doing a panel-type of testing such as, for example, 2 types of enzyme testing for patients for who are suspected of having either type 1 Gaucher disease or acid sphingomyelinase deficiency type B. And that certainly would pertain to individuals who have mucopolysaccharidoses, which are suspected. The types of enzyme assays usually traditionally, these disorders are diagnosed by showing deficiency of the catalytic enzyme in blood testing, which can be done on different substances, urine, blood, cerebrospinal fluid. Currently, it's become quite popular to do this type of testing on dry blood spots, which have the advantage of being easily obtained, preserve well, and easily mail perhaps to a central laboratory, which may have to do the types of specialized testing which are required. And of course, once a diagnosis is made, or sometimes even when it's suspected, for example in women who are Fabry heterozygotes where the enzyme deficiency tests are not specific, genetic testing to detect the pathologic mutations is also necessary.

Nurse Viall:
Back to Gary. His physical examination was not indicative of a specific diagnosis, so there were no angiokeratomas or corneal deposits, which if present are highly suggestive, but not pathogenic. He undergoes blood and urine biomarker testing, and lyso-GB3 is revealed. So, which LSD with the presence of lyso-GB3 would prompt you to investigate further for Gary's diagnosis. Number 1, Fabry disease. Number 2, Gaucher disease. Number 3, Neimann-Pick disease. And number 4, Pompe disease. The answer is number 1, Fabry

disease.

Dr. Weinreb?

Dr. Weinreb:
Biomarkers are useful throughout clinical medicine. We usually refer to them as being surrogates because they are not oftentimes directly associated with the primary pathophysiology of the disease, but they sort of are downstream affects which can then be identified and suggestive of either the severity of the disease, the response to therapy, the progress of the disease. However, there are some primary biomarkers which are specific for enzymes associated with different lysosomal disorders diseases. For example, lyso-GB1 is a highly specific biomarker for Gaucher disease because it is actually a substrate which is accumulated within the disease. Lyso-GB3 is another specific biomarker, but for Fabry disease, and this correlates with the presence and possibly, with the severity of Fabry disease. Oligosaccharides are biomarkers for Pompe disease, in which the accumulating substrate is glycogen which is broken down to various oligosaccharides by the glucosidase enzyme, which is defective in that disease. To date, most biomarkers are insufficiently sensitive or specific to be used as definitive diagnosis for most other lysosomal storage diseases.

Now, also, lysosomal storage diseases share symptoms with other much more common disorders, including tendency to infections, a predisposition in some cases to malignancies. Most difficult, psychiatric disorders, which can manifest relatively early in life, but in some of the late-onset disorders, even later in life and can certainly be very confounding in terms of making a diagnosis. And then there are many other neuromuscular disorders which are not due to LSDs which need to be ruled out. So, by and large the eventual diagnosis is based on combined clinical observations requiring astute and observant clinicians, as well as a panel of test results, which may not only be blood results, but sometimes can be imaging results as well.

Nurse Viall:
Which of the following is an appropriate biomarker to help determine the presence of Gaucher disease? Number 1, alpha-L-iduronidase. Number 2, lyso-GB1. Number 3, lyso-GB3. Number 4, oligosaccharides. And the answer is lyso-GB1.

Back to Dr. Weinreb. Can you talk to us about treatment?

Dr. Weinreb:
Okay. Yes. In some respects, this is perhaps the most important subject because up until about 30 years ago, there was no treatment for any of these disorders, and consequently, they were associated with very, very substantial morbidity and early mortality. So, as a general rule, the goals for treating LSDs first of all are directed at trying to reduce the accumulated substrate in the lysosomes, either by increasing the degradation of the substrate, or by decreasing the synthesis of the substrate, and in that way restoring physiologic balance and preventing the downstream toxicity that are caused by the substrate accumulation. If possible, it would be fantastic if one could actually reverse symptoms that are present and restore the patient to perfectly normal function.

Unfortunately, sometimes that's not possible because oftentimes by the time diagnosis is made, irreversible manifestations are present. So, in that circumstance at least the goal is to reduce or at the very least stabilize and prevent progression of the disease. We hope to be able to prevent or minimize long-term complications which is something which is still an area of active investigation as some of these may not develop until much later in life and may not even be recognized yet. We may still be in the process of learning about some of these. As with most diseases, certainly we have a goal of improving patient quality of life, mobility and functioning, mental health and we are very interested now in terms of pursuing this goal and getting patient-reported outcomes to the physicians or to the various studies that are being done of these disorders and involving the patient themselves directly in their management and in their assessment of their disease. Again, where possible, we aim to achieve normal life expectancy. I mentioned improved family quality of life because when a child particularly is born with such a disorder, or even adolescent or young adult, caring that individual presents a particular burden to the family and has ramifications as far as siblings are concerned. So, again, addressing all of these issues is an important part of management. And finally, treatment at this time is quite expensive, so it continues to be a goal to attain some degree of cost-effectiveness, particularly as some individuals may require treatment for their entire life.

Because these diseases are so complicated from a clinical viewpoint, a multi-member team effort is usually required and it's very good to be able to have resources such as a center which specializes in these disorders as a consulting resource for the primary physician who is taking care of the patient. What's depicted here is just a short representation of the numbers of subspecialists who need to be integrated into the care of the patient in order to provide them with the best possible care that they can have, but again, I think it's very important that the primary care physician – and that individual may not always be a physician, it may be a Nurse Practitioner or a Physician Assistant, or even sometimes a highly trained and skilled nurse who is sort of the coordinator for the care. But again, this type of team effort is definitely extremely important for optimal management.

So, we can sort of look at 3 different general types of treatment categories. There are the specific treatments which are directly

addressing the enzyme deficiencies. There needs to be symptomatic treatment addressed to major manifestations of the disease which are actually causing symptoms. But on top of that, sometimes we need to aim at a more less specific supportive type of care whether it be pain management, psychological support, other physical therapy, occupational therapy, so forth. So again, treatments need to be not just specific, one needs to address all aspects of discomfort of the patient.

Nurse Viall:
Returning to Gary, he has not been diagnosed with Fabry disease based on that lyso-GB3. None of his baseline values, like renal function, are yet troublesome. So, you've arranged genetic counseling for him, and treatment is going to be initiated. He asks what treatment he is most likely to receive. Which types of treatment are currently commercially available for Gary? Number 1, enzyme replacement therapy, or ERT, and substrate reduction therapy, or SRT. Number 2, ERT and pharmacological chaperone therapy, or PCT. Number 3, SRT and PCT. Number 4, ERT and gene therapy. And the answer is enzyme replacement therapy, or ERT, and pharmacological chaperone therapy, or chaperone therapy.

Okay. Back to Dr. Weinreb.

Dr. Weinreb:
Okay. So, my task at this point is to help you be able to answer that question as well as understand the treatment options for patients with LSDs, and this slide, which I don't want to spend too much time on, but it does cover the major therapeutic approaches which are used in 2022 for addressing these diseases. Some of these are already FDA approved and commercially available, some of them are still within the experimental phase of development.

So, enzyme replacement therapy is directed at infusing a pharmacologic enzyme which has normal enzyme activity which is able to be transported into the lysosome usually with a specific receptor. In most cases, the mannose-6-phosphate receptor like in the case of Gaucher disease. These different pharmacologic enzymes into the lysosome itself, they can sort of take the place of the mutant enzymes which oftentimes don't even get there in sufficient amounts and hydrolyze the substrates that are required.

The substrate reduction therapy has a somewhat different approach. There what we try to do is use certain small molecules, primarily which can usually be given by mouth, to inhibit the synthesis of the molecule which can't be hydrolyzed by the defective enzyme, and in so doing, one can actually decrease the burden of the substrate and allow, in some cases, the deficient enzyme to at least attempt to catch up with the need for breakdown of substrate.

Another approach which has been taken, which is sort of an attempt to restore enzyme activity within the body is to do a stem cell, or what we used to call a bone marrow transplant, in the hopes that by administering what would primarily be donated by an HLA identical individual who does not have the disease. Normal blood cells which can then synthesize and then export the enzyme to the cells where it's required. That has not proven to be very commonly used for lysosomal storage disorders partly because those blood cells usually don't get across the blood-brain barrier, nor do the enzymes if they're made, and secondly, the treatment itself still has significant toxicity, although it certainly much more feasible now than it was even 10 years ago.

Another approach is to attempt to administer a small molecule with generally oral drug which can attach to the mutant enzyme while it's still in the enzyme factory in the cell, the enzyme in the endoplasmic reticulum, and actually change its confirmation so that it can go from an inactive enzyme to an active enzyme which can then be transported or trafficked successfully to the lysosome where it will then be active and work. Again, there are not too many current examples of this therapy. There is one such therapy currently in use for Fabry disease.

And then, experimentally, there is the whole question now of gene therapy which can be done in 2 major ways. It's possible to have a packaged virus, which is not pathological which will not replicate within cells, but which can be modified to actually transport a normal gene to the cell which requires it, and in that way enabling normal production, transcription, and translation of the enzyme which is otherwise defective. This typically is being done now with viruses which are in the AAV classification, and in many cases, these viruses are direct to the liver where they get into liver cells and the liver cells are then sort of working like a factory to provide permanent and ongoing enzyme replacement therapy. Plus, this approach can also be used sometimes within the central nervous system.

And then there's an approach which is called ex vivo gene therapy, which is similar in many respects to hematopoietic stem cell transplantation, except in this place – in this regard, stem cells are harvested from the patient themselves and they are then transfected with the corrected gene and then they are reinfused back into the patient where they can grow within the bone marrow and again provide a continuing enzyme therapy.

So, these are the schemas that are currently available. Enzyme therapy is both the most commonly used approach for at least some of the lysosomal storage diseases. Again, primarily those which did not require the enzyme to get within the brain. The first enzyme treatment used for an LSD was for Gaucher disease, which was about 31 years ago, and that opened the door to similar therapies for

many other – or at least for a number of other LSDs. Actually, some people regard this as being the current gold standard treatment and you can see there's treatment such enzyme replacement therapy for Gaucher disease, Fabry disease, Pompe disease, just recently for ASMdb olipudase was approved by the FDA, and there are a number of mucopolysaccharide storage diseases which are addressed with enzyme therapy. And then a disease which I didn't mention before called lysosomal lipase deficiency, which can be a devastating disease in both adults as well as in infants leading to liver failure and the treatment for this, sebelipase alfa, has recently been shown to be highly effective.

What characterizes all of these ERTs is that they have to be administered intravenously and usually on a weekly or biweekly schedule, although some patients once they stabilize, can be treated somewhat less frequently. The advantages of ERT is that they have been shown to improve heart, pulmonary, and hematologic status in some of those disorders that I mentioned just a minute ago.

Many of the treatment studies have shown sustained efficacy as well as potency and excellent clinical responses. So, for example with Gaucher disease, I and some collaborators recently reported results for patients who have been treated for over 20 years and we were very happy to note that the early responses have been sustained over that period of time. And perhaps from a practical viewpoint, it was also very encouraging to note that patient compliance with the treatment was surprisingly good, and many patients had no problem staying on this treatment for even more than 20 years.

For Fabry disease, the enzyme replacement therapy, there are 2 internationally, 1 in the United States. But the enzyme treatment does seem to suggest that if started sufficiently early, it can slow at least progression of renal disease and slow down progression to end-stage kidney disease, and the same is true of heart failure, cardiomyopathy, and end-stage cardiac disease. The key here though is early institution of therapy. If one starts treatment after somebody is already symptomatic in regard to kidney or heart disease, they may get some improvement, but it will not stop the inevitable progression of the disease. There are of course some potential drawbacks to enzyme replacement therapy depending on the disorder. Allergic reactions due to development of antibodies to the manufactured enzyme can be substantial. Gaucher disease we were lucky because very few patients actually developed antibodies, maybe because many of them already had at least the residual amount of enzyme present. In other disease such as Fabry disease, Pompe disease, the likelihood of developing these antibodies and allergic reactions, or even anaphylaxis, can be substantial and sometimes one actually has to do immune suppression in order to successfully treat patients. And then, of course, there's the issue of venous access, which can sometimes be difficult. If someone is requiring IV injections every couple of weeks, there's long-term costs. These medications are quite expensive and even the infusion expense can be difficult. And one of the current treatments, which I guess we can refer to as being first generation, are large molecules and they cannot cross the blood-brain barrier in general, and in fact they may also have poor access to tissues which are not well vascularized due to infarction or the damage from the disease itself.

Nurse Viall:
So, back to our post-test, in enzyme replacement therapy, or ERT, what most distinguishes second generation from first generation agents? Number 1, they're easier to synthesize. Number 2, they are smaller molecule agents that can cross the blood-brain barrier. Number 3, they have a shorter half-life. Number 4, they're less expensive. And the answer is number 2, they are smaller molecule agents that can cross the blood-brain barrier.

Dr. Weinreb:
So, I sort of mentioned substrate reduction therapy, so I'm going to try to not be too lengthy on this slide. The aim is to inhibit the biosynthesis of the substrates that accumulate due to the specific lysosomal enzyme deficiencies, thus reducing the need for enzymatic breakdown and restoring homeostasis. Currently there are, for LSDs, 2 approved substrate reduction therapies, miglustat and eliglustat, both of which happen to be treatments for type 1 Gaucher disease, although miglustat is now also being used in Neimann-Pick type C disease. The advantages of substrate reduction therapy agents are that they are low molecular weight products, which can usually distribute well throughout all the organs of the body. Many of them do cross the blood-brain barrier with the exception, unfortunately, of eliglustat which does get in, but it's transported out as quickly as it gets in, and therefore it has not proven to be a good drug for treating the neuronopathic Gaucher disease. These drugs are usually able to be administered orally, they usually have a consistent dosage, they don't cause antibodies to be formed, but they can have some specific side effects such as, in the case of miglustat, primarily GI problems and neuropathy. They may or may not show slower clinical improvements than ERT. This is particularly true with miglustat, not really noted to be the case with eliglustat, and in the case of eliglustat, there is the complication that, as with many drugs which have to be metabolized by the liver generated cytochrome enzymes, there is the potential for drug interactions and that will probably be true of other substrate reduction therapies as they are developed.

Chaperone therapy, again I mentioned that they bind to mutant enzymes and stabilize their structure while they're in the endoplasmic reticulum, which helps to avoid there being degraded in what's called the proteosome in the cytoplasm and promotes trafficking to the lysosome. At the present time there is only one pharmacologic chaperone therapy, which is migalastat, which is approved for patients with Fabry disease, but only for those who have mutations where there is actual synthesis of the mutant enzyme. There are some

individuals who just don't generate any enzyme whatsoever because of the mutations they have, and therefore there is nothing to be chaperoned. And there are other such PCTs for Fabry disease and other LSDs under study. Again, as small molecules, these can cross the blood-brain barrier, they can be given orally, and in preventing the degradation of proteins, this allows them to perform enzymatic function and reduces the intracellular pathology which is followed by something call endoplasmic reticulum stress which doesn't directly have to do with the catalytic properties of the enzyme, but it actually can lead to pathology just caused by the buildup of the mutant enzyme proteins within the cell itself, and it's believed that that may contribute to some late complications in patients with LSDs. And as you can see with Fabry disease, they may be restricted only for specific mutations.

I talked about hemopoietic stem cell transplantation. This was experimental treatment for LSDs even before the advent of ERT, although at the time we didn't know that much about doing stem cell or bone marrow transplant either in terms of the complications issues, such as graft versus – graft versus host disease, compatibility of donor to recipient, and currently it is being used, however, for some specific LSDs as a type of bridge therapy during the period of engraftment at which time it's used in conjunction with enzyme replacement therapy. There was some hope that this treatment might be beneficial for a very difficult neurologic disease known as Krabbe disease. Even when patients have responded, it appears, however, that later observation suggests that progression does occur. So, this is again, a current challenge looking at where is the proper place for this type of therapy. The drawbacks clearly relate to high morbidity and mortality, which can be related to rejection or infection due to immune suppression, and as I mentioned, there may be reduced efficacy when performed later in the disease course. So, if one is going to do this type of HSCT, it really needs to be done in very young infants, and now they're starting to, based on consideration to whether it could be done in utero, which is particularly fascinating.

As far as somatic gene therapy, this relates to the not germline therapy. None of the gene therapies that we are currently using anywhere in the world are designed to actually correct the disease and the ovum or the sperm. When attempted doing that was done in China by one individual who was felt to be unethical, and he was actually sentenced to a prison sentence there. So, what we are looking at is treating the – trying to correct the gene abnormalities in the somatic cells, such as blood stem cells, and in that way being able to provide a permanent continuous source of the enzyme. So, here one develops a functional copy of the defective gene to cells, and using viral or sometimes nonviral derived vectors, once the corrected gene into whichever it's target cell, it does manufacture enzyme there and hopefully distribute it either to that cell itself, or to other cells to which it can be transported and correct the abnormalities. The advantages of them now are it's generally easy and relatively inexpensive to identify the defective gene in patients with a specific LSD, and should this be successful, it would obviate the need for long-term continuing therapy. The drawbacks again, may be that there may be delayed onset of action to the graft that takes place. Again, there is introduction of foreign DNA, both the viral DNA as well as the enzyme itself. There's risk of antigenicity of the viral vector and risk associated with immunosuppressive regimens which are usually necessary for successful engraftment of these agents, or sometimes conditioning regimens to make space within the bone marrow for the new stem cells to take residence.

So, some examples of these treatments are these autologous SteLL in vivo treatments that I mentioned. We're also starting to see investigation going on right now of several new substrate reduction therapy drugs. I just saw today, in fact, that a trial of a drug called venglustat, which is a new generation drug for neuronopathic Gaucher disease was just reported in the literature.

And then there are some of these novel ERT strategies which attempt to capitalize on the advantages to ERT, but just make it better. So, these are second generation agents which are so-called nano-packaged sometimes with lipid membranes around them which can enable stable enzyme molecules to cross the blood-brain barrier through these vesicles that exist, and they sometimes enhance the plasma half-life to allow less frequent infusions. Some of these agents can actually be given intrathecally or even directly into the ventricles, and there's has been some studies particularly with gene therapy, of direct injection, obviously with imaging guidance, into the brain itself. And then there are some modified enzymes which can be conjugated to other proteins which can bind to the endothelial cells in the brain, which constitute the blood-brain barrier, and then be transported across. So, these are sort of like a type of chaperone as well. Not in the same sense that I previously discussed.

Nurse Viall:
Well, returning to Gary's case, he's been receiving regular infusions of agalsidase-beta for 6 months, and although his disease hasn't progressed and his treatment is showing efficacy, he is really impatient to see some dramatic changes and kind of discouraged by the idea that he's going to need these time-consuming biweekly infusions on an indefinite basis. So, what do you think would be the best way to convince Gary to persist with his treatment? Number 1, pointing out his condition will deteriorate steadily if he doesn't continue the treatment. Number 2, explaining that the improvements can't be seen, and he should trust you they're occurring. Number 3, helping him understand the benefits of continued treatment, recognizing some positive changes that have occurred already, and periodically update him about research, the likelihood that new therapies will emerge in the future, and that he may be eligible to participate in new clinical trials as they become available. And number 4, referring him to a psychologist for counseling. In this case, number 3 is probably the best answer.

Back to Dr. Weinreb.

Dr. Weinreb:
Much of the material in this slide is fairly evident but sometimes not always carried into practice. So, clearly communication is very important both for us to successfully treat individuals with these and other disorders, and it can actually enhance the quality of life of the patient as well. So, it's very important to explain what's going on to both the patient and oftentimes the family members as well. And I think in such a way, one is likely to get better patient adherence if they understand what's going on. For example, in Gary's case he would not be physically aware of a significant decrease in his lyso-GB3, which might, on the other hand, be telling the clinician that future improvement is likely to happen. So, that could be explained to him.

Nurse Viall:
So, to continue with Gary, he comes back to your office about 9 months after starting his ERT and reports he has begun to adjust to the need for his current treatment. He tells you that although his GI symptoms have diminished after a few months on the ERT, he has recently been experiencing a resurgence of those symptoms, and he describes an alternating diarrhea and constipation as well as some bloating and cramping, and he has become kind of concerned that his ERT is not working to control his Fabry disease. So, what would you do first in response to Gary's reported symptoms? Number 1, explore the possibility that he has irritable bowel syndrome, or IBS, or another GI diagnosis unrelated to Fabry disease. Number 2, change Gary's LSD treatment. Number 3, explain to Gary that his symptoms are most likely psychosomatic, and he should find ways to ease his anxiety. And number 4, tell Gary to keep a record of his bowel fluctuations for the next 6 months and report any changes to you. And in this case, the answer is to explore the possibility with Gary that he may have something unrelated to his Fabry disease.

Back to you, Dr. Weinreb.

Dr. Weinreb:
Okay, I think it's very important to remember that patients with lysosomal storage diseases, or for that matter, any other disease you're treating, can have unrelated complications and when somebody seems to be doing well and then seems to regress, certainly one can consider the possibility they're not responding to therapy, but I think before reaching that conclusion, one should really carefully look for the possibility that some other problem has emerged and deal with that appropriately. In Gary's case, for example, knowing that his lyso-GB3 is still normal, or close to normal with treatment, would again strongly suggest that something else is going on. So, again, it's very important that as we treat patients with these diseases that they need to be monitored closely and they need to be monitored regularly. Various tests oftentimes need to be done again to be sure that they're responding optimally to therapy, that they're compliant with therapy. So, again, this sometimes needs to be done by the primary physician sometimes in conjunction with specialists. But following patients carefully is very, very important.

Nurse Viall:
And to conclude our case with Gary, IBS was confirmed, and you and Gary have agreed that the most likely cause of the development of this was stress and reaction to starting his new therapy and kind of the fear it wouldn't help him. So, Gary started taking over the counter medications to control his diarrhea and constipation, you were able to refer him to a nutritionist to help designating a diet that would minimize his symptoms, and you could refer him to a psychologist to create a stress-reduction regimen. So, he's changing his diet, he started practicing meditation which is helping him relieve stress. Overall, his symptoms are beginning to diminish, and he's really encouraged by this progress. You urge him to report any new or different symptoms to you promptly.

Dr. Weinreb:
So again, I mentioned before that long-term management also oftentimes requires supportive therapy, so again, the slides indicate some of those interventions, physical therapy, speech therapy, social work, psychology, genetic counselling very, very important. And then, oftentimes referral to patient advocacy organizations, and even industry support programs which can be very useful adjunctive resources for us clinicians to help manage these patients. And here's an example of just a number of – a very small number of the advocacy groups which are active and have been major contributors to patient care and patient support, and as I say, this is a very short list. I can't tell you how helpful they have been to me personally in terms of helping manage my patients.

Nurse Viall:
That concludes our program. So, thank you very much to our audience for joining us, and Dr. Weinreb. It was a pleasure presenting with you today. For our audience, please remember that in order to receive your CE/CME credit, you must compete the program evaluation. Again, thank you so much for being a part of this important activity.

Dr. Weinreb:
Again, thank you very much, Sarah, and thank you to everybody who listened.

Announcer Close:

You have been listening to CME on ReachMD. This activity is provided by Partners for Advancing Clinical Education (PACE) in partnership with Smart Patients. and is supported by an educational grant from Sanofi.

To receive your free CME credit, or to download this activity, go to ReachMD.com/CME. Thank you for listening.