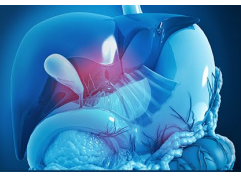
# Improving Diagnosis and Clinical Monitoring of Acid Sphingomyelinase Deficiency



**OVERVIEW**

Acid sphingomyelinase deficiency (ASMD) is a lysosomal storage disorder that causes accumulation of sphingomyelin in various organs. In addition to a low incidence, ASMD has a heterogeneous presentation that makes management challenging. Join experts Margaret McGovern, MD, PhD, and Pramod Mistry, MD, PhD, in this review of the diagnosis and treatment of patients with ASMD. Dr. McGovern will discuss the pathophysiology of ASMD as well as the diagnosis, classification, and initial evaluation of this disorder. Dr. Mistry will then review ongoing disease management as well as a novel enzyme replacement therapy, olipudase alfa, which has shown promising results in clinical trials.

**CONTENT AREAS**

- Pathophysiology
- Clinical presentation
- Classification
- Diagnosis
- Symptom management
- Emerging treatments

**TARGET AUDIENCE**

This activity is intended for medical geneticists, metabolic disease specialists, along with other clinicians providing care to patients with ASMD, including pediatricians, internists, pulmonologists, neurologists, hepatologists, gastroenterologists, hematologists and genetic counselors.

**FACULTY**

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This educational activity is supported by an educational grant from Genzyme.

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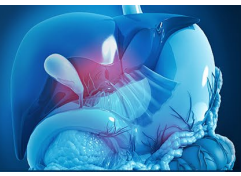

**Learning Objectives**

At the conclusion of this activity, participants should be better able to:

- Describe the disease spectrum of ASMD disease subtypes A, B, and A/B
- Diagnose patients suspected of having ASMD
- Perform comprehensive clinical monitoring of patients with ASMD
- Summarize the ongoing clinical trials and research that are evaluating new treatments for ASMD

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Pramod Mistry, MD, PhD
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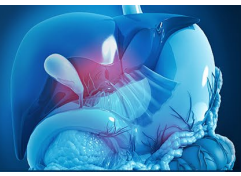

Amber Lea Lambert, MSN, FNP-C, DNP (Nurse Reviewer)

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The estimated time to complete the activity is 1.0 hour.

This activity was released on May 27, 2022 and is eligible for credit through May 27, 2023.

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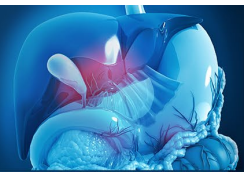
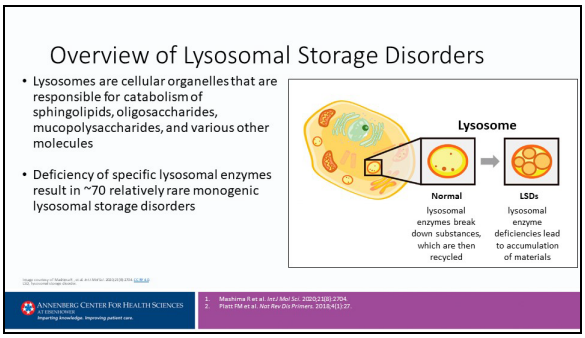


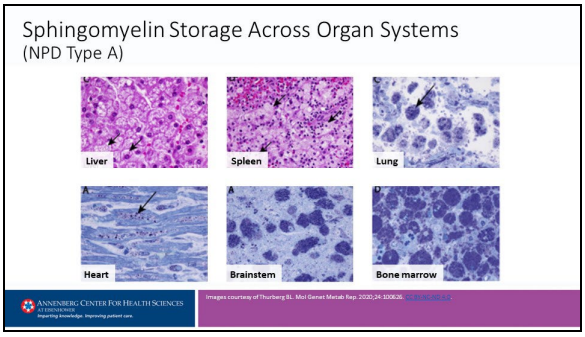
## DEFINING ASMD

Today we're going to be talking about improving the diagnosis and how to clinically monitor patients with acid sphingomyelinase deficiency or ASMD. ASMD is a lysosomal storage disorder and, just to remind you all, lysosomes are cellular organelles that are responsible for the catabolism of complex molecules, such as sphingolipids, oligosaccharides, mucopolysaccharides and various other molecules. The deficiency of specific lysosomal enzymes results in approximately 70 relatively rare, monogenic, lysosomal storage disorders.

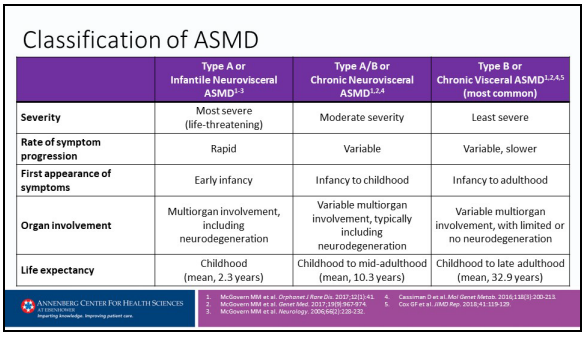



As you can see in the cartoon on this slide, normally the lysosomal enzymes break down substances to their component parts which can then be recycled. If a particular lysosomal enzyme is deficient, accumulation of the complex macromolecule occurs on a continuous basis for the lifetime of the patient. These are progressive disorders.

Acid sphingomyelinase deficiency is inherited as an autosomal recessive trait caused by mutations in the *SMPD1* gene and leads to the deficiency of acid sphingomyelinase. This enzyme is necessary for the metabolism of sphingomyelin, a lipid that is found nearly ubiquitously in cell membranes. In ASMD, sphingomyelin accumulates in the alveolar macrophages, the bone marrow, lymph nodes, tissue macrophages in the liver and spleen and, in severe cases, neurons. Commonly, the disorder is known as Niemann-Pick disease, types A and B.




Here you can see the pathologic images of sphingomyelin storage across organ systems. These samples happen to come from a patient with the most severe form of the disorder, Niemann-Pick disease type A. What you can see is the ballooned storage in the liver and in the spleen, in tissue macrophage, the blue staining in the long and alveolar macrophages. You can find storage in the heart, in the brainstem and the bone marrow.




| | Type A or Infantile Neurovisceral ASMD[1-3] | Type A/B or Chronic Neurovisceral ASMD[1,2,4] | Type B or Chronic Visceral ASMD[1,2,4,5] (most common) |
|---|---|---|---|
| **Severity** | Most severe (life-threatening) | Moderate severity | Least severe |
| **Rate of symptom progression** | Rapid | Variable | Variable, slower |
| **First appearance of symptoms** | Early infancy | Infancy to childhood | Infancy to adulthood |
| **Organ involvement** | Multiorgan involvement, including neurodegeneration | Variable multiorgan involvement, typically including neurodegeneration | Variable multiorgan involvement, with limited or no neurodegeneration |
| **Life expectancy** | Childhood (mean, 2.3 years) | Childhood to mid-adulthood (mean, 10.3 years) | Childhood to late adulthood (mean, 32.9 years) |

The classification of ASMD includes the type A, or infantile neurovisceral form, which is the most severe and life-threatening form of the disorder. Patients with this form have rapid progression of symptoms that present first in early infancy with multiorgan involvement,

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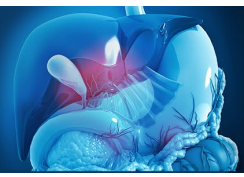
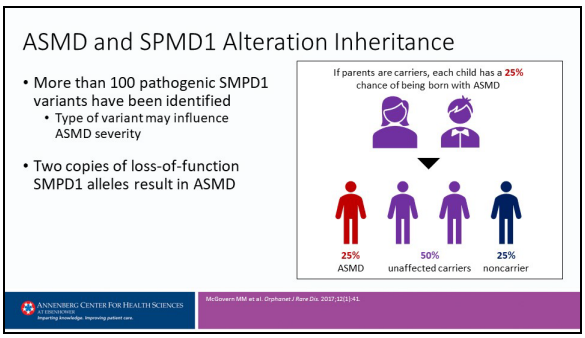


including neurodegeneration. Most children with the type A form of ASMD succumb to their disease in early childhood at a mean of 2.3 years.

Type A/B, or chronic neurovisceral ASMD, is a moderate severity disorder with a variable rate of symptom progression with symptoms appearing first in infancy or early childhood, again with multiorgan involvement, sometimes including neurodegeneration, but always including some neurologic findings and life expectancy from childhood to mid-adulthood.

In the type B or chronic visceral form of the disorder, this is the least severe with variable and slower progression of symptoms, presentation anywhere from infancy to adulthood, variable multiorgan involvement, but limited to no neurodegeneration. These patients can live well into adulthood.

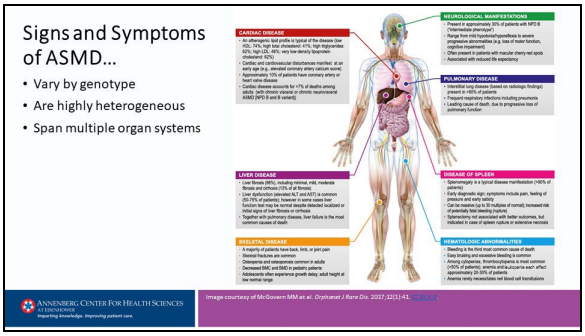
A precise estimate of the incidence is difficult, due to frequent underdiagnosis or misdiagnosis of this disorder, but is estimated at about 0.5 cases per 100,000 live births. Niemann-Pick disease type A has its highest frequency in the Ashkenazi Jewish community, where a carrier frequency of approximately 1% has been documented and 2-3 cases per 100,000 live births. But both forms of the disorder are panethnic.




More than 100 pathogenic *SMPD1* variants have been identified and the specific underlying mutation can influence ASMD severity. Two copies of loss-of-function *SMPD1* alleles result in ASMD, and it's inherited, as you can see in the cartoon on this slide, as a classic autosomal recessive disorder.

## Guidelines for the Diagnosis of ASMD

Groups of experts have developed guidelines for the diagnosis of ASMD, and it's important to note that the signs and symptoms vary by genotype, are highly heterogeneous and span multiple organ systems. And this slide contains a lot of information, but just thinking from head to toe, the clinical manifestations of ASMD can include neurologic disorder, present in about 30% of patients with Niemann-Pick disease intermediate phenotype, ranging from mild hypotonia or hyporeflexia to severe progressive abnormalities. These findings are often present in patients who have a macular cherry-red spot and are associated with a reduced life expectancy.




Cardiac disease is marked by an atherogenic lipid profile which is very typical of the disorder and, in particular, a low HDL. Cardiac and cardiovascular disturbances manifest at an early age, including elevated coronary artery calcium

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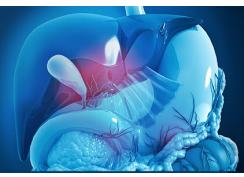


score, and about 10% of patients have coronary artery or heart valve disease. Cardiac disease accounts for about 7% of deaths among adults with the chronic form of ASMD.

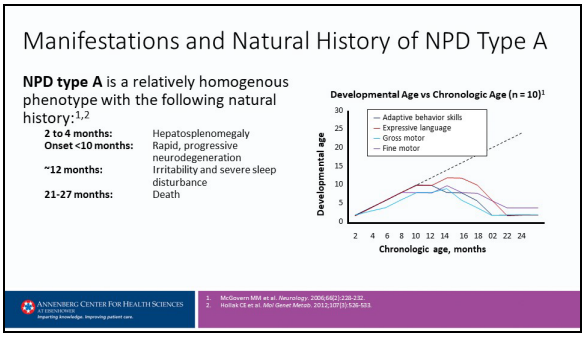
Interstitial lung disease, based on radiologic findings, is present in the majority of patients, and frequent respiratory infections, including pneumonia, occur. This is a leading cause of death due to progressive loss of pulmonary function. It should be noted, however, that the imaging findings can be profound prior to clinical deterioration of pulmonary function.

Liver fibrosis, including varying degrees of fibrosis and cirrhosis, occur in many patients. Liver dysfunction, noted by elevated liver enzymes, is common. However, in a lot of cases, liver function tests may be normal despite detecting localized or initial signs of liver fibrosis or cirrhosis. Together with pulmonary disease, liver failure is one of the most common causes of death.

Splenomegaly is a very typical disease manifestation and an early diagnostic sign. Patients can have symptoms from their enlarged spleen, including pain, a feeling of pressure and early satiety. Splenomegaly can be massive, up to 30 multiples of normal, and there is a potential risk for fatal bleeding. Splenectomy has not been found to be associated with better outcomes, but is indicated in case of splenic rupture.

The skeleton is also impacted by ASMD, and a majority of patients have back, limb or joint pain, and skeletal fractures are common. Osteopenia and osteoporosis are commonly found in adults, and there's decrease BMC and BMD in pediatric patients. Adolescent patients often experience growth delay, but with some catch up in early adulthood and early adult heights are typically in the normal, low-normal range.

Hematologic abnormalities are frequently found, and bleeding is the third most common cause of death. These patients also can have easy bruising and concomitantly have a low platelet count. Among the cytopenias, thrombocytopenia is the most common and anemia and leukopenia each affect about 20% to 30% of patients.




A study was done to assess the manifestations and natural history of Niemann-Pick disease type A. This form of the disorder has a relatively homogeneous phenotype, with hepatosplenomegaly usually detected on normal newborn examination by the pediatrician at about 2-4 months of age. Then these babies go on to develop rapid progressive neurodegeneration prior to the age of 10 months and, by 12 months, have severe irritability and sleep disturbance, and most succumbing between the ages of 21-27 months. You can see that all of the major milestones, adaptive behavioral skills, expressive language, gross motor, fine motor skills, all begin to fall off the normal curve between the ages of 8-10 months, with a rapid decline. These infants, some of them will get to sitting, rarely do they get to crawling. They don't get to walking.

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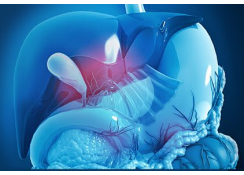
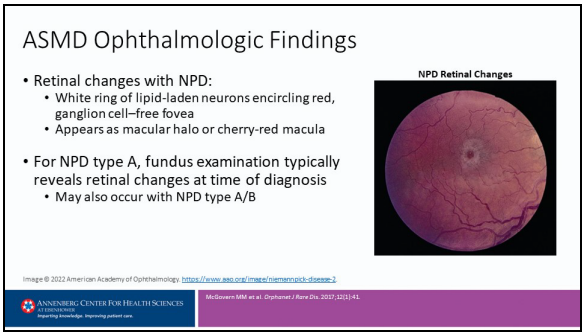
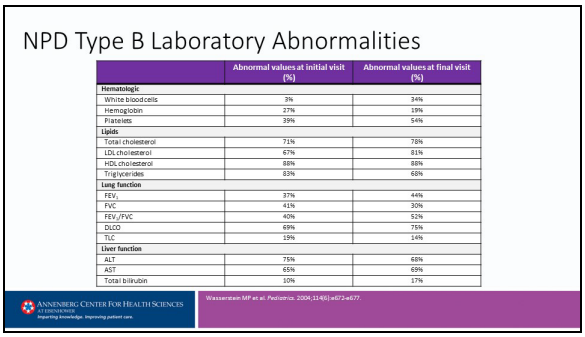


They don't develop their language skills and this is a devastating neurodegenerative disorder of infancy.




There are retinal changes that are present in many patients with Niemann-Pick disease, the most classic being the so-called cherry-red spot. This is a white ring of lipid-laden neurons encircling the normal red, ganglion cell-free fovea, as you can see here in this slide. This appears as the classic macular halo or cherry-red macula. For Niemann-Pick disease type A, fundus examination typically reveals retinal changes at the time of diagnosis, but this finding in the eye also can occur with patients with the so-called intermediate form, Niemann-Pick disease type A/B.

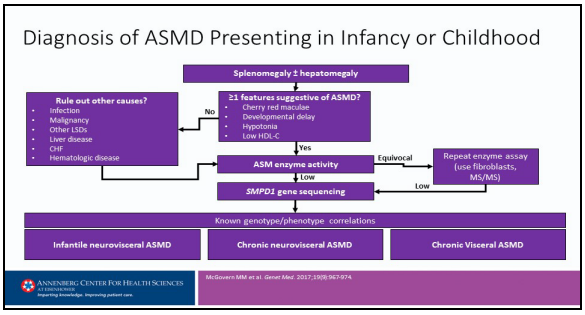
The manifestations and natural history of Niemann-Pick disease type [B] have been described in a series of descriptions of small numbers of patients. This is a phenotypically heterogeneous disorder. Most common initial presentation is hepatomegaly and splenomegaly, but other common findings and complaints are bleeding, dyspnea, pulmonary infections, joint and limb pain, bruising, headaches, bone fractures and diarrhea.




| | Abnormal values at initial visit (%) | Abnormal values at final visit (%) |
|---|---|---|
| **Hematologic** | | |
| White blood cells | 3% | 34% |
| Hemoglobin | 27% | 19% |
| Platelets | 39% | 54% |
| **Lipids** | | |
| Total cholesterol | 71% | 78% |
| LDL cholesterol | 67% | 81% |
| HDL cholesterol | 88% | 88% |
| Triglycerides | 83% | 68% |
| **Lung function** | | |
| $FEV_1$ | 37% | 44% |
| FVC | 41% | 30% |
| FEV$_1$/FVC | 40% | 52% |
| DLCO | 69% | 76% |
| TLC | 19% | 14% |
| **Liver function** | | |
| ALT | 75% | 68% |
| AST | 65% | 69% |
| Total bilirubin | 10% | 17% |

Typical laboratory abnormalities are summarized on this slide and can include hematologic findings, the lipid abnormalities that I previously described, including low HDL cholesterol, abnormalities on pulmonary function testing, one of most important and notable being the DLCO, which is typically decreased from normal, and abnormal liver function tests.

The natural history of the intermediate form of Niemann-Pick disease, so-called type A/B or B variant, is phenotypically heterogeneous. The somatic features are very similar to those in Niemann-Pick disease type B. These patients, however, may present with a cherry-red macula, and their neurologic manifestations can include ataxia, gross motor delays and learning disabilities. The presentation in general is more severe than type B, but less severe than type A, and these patients do survive early childhood.



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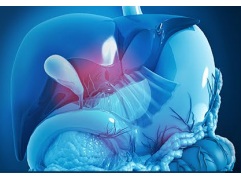
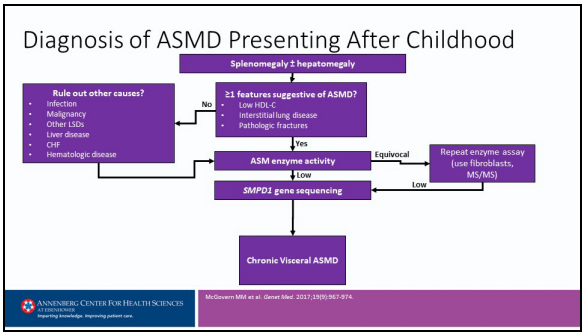


The diagnosis of ASMD presenting in infancy or childhood is depicted in this algorithm. Typically, the first finding, clinical finding, is hepatosplenomegaly, and when a patient is identified with hepatosplenomegaly, if there are other features suggestive of ASMD—such as a cherry-red macula, developmental delay, hypotonia, low HDL cholesterol—the next step would be to do ASM enzyme activity. If that's low, to then go on to gene sequencing to identify the particular genetic mutation which, in some cases, can give information about genotype phenotype. If those other suggestive features of ASMD are not present, then the clinician needs to rule out other causes for hepatosplenomegaly, which can include things such as infection, malignancy, other lysosomal storage diseases, liver disease, congestive heart failure or hematologic disorder. The bottom line is the gold standard for diagnosis of this disorder is measurement of the enzyme activity, followed by gene sequencing.

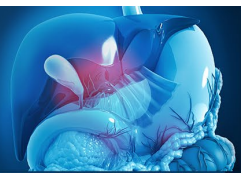



For ASMD presenting after childhood, again typically by the finding of hepatosplenomegaly, if there are features suggestive of ASMD, the same recommendation. Obtain an ASM enzyme activity, followed by gene sequencing if the enzyme activity is low. If there are no other suggestive features of ASMD, again the clinician needs to rule out other causes of hepatosplenomegaly.

The assessment of ASM activity is required for a diagnosis. Other clinical and laboratory testing may be confirmatory, but really cannot substitute for enzymatic testing because some of the features of ASMD overlap with other disorders, including other lysosomal disorders such as Gaucher disease. This testing can be performed on several different tissues, including isolated peripheral blood leukocytes, dried blood spots or skin fibroblasts. The low level of ASM activity, documented by this analysis, confirms a diagnosis of ASMD.

There are now best practices for how to do this testing and tandem mass spec is the preferred method because this allows for multiplexing analysis of enzyme activity. At the same time that one is measuring ASM, the other disorders, such as Gaucher and glucocerebrosidase deficiency, can be excluded at the same time, decreasing cost of working up the patient and improving speed to diagnosis. Compared with fluorometric measurements, which were more frequently used in the past, tandem mass spec has a higher specificity and doesn't require any radiochemicals. Although several types of samples can be used, as I already told you, most laboratories really require just a simple whole blood specimen.

Sequencing of the gene also does play a role in ASMD evaluation. More than 180 pathogenic *SMPD1* mutations have been identified and several genotype-phenotype associations have been made. Not surprising, frameshift mutations typically result in little or no residual ASM activity and would be anticipated to result in more severe disease, which is what is observed. Missense and in-frame deletions typically result in greater than 5% residual ASM activity and result in less severe disease. Some specific genotype-phenotype associations that



have been made include the finding that mutation R610 deletion is the most common mutation and is associated with an attenuated NPD type B phenotype, that is a mild phenotype. Whereas these 3 mutations, R496L, L302P and frameshift P330, account for most NPD type A in the Ashkenazi Jewish population. The mutation A359D accounts for most cases of Niemann-Pick disease type B in Chile, and these patients have higher rates of clinically significant liver disease. Finally, the Q292K is a mutation that's typically associated with neurologic involvement, including in those patients with the Niemann-Pick disease type A/B phenotype or the intermediate form.

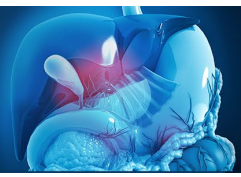
The differential diagnosis of ASMD does include Gaucher disease because the clinical features do overlap. That's why the recommendation is that parallel enzymatic testing for ASMD and Gaucher disease occur at the same time. There are other potential causes of hepatosplenomegaly, and particularly in infancy or early childhood, the clinician needs to be thinking about these other disorders. These would include hex-A deficiency, Sandhoff disease, Niemann-Pick disease type C, Wolman disease, the mucopolysaccharidoses and the oligosaccharidoses. Then, of course, some infectious diseases, hematologic malignancies and other genetic disorders, such as glycogen storage diseases, can have hepatosplenomegaly as a presenting symptom. Other potential causes of interstitial lung disease also need to be considered, including environmental exposures and connective tissue diseases and infections.

## Clinical Management and Treatment Monitoring Part 1

Once a diagnosis has been established, then the clinical management and treatment monitoring must be initiated. The initial evaluations and consultations after diagnosis of Niemann-Pick disease A should include a comprehensive ophthalmologic examination if it has not yet been performed, a neurologic evaluation, CBC, other blood tests such as serum chemistries, a dietary consultation because nutrition and feeding becomes a major problem in infants with this form of the disorder, occupational and physical therapy evaluations, and consultation with a medical geneticist or genetic counselor.

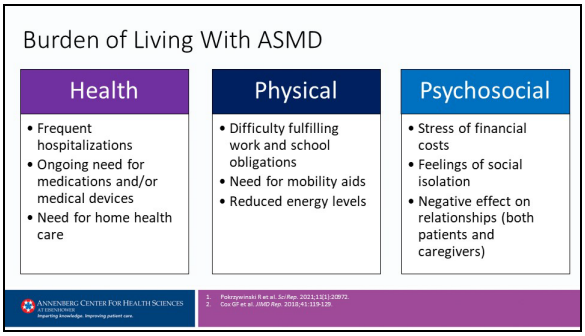
Unfortunately, there's no definitive treatment for NPD type A. These babies can benefit for some period of time from physical and occupational therapy, but with the care team agreeing upon realistic goals. In some families, the decision is made to employ a feeding tube for nutrition and that's a conversation that should occur in consultation with the family to gain agreement about the approach. In some cases, sedatives for irritability and sleep disturbance are necessary since this can impact the entire family. Family counseling and early involvement of the palliative care team can be very helpful.

Initial evaluations after the diagnosis of the intermediate form, NPD A/B or type B, should include a chest x-ray to determine the extent of interstitial lung disease, but with the caveat the x-ray can look far worse than the clinical picture in the patient, at least initially. Pulmonary function testing once the patient is old enough to cooperate with that, which is usually around the age of 5 or 6, including an assessment of DLCO. Bone age in children younger than 18



years, and typically the bone age lags behind chronologic age, which makes sense with that finding that's been observed in several studies that growth occurs well into the 20s. Ophthalmologic examination, because those intermediate form patients can have a cherry-red spot, and also a neurologic exam, a baseline in all patients, baseline laboratory studies and, again, consultation with a medical geneticist or genetic counselor.

Again, unfortunately, there's not currently definitive treatment for either NPD A/B or B, and the management's based primarily on organ system-directed management, the goal always being to lessen the impact of symptoms, both for treatment and lifestyle intervention. There are reports in the literature of bone marrow transplantation and total lung lavage in this patient population, but each of these confer minimal benefit with high risk, and really are not considered a standard treatment.



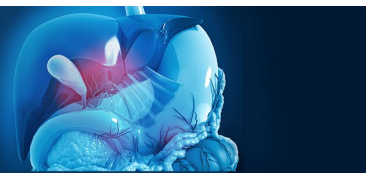

There is significant burden of living with ASMD. On the health front, there are frequent hospitalizations, ongoing need for medications or medical devices and, in some cases, need for home health care. Physically, these patients can experience extreme fatigue and have difficulty fulfilling work and school obligations. They sometimes need mobility aids. They have reduced energy. There are psychosocial costs, the stress of the financial burden, feelings of social isolation and negative impact on relationships.

The role of clinical trials is very important in rare diseases such as ASMD, and discussions with patients and caregivers about these opportunities should be held. Clinical trials, in general, for these rare diseases, can be very challenging to implement and there can be reluctance among patients and caregivers to participate, which can further delay development of new treatments. Key points to bring up when discussing a trial is to describe the best current treatment options, then present the clinical trial option, explain the differences between the clinical trial drug and current treatment, of course reiterating that participation is completely voluntary, using diagrams to show differences in trial groups and then, of course, elicit and thoroughly answer any questions that the caregiver or patient have.

## Clinical Management and Treatment Monitoring Part 2

I am going to be discussing the clinical management and treatment monitoring of acid sphingomyelinase deficiency. Dr. McGovern has provided an authoritative and comprehensive description of phenotype and natural history, and that has been foundational for us to develop standard of care for how we monitor patients over time and ensure that they don't come to any harm from their acid sphingomyelinase deficiency.

# Improving Diagnosis and Clinical Monitoring of Acid Sphingomyelinase Deficiency



## Ongoing Surveillance for NPD A/B and B

| System/Concern | Evaluation | Frequency |
|---|---|---|
| Growth/Nutrition | Measurement of growth parameters<br>Evaluation of nutritional status & safety of oral intake | At each visit |
| Cardiac | Electrocardiogram | Annually |
| | Echocardiogram | Every 2-4 years |
| Liver function | Serum chemistries including liver transaminases (ALT, AST), albumin, & clotting factors | At least annually |
| Hematologic | Assessment for fatigue, abdominal pain, & increase in bleeding<br>Platelet count | |
| Hepatosplenomegaly | Radiologic measurements of liver & spleen size | At baseline & as needed |
| Pulmonary | Assessment for shortness of breath | At each visit |
| | Pulmonary function testing | Annually |
| | Chest radiograph | Every 2-4 years |
| Neurologic | Assessment of neurologic function & frequency of headaches | At least annually |
| Developmental | Monitoring developmental progress & educational needs<br>Evaluation of occupational and physical therapy needs | At each visit |
| Hyperlipidemia | Fasting lipid profile | At least annually |
| Musculoskeletal | Assessment for extremity pain | At each visit |
| | Bone density assessment (DEXA) | Every 2-4 years |
| Family support | Assessment for any change in social, domestic, or school- or work-related activities | At each visit |

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Wasserstein MP, Schuchman EH. February 25, 2021. Accessed March 7, 2022.

As you heard from Dr. McGovern, this is a multisystemic disease and therefore, when we see patients in the clinic, we monitor growth and nutrition, cardiac function, liver function, hematologic parameters, how severe the hepatosplenomegaly is. Thus, for example, if splenomegaly suddenly starts to get worse, it may indicate development of cirrhosis and portal hypertension. Pulmonary monitoring with lung function tests, chest x-ray and clinical symptom assessment is extremely important because, as you heard, lung is a very major target of the disease. Moreover, we include neurological assessments as well as, in children, developmental assessments.

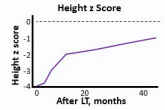
This is a metabolic disorder causing profound disturbance of lipid metabolism and, thus, lipid profile monitoring is important at least annually. We monitor the musculoskeletal system and then, of course, we want to look after the patient as a whole, in a holistic manner, understanding the diverse impacts of living with a genetic disease and with a chronic disease. This is a wonderful table to give you a benchmark in the clinic how often these assessments should be carried out.

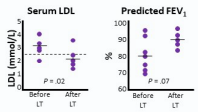
The ongoing management of liver disease is extremely important because, as you heard from Dr. McGovern, the liver, along with the hematologic system as well as the pulmonary system, are major targets of this devastating rare disease. Liver disease is a major cause of morbidity and mortality in acid sphingomyelinase deficiency and it is primarily driven by the accumulation of sphingomyelin, as you can see. Therefore, it becomes very important to avoid any cofactors in patients so that we don't have additional contributing factors in the progression of liver disease, and thus counseling and monitoring for alcohol use is very important. We advise patients not to have any alcohol. Weight management is important because obesity and fatty liver disease superimposed on ASMD could amplify the rate at which the liver disease progresses.

As the disease in the liver progresses, patients develop portal hypertension and develop esophageal varices, and we can now prevent bleeding episodes with beta blockers, and this has been shown to be transformative in care of patients with cirrhosis in general. There are a significant number of holes in the literature where patients' liver disease has progressed to liver failure and hepatic decompensation and liver transplantation has been carried out as a life-saving procedure in these desperately ill patients.

## Liver Transplantation for ASMD (NPD Type B)

- Can stably restore liver function
- Has been shown to improve hematologic and lipid parameters
- Has been shown to improve pulmonary function and resolve interstitial lung disease
- May lead to catch-up growth
- Neurologic delays typically maintained

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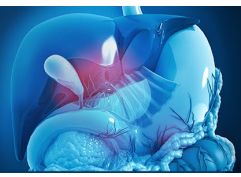
Liu T et al. Liver Transpl. 2019;25(8):1233-1240.



Here is an example of one such patient. As you can see on the right-hand side, the patient received a liver transplant and, at the time of transplant, the patient had severe growth failure with height z-score of -4, and over the next 20 and 40 months following liver transplantation, there was remarkable reversal of growth failure. Concomitantly, the hyperlipidemia, the high LDL cholesterol, declined very nicely after liver transplantation. Moreover, the lung function improved. There was a trend towards improvement in lung function. This is a systemic therapy and neurological delays have been typically unaffected by liver transplantation, but most certainly it has saved the life of these individual patients from life-threatening liver failure.

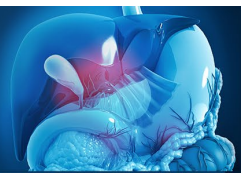
Managing splenomegaly is a significant issue when we see these patients in the clinic. Unfortunately, there are no satisfactory treatments. We caution patients to reduce contact sports to decrease direct trauma to the spleen, to prevent spleen rupture. We do not recommend splenectomy in these patients because it will exacerbate deposition of the sphingomyelin in cells in other sites, such as the liver, and also will lead to acceleration of pulmonary disease. If necessary, due to massive splenomegaly that may cause pressure symptoms and early satiety and malnutrition, splenectomy could be limited to partial splenectomy or partial splenic embolization. The former is the more preferred approach in my practice.

Management of cardiovascular system are a major component of taking care of these patients with this chronic liver disease because of the atherogenic dyslipidemia and high frequency of premature coronary artery disease. Thus, we recommend that there should be diet modification in consultation with registered dietitian to limit the intake of saturated fats and cholesterol. We recommend regular physical activity in consultant with physical therapists to maintain the cardiovascular health. Lipid-lowering therapy for the atherogenic dyslipidemia is very important and could be based on current guidelines, including the use of statins or the other types of cholesterol-lowering therapies. If statins are used, of course, it is important to frequently monitor liver function to prevent or to identify early any onset of statin-induced liver injury.

This lipid-storage disease can result in deposition of storage cells in the heart walls and that can eventually lead to valvular insufficiency and that may require pharmacotherapy according to current guidelines, underscoring the need for regular echocardiography to monitor this aspect of cardiac health.

Management of lung dysfunction is one of the central pillars of taking care of these patients. Again, as with liver disease, we recommend lifestyle modification, not to have any exposure, first or secondhand exposure, to tobacco smoke and avoid the use of electronic cigarettes. Supplemental oxygen and bronchodilators would improve the quality of life and dyspnea in these patients. Pulmonary infections are common in acid sphingomyelinase deficiency and they should be managed promptly and preemptively, according to the guidelines for the general population.

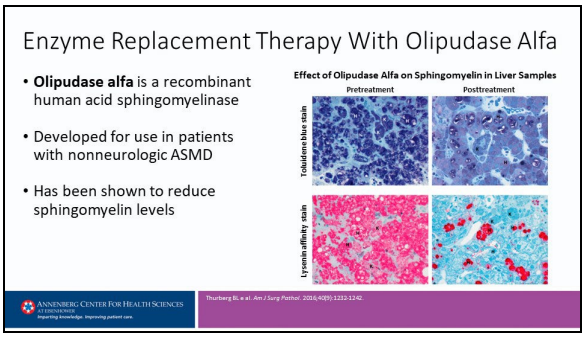
Improving growth in the children affected with acid sphingomyelinase deficiency is very important because, if these children, as they enter adulthood, they may have permanent



impact of failure of growth in terms of lower peak bone mass and other aspects. We provide standard counseling regarding lifestyle for skeletal loss. It is important to monitor around 18 to 20 that the patients have achieved a peak bone mass and this can be aided significantly by dietary modification to ensure adequate vitamin D and calcium intake, supplemented, if necessary, by calcium and vitamin D supplements. Weight-bearing exercise is extremely beneficial for bone health and to prevent bone loss. This is important because, as we heard from Dr. McGovern, fragility fractures are a significant cause of morbidity in these patients over time and we can really intervene at the earliest beginnings of osteoporosis. We do not recommend bisphosphonates as they have been found to inhibit acid sphingomyelinase activity and therefore any residual activity patients have will be further reduced and aggravating the rate of progression of ASMD. Physical therapy can aid musculoskeletal pain and improve overall health and well-being.

## Emerging Therapies: Efficacy and Safety Data from Phase 3 Trials

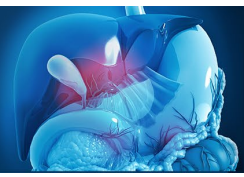
We are going to be talking about emerging specific therapies for acid sphingomyelinase deficiency. We will discuss the efficacy and safety data from phase 1 and 2 trials and emerging phase 3 trials that were just published a few days ago.

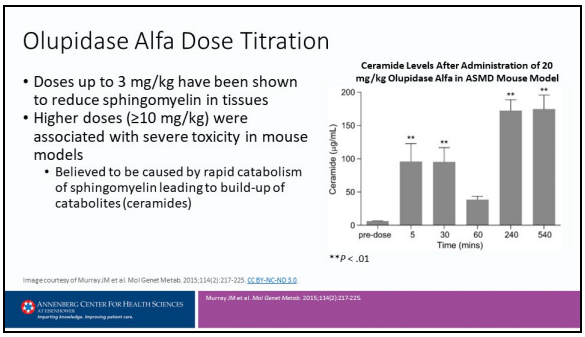



Enzyme replacement therapy with olipudase alfa is a recombinant human acid sphingomyelinase produced in recombinant Chinese hamster ovary cells like many other enzyme replacement therapies for lysosomal diseases. It has been developed based on pioneering work of Dr. Ed Schuchman at the Mount Sinai School of Medicine for use in patients with a nonneurological form of acid sphingomyelinase deficiency, namely Niemann-Pick type B and type A/B. As you can see, the figures on the right-hand side of liver biopsy, it has been shown to reduce sphingomyelinase levels. On the top panel, we see the staining of Kupffer cells and hepatocytes indicated by K and H on a liver biopsy, stained with toluidine blue stain, with stains for sphingomyelin, and that is at baseline. Following treatment, you can see really quite striking reversal of the accumulation of sphingomyelin in the hepatocytes as well as in Kupffer cell.

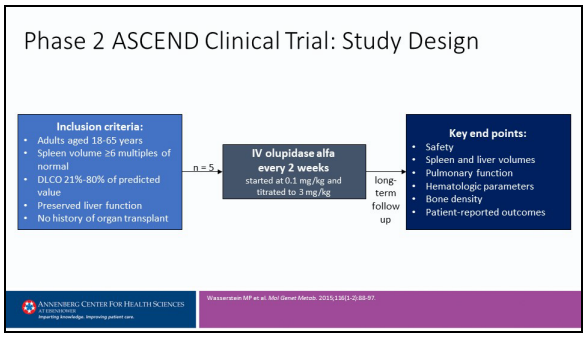
In the lower panel is another stain to look for this abnormal lipid accumulation using lysenin affinity stain. Again, you see, using this different approach, that it's really quite dramatic reduction of acid sphingomyelin in hepatocytes as well as in Kupffer cells. In fact, there is almost clearing in the Kupffer cell but there is some residual accumulation in the hepatocytes.

# Improving Diagnosis and Clinical Monitoring of Acid Sphingomyelinase Deficiency





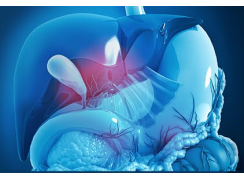

In the early studies, olipudase alfa was dose titrated and up to a dose of about 3 mg/kg was shown to reduce sphingomyelin in tissues very effectively. In the early studies, it was found that very high doses, such as greater than 10 mg/kg body weight, were associated with severe toxicity in the mouse. This was due to rapid catabolism of the accumulated sphingomyelin that led to a surge in ceramide. That is shown in the right-hand panel which, following administration of a pretty high dose of olipudase alfa in a mouse model of sphingomyelinase, you can see that at baseline there is no ceramide, but after 5 minutes and over the ensuring hours, there is a very significant rise of ceramide, which can trigger an inflammatory response. Note that this is something that happens at very high doses and so doses up to 5 mg/kg have actually been shown not to have this kind of ceramide release phenomenon.

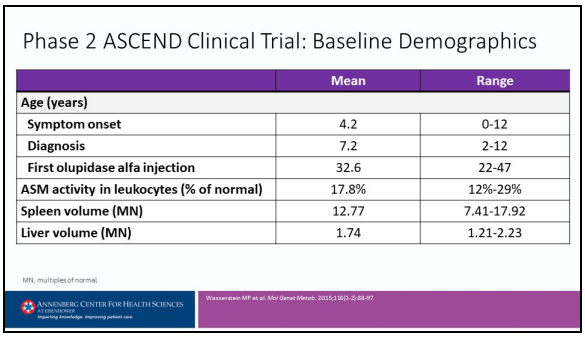



In the phase 2 clinical trial, it involved 5 patients, as shown in this schematic. The inclusion criteria were adults, aged 18 to 65 years, spleen volume greater than 6 multiples of normal. Lung function was involved with DLCO 21% to 80% of predicted value. The liver function was preserved in these 5 patients and there had been no organ transplantation in these individuals.

These individuals started olipudase alfa every 2 weeks, starting at a very low dose of 0.1 mg/kg and, over time, escalated to 3 mg/kg. The patients were followed long term. This was a phase 2 study. It was non-blinded. The key end points were safety, reduction of spleen and liver volumes, any improvement in lung function, any improvement in hematologic parameters and bone density, as well as patient-reported outcomes. And this study was led by Dr. Melissa Wasserstein at Montefiore Hospital.

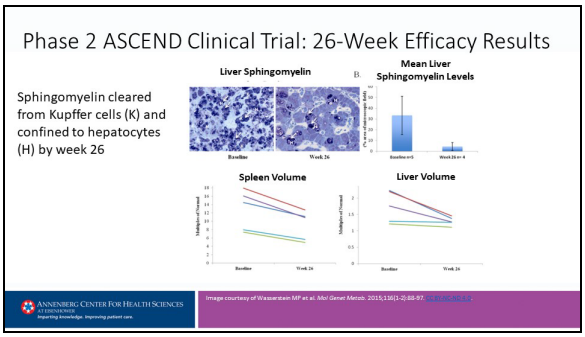
# Improving Diagnosis and Clinical Monitoring of Acid Sphingomyelinase Deficiency



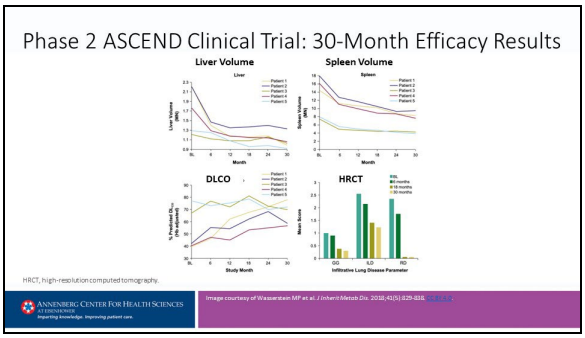



These are the patients' demographics at the baseline in the phase 2 ASCEND clinical trial. Patients had symptom onset from the age of 4.2 years, ranging from 0 to 12 years. As you can see, these individuals who were adults had lived with this chronic disease for a very long period of time. There was a significant gap between the onset of symptoms and the diagnosis, which was 7.2 years. It was very late in the natural history, when they were becoming quite sick, that they had the opportunity to have the first infusions of olipudase alfa, as you can see, 22 years. As we map the natural history, there is early onset in childhood, late diagnosis, and then living with the disease for up to 3 decades.

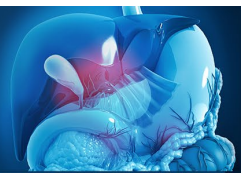
The acid sphingomyelinase activity was diagnostically low. Patients had very significant splenomegaly, averaging 12.7 multiples of normal, ranging from 7 to 17 multiples of normal. There was very significant hepatomegaly, averaging 1.74 multiples of normal, ranging from 1.21 to 2.23 multiples of normal.




Here are the results of the phase 2 ASCEND clinical trial at 26 weeks to show the efficacy. Again, what you're seeing is toluidine blue staining of liver biopsy showing heavy infiltration of this toxic sphingolipid, sphingomyelin in hepatocytes and Kupffer cells. At week 26, there is a dramatic reversal of that. On the right-hand panel, on the top, you can see the quantification of the inclusions of the sphingomyelin. Concomitantly, there was a decline in splenomegaly, as well as in hepatomegaly, in every one of these patients and these were the results that were obtained within only 6 months and these are remarkable signs of exquisite efficacy of olipudase alfa.



# Improving Diagnosis and Clinical Monitoring of Acid Sphingomyelinase Deficiency

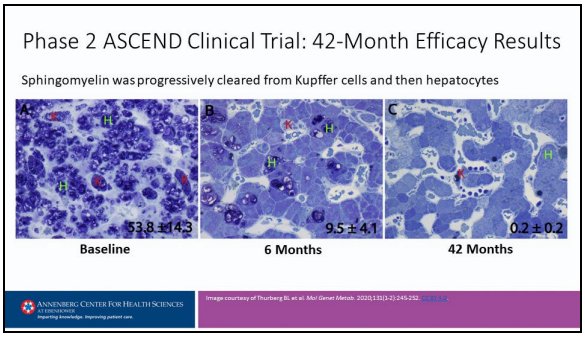


In the phase 2 trial at 30 months, these are the data on the reversal of hepatomegaly as well as splenomegaly. As you can see that the reversal of organomegaly was sustained over time for up

to almost 3 years and, in many patients, there was incremental reduction of splenomegaly and liver volume over time. Concomitantly, there was a gratifying improvement in lung function, as shown here with rising DLCO and one of the most encouraging aspects of this data is that this improvement continues, particularly in patients who started with very low DLCO at the bottom of this figure, figure 3, and they had only 40% predicted, these 3 individuals, and you see that it grows and these are the kind of responses that can often be associated with being able to wean off home oxygen therapy.

The high-resolution CT scan also showed commensurate improvement in various indicators of infiltrative lung disease, as shown here, whether they were ground-glass opacities or interstitial lung disease burden and reticular shadowing in the lungs.

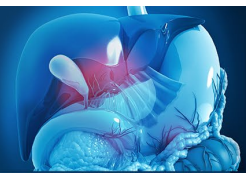
As these patients continued on olipudase alfa for 42 months—and here is a summary of the efficacy at 42 months—interestingly and very encouraging, olipudase alfa improved lipid profiles from atherogenic profile to marked reversal of that pattern. There was progressive reduction of proatherogenic lipid markers with reduction of total cholesterol, reduction of LDL cholesterol, reduction of VLDL cholesterol as well as reduction of triglycerides. Excitingly, there was progressive improvement in the antiatherogenic lipid marker HDL cholesterol. As you heard from Dr. McGovern, HDL levels are very low in these patients at baseline and there was a marked improvement in HDL cholesterol concomitantly with rise of apolipoprotein A-I.

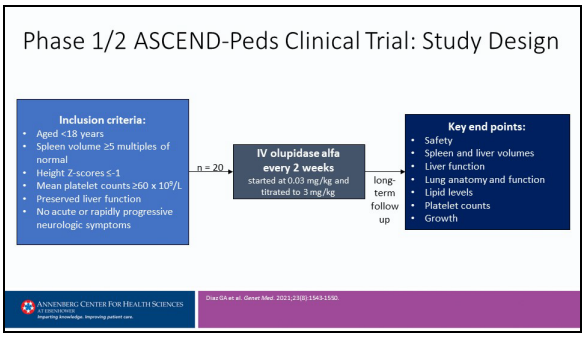



Here are the data at 42 months showing disappearance of sphingomyelin accumulation. As you can see at the baseline, there is toxic accumulation of sphingomyelin in Kupffer cells as well as hepatocytes (hepatocytes indicated with an H, Kupffer cells with a K) and this is a stain with toluidine blue. At 6 months already, as we discussed, there is a marked decline in these, in these toxic inclusions of sphingomyelin and, at 42 months, there is virtual disappearance. If one were to look at this biopsy, on the whole it would be posed as normal.

Safety, of course, was a very important objective of the phase 2 clinical trials. We found that all patients experienced mild treatment-emergent adverse events. No patients experienced severe treatment-emergent adverse events. The most common events were headaches, nausea, abdominal discomfort, arthralgia and fatigue.

# Improving Diagnosis and Clinical Monitoring of Acid Sphingomyelinase Deficiency






Now we switch our attention to the phase 1/2 ASCEND-Pediatric clinical trial. As we have learned today, there is a huge burden of the disease in children affected by acid sphingomyelinase deficiency and we've just learned how this disease responds to olipudase alfa in adults. We will now examine the outcome of the clinical trial in children.

Here, the inclusion criteria were age less than 18 years. Spleen volume was 5 multiples of normal or greater. Height scores were low, at less than -1 z-score. Mean platelet counts were greater than 60,000. Patients had preserved liver function and there were no acute or rapidly progressive neurologic symptoms. Twenty patients in a global study met these inclusion criteria and they started intravenous olipudase alfa every 2 weeks at the low dose of 0.03 mg/kg and then escalated gradually to a maximum of 3 mg/kg every 2 weeks. Patients were followed long term to monitor for the key end points: safety, of course, spleen and liver volumes, liver function, lung anatomy and function, lipid levels, platelet counts, as well as growth parameters.

Phase 1/2 ASCEND-Peds Clinical Trial: Baseline Demographics

| | Adolescent (12-17 y) (n = 4) | Child (6-11 y) (n = 9) | Infant/early child (<6 y) (n = 7) | Overall (n = 20) |
|---|---|---|---|---|
| **Age (years)** | | | | |
| **Symptom onset** | 1.4 | 1.6 | 1.2 | 1.4 |
| **Diagnosis** | 2.1 | 3.4 | 1.6 | 2.5 |
| **Enrollment** | 14.8 | 8.7 | 3.4 | 8.0 |
| **ASM activity in leukocytes (nmol/h/mg)** | 0.21 | 0.13 | 0.10 | 0.14 |
| **Severe splenomegaly (>15 MN)** | 25.0% | 55.6% | 85.7% | 60.0% |

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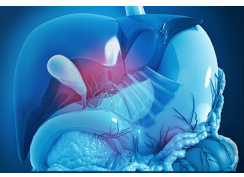
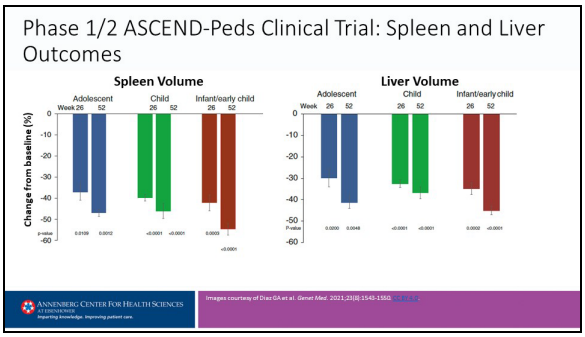
These were the patients, a summary of demographics of the patients. As you can see, they span all of the childhood, from adolescence, 4 patients; childhood, 6 to 11 patients; and early childhood or infancy, less than 6 years, and there were 7 patients in that group. The children, 6- to 11-year-old children, included 9 individuals and there were 4 adolescents. By definition, all of these patients had severe disease indicated by symptom onset within the first 1 or 2 years of life, leading to a diagnosis very rapidly, but somewhat delayed after 2½ years.

And then, patients lived with this disease, these children, for a period of time before they had an opportunity to participate in the clinical trial, and so the average mean age of enrollment was 8 years after the diagnosis, and then ranging from 3.4 years to 14.8 years. These children had diagnostically low acid sphingomyelinase activity and peripheral blood leukocytes and a significant number of these children had very severe splenomegaly, as one would expect, averaging about 60% of the children having splenomegaly that was greater than 15 multiples of normal.

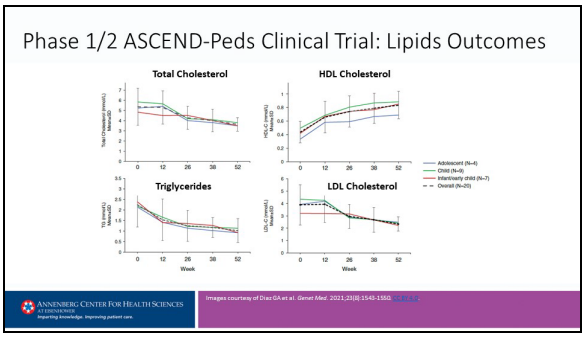
# Improving Diagnosis and Clinical Monitoring of Acid Sphingomyelinase Deficiency



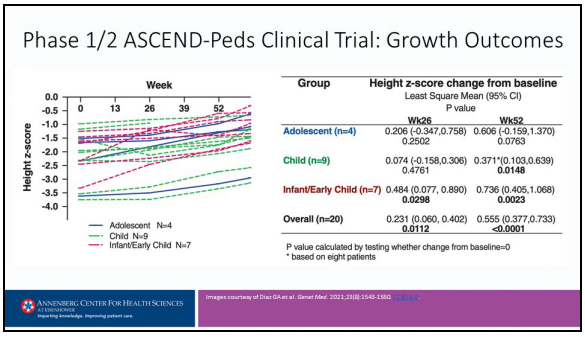



Here are the data stratified according to the childhood stage for the reversal of hepatosplenomegaly, and what you can see is the effect of olipudase alfa at week 26 and week 52, shown in adolescents, in the childhood group and in the infant or early childhood group. In every one of these groups, there is a dramatic decline in splenomegaly at 6 months and at 1 year, up to greater than -50%. Gratifyingly, the youngest children have the most striking reduction of splenomegaly, but this is uniform throughout the ages in the childhood.

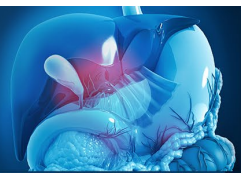
We see exactly similar trends with the reversal of liver disease, indicated by hepatomegaly, and these are very highly significant changes from baseline, at 6 months and 1 year in the adolescents, in the infants and early childhood individuals and also the older childhood group. Again, like with reversal of liver disease, you see the most striking reversal of disease in the infants and early childhood, although we see the same trends in other groups across childhood.




It was exciting to watch concurrent improvement in the atherogenic lipid profile, so there was a striking reduction of atherogenic dyslipidemia indicated by progressive fall of total cholesterol which was related to fall in LDL cholesterol, but combined with a very striking rise of HDL cholesterol. Triglycerides also fell, reflecting a reversal of the VLDL lipoprotein. On this figure, you can see that there is a reduction in VLDL as well as LDL and a beneficial rise of high-density lipoprotein.



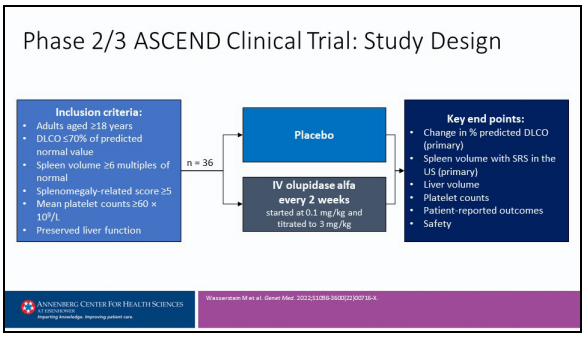

These were very gratifying data on striking reversal of growth failure shown as Height z-score in each individual 20 children enrolled in the clinical trial. Overall, the trend is reversal over a 1-year period. These are very impressive data compared to as we have come to expect in other lysosomal diseases. By least mean square analysis, these improvements in growth failure



were all, were significant in the childhood age as well as in the infants at 1 year, and there was a trend towards statistical significance in the adolescents, again underscoring that earlier treatment would prevent this growth failure that can meld into the adolescents and then into early adulthood.

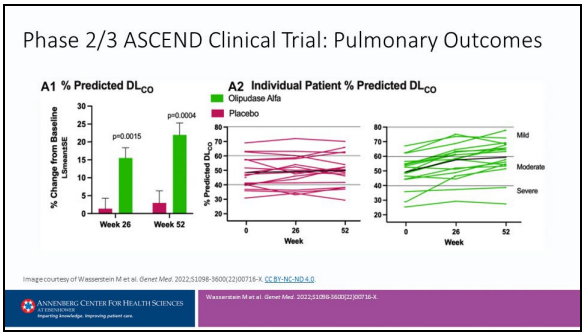
The safety outcomes, of course, are extremely important, and we found that all patients experienced at least 1 treatment-emergent adverse event, which were mostly mild, 88%. One patient had a serious treatment-related adverse event, anaphylaxis, but successfully continued treatment after desensitization. The common adverse events included fever, cough, vomiting, nasopharyngitis, diarrhea, headache, nausea, rhinitis, oropharyngeal pain, ear pain and rhinorrhea. Other events considered related to treatment included injection reactions, such as itching, fever and vomiting.

We have seen the very promising data from a phase 1 trial in adults and then the ASCEND phase 1/2 trial, also in children. I'm very pleased to say, just in the last few days, the phase 2/3 clinical trial data were published in *Genetics in Medicine* and a multinational study led by my colleague, Dr. Melissa Wasserstein at Montefiore Hospital.



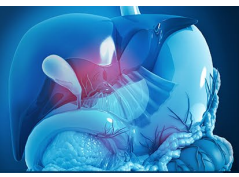

This was the randomized, placebo-controlled clinical trial evaluating olipudase alfa enzyme replacement therapy for chronic acid sphingomyelinase deficiency in adults at 1 year. The goal of the trial was to assess the efficacy and safety of this enzyme replacement therapy for non-central nervous system manifestations of acid sphingomyelinase deficiency.

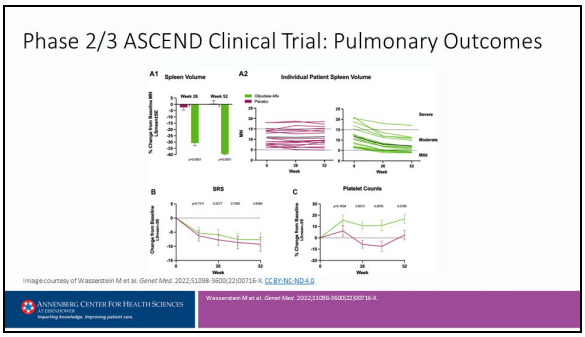
This clinical trial enrolled 36 adults and they were randomized 1:1 to receive olipudase alfa or placebo, intravenously, every 2 weeks, with an intra-patient dose escalation to 3 mg/kg. The primary efficacy end points were percent of change from baseline to week 52 in percent predicted diffusing capacity of the lung for carbon monoxide and spleen volume, combined with splenomegaly-related score, in the United States. Other outcomes included liver volume, liver function, sphingomyelin content, pulmonary imaging and pulmonary function, platelet levels, lipid levels and pharmacodynamics.




The results showed that by least square mean percentage change from baseline to week 52, it favored olipudase alfa over placebo for percent predicted diffusing capacity of the lung for carbon monoxide, 22% vs 3%, which was highly statistically significant.

# Improving Diagnosis and Clinical Monitoring of Acid Sphingomyelinase Deficiency






Spleen volume decreased concurrently, averaging 39% decrease in the olipudase group and was a 0.5% increase in the placebo, again highly statistically significant. Concomitantly, there was a decline in liver volume that was also highly significant compared to placebo. Splenomegaly-related score decreased in both groups. Other clinical outcomes improved in the olipudase alfa group compared with the placebo group. There were no treatment-related serious adverse events or adverse event–related discontinuations. Most adverse events were mild.

In conclusion, therefore, olipudase alfa was well tolerated in this major placebo-controlled clinical trial and associated with significant and comprehensive improvements in disease pathology and clinically relevant end points compared with placebo in adults with acid sphingomyelinase deficiency.

There are other preclinical investigational treatments for acid sphingomyelinase deficiency and these include gene therapy with an adeno-associated viral factor, specifically AAV9, to deliver human acid sphingomyelinase. Currently, there are preliminary studies ongoing in animal models. Another novel approach has been inhibition of fatty acid amide hydrolase to reduce degradation of the endocannabinoid system 2. Currently in preliminary studies in mouse models and in vitro studies published in this reference cited here, number 2 here, by Bartoli and colleagues in EMBO Molecular Medicine, there are promising responses for this type of approach to treatment.

In summary, therefore, acid sphingomyelinase deficiency, Niemann-Pick type A, type B or type A/B, comprises a group of potentially life-threatening disorders caused by deficiency in acid sphingomyelinase enzyme in the lysosome and the accumulation of sphingomyelin in lysosomes of cells. Acid sphingomyelinase deficiency is caused by gene mutations in the accompanying gene, called the *SMPD1*. Common presenting symptoms include hepatosplenomegaly, but Niemann-Pick B and type A/B are renowned for being extremely heterogeneous disorders. Olipudase alfa is an investigational treatment that has been shown to safely reduce liver and spleen volume, lipid levels and other signs and symptoms of ASMD, such as lung disease and growth failure.