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INTRODUCTION TO ALPHA-MANNOSIDOSIS

Barbara Burton, MD: Let's begin by defining alpha-mannosidosis. This is an inherited metabolic disorder caused by faulty or absent alpha-mannosidase enzyme activity in lysosomes. This leads to accumulation of mannose-containing oligosaccharides, leading into cellular dysfunction and apoptosis. The disorder is the result of the presence of 2 pathogenic variants in the *MAN2B1* gene. The incidence is estimated to be between 1 in 250,000 and 1 in 1 million live births.

To give you an idea of what alpha-mannosidosis looks like, I want to begin with a brief case vignette. This patient was the second child born to Palestinian parents who are first cousins. He was felt to be completely normal and healthy at birth. But then he began to experience hospital admissions between 7 and 11 months of age for reactive airway disease. A chest x-ray done at 10 months of age revealed findings suggestive of dysostosis multiplex. At 11 months, hepatomegaly was noted. As a result, he was referred to a geneticist who suspected an MPS disorder and obtained urine GAG analysis which was normal. At that time, a liver biopsy was recommended.

The parents sought a second opinion with regard to whether their child should undergo a liver biopsy and saw a hepatologist at our institution. At that time, physical examination revealed coarse facial features, frontal bossing and a broad nasal bridge. The liver edge was palpable 5 cm below the costal margin and the spleen was also palpable 5 cm below the costal margin. There was lumbar kyphosis and mild hypotonic. This led to the suspicion of a storage disorder and referral to me in the Division of Genetics. At that time, urine GAGs were repeated and were normal. A urine oligosaccharide panel was obtained and was abnormal. A lysosomal enzyme panel revealed deficient activity of the enzyme alpha-mannosidase.

And we'll come back to this case a little later in the program. But, as you can see, patients with alpha-mannosidosis may present to a variety of different types of physicians. Primary care pediatricians, of course, would be one important group because they're seeing the children frequently, and that was certainly true with the case I just described. But also, there are a variety of pediatric specialists that might see the patient. I mentioned a hepatologist in the case of my patient, but it also could be a gastroenterologist. Because of the skeletal findings, there could be an orthopedic surgeon involved and a variety of other practitioners. But I think the bottom line is that patients with suspicion for alpha-mannosidosis should probably be referred to a specialist for further diagnostic workup and management.

Laura Buch, MSPAS, PA-C: I absolutely agree that it's very important to have early referrals and time for diagnosis as there is treatment available for this diagnosis and that management and treatment opportunities for the patient are going to be most important and impactful at younger ages.

IDENTIFICATION AND DIAGNOSIS

Barbara Burton, MD: Let's talk a little bit more about the identification of alpha-mannosidosis by talking about the fact that there have been 3 phenotypic subtypes of the disorder identified. Now, it's important to recognize, of course, that alpha-mannosidosis, like other lysosomal diseases, occurs along a spectrum of severity, but I think that thinking of these 3 basic subtypes can be helpful in both clinical management and decision-making with regard to treatment.

The first subtype is referred to as type 1 and this is the mildest of the subtypes in that symptoms appear somewhat later in life and the progression of the disorder is very slow. Typically, type 1 is not diagnosed until after 10 years of age. There's no overt skeletal involvement and the predominant manifestations in type 1 are hearing loss, intellectual disability or developmental delay, ataxia although that's a relatively late finding, psychiatric manifestations and, in adult life, arthritis and also, in some cases, other autoimmune disorders.

Type 2 is the moderate form of alpha-mannosidosis, usually diagnosed at an age less than 10 years and with slow progression. Again, we do see ataxia developing in adult life, but these patients also have skeletal involvement, they have speech and developmental delay, motor disturbances and may show the characteristic mildly coarse facial features that we associate with the disorder. We also may see hepatosplenomegaly, recurrent infections and hernias.

And then finally we have the most severe of the subtypes which is type 3 which, like the patient I presented earlier, presents in early infancy. The progression of the disorder is rapid and it's associated with early death from primary CNS involvement or progressive myopathy. Again, we see skeletal abnormalities like kyphosis and joint restriction, facial dysmorphia, profound hearing loss, hepatosplenomegaly and marked and progressive deterioration in motor and cognitive function. And you can hear from that description the tremendous overlap that does exist with the findings in the MPS disorders and, of course, this is what was suspected in the case that I initially presented.

Having briefly reviewed those subtypes, you can see that the diagnosis and classification is somewhat complex because of the significant variability and overlap between the subtypes and the diagnosis of the disorder may be complex because of the overlap with the findings in other storage disorders in the earlier onset patients, but with conditions that simply result in intellectual disability and hearing loss in the older patients where the progression of the disorder may not be that obvious.

Now, the American College of Medical Genetics has issued some guidelines for genetic testing that can be helpful in recognizing alpha-mannosidosis. The ACMG has strongly recommended either exome sequencing or genome sequencing as a first- or a second-tier test for patients with more than 1 congenital anomaly prior to 1 year of age or for patients with developmental delay and/or intellectual disability with onset prior to 18 years of age. If you do this, this will lead to the diagnosis of alpha-mannosidosis because developmental delay and intellectual disability are really a hallmark of the disorder. But of course this has to be guided by clinical judgment, and there may be situations, like the case I first presented, where you strongly suspect a storage disorder or even alpha-mannosidosis and may go directly to the diagnosis by biochemical means without the need for exome or genome sequencing.

Some diagnostic algorithms have been proposed in the literature for diagnosis and this can be helpful. One of these indicates that if you have the combination of hearing impairment and/or speech delay with at least 2 other manifestations, including on that list cognitive delay, motor disturbances, or characteristic facial features, then you should refer to an expert metabolic center to proceed with diagnostic testing. If you have hearing impairment and are speech delayed, but don't have those other 2 manifestations, then, of course, you need to continue to monitor the patient. And if further findings appear, then you would take the same course.

For patients greater than 10 years of age, the proposed algorithm suggests that if you have intellectual disability and motor impairment regression and/or psychiatric manifestations combined with at least 2 of the following: hearing impairment, intellectual disability, motor disturbance, or skeletal disorders, then that referral should occur. Without those, again, continued monitoring is in order. I think if we follow, of course, the ACMG guidelines, we will jump over this process and get more directly to the diagnosis.

In 2024, there was a Delphi process that was conducted with a global group of experts in alpha-mannosidosis, and a number of recommendations came out of that process. They were in 3 key areas: assessments in newly-diagnosed patients; routine follow-up care; and treatment-related follow-up care. In newly-diagnosed patients, they addressed both genetic testing and baseline assessments.

The Global Delphi Consensus Recommendation regarding genetic testing tells us that patients with alpha-mannosidosis who are diagnosed on biochemical grounds, in other words with measurement of alpha-mannosidase activity and/or plasma and urine oligosaccharides, should still have genetic testing for confirmation of the diagnosis and for identification of the specific variants in the *MAN2B1* gene. This is going to be helpful for genetic counseling purposes and a genetic counselor should be involved to assess assessing relatives of the patient who may also be at risk for having the disorder. This would specifically refer to siblings who may not have been diagnosed as yet, younger siblings, or even sometimes older siblings who may have clinical manifestations and have not yet had a diagnosis. Certainly, testing is appropriate in those circumstances.

Baseline recommendations for patients with a new diagnosis of alpha-mannosidosis are designed to really establish the burden of disease in the various organ systems that can be involved and include many things beyond physical examination, such as audiology testing for hearing loss, laboratory assessment assessing both oligosaccharides and also immunoglobulins since immunoglobulin deficiency is common and may lead to predisposition for serious infections. Also, skeletal survey and orthopedic assessment, cognitive and neurocognitive testing, ophthalmology exam, pulmonary function testing and assessment of cardiology function, cardiac function. Additional evaluations should, of course, be based on physical findings at diagnosis and should be individualized

based on disease severity and the patient's ability to perform some of the recommended assessments.

To summarize, the key signs and symptoms of alpha-mannosidosis include developmental delay including involvement of both speech and motor delay, motor disturbances such as ataxia, hearing loss, skeletal abnormalities. Later, psychiatric symptoms and patients with suspected alpha-mannosidosis should receive genetic testing that may be combined with biochemical testing and should be referred to a specialist for further evaluation and treatment. And certainly there's a prominent role here for medical geneticists and other specialists.

Laura Buch, MSPAS, PA-C: Dr. Burton. I think this is a great point to how so very many patients find us in medical genetics. They come to us from a variety of different specialists who have concerns based on for what they were evaluating the patient. Being open to a lot of different referrals and seeing the specialists involved as the patient makes their way along their diagnostic odyssey to our clinics in medical genetics I think is a very important aspect of their care and the education that we can continue to provide.

IMPLEMENTING AND MONITORING STANDARD OF CARE TREATMENT

Laura Buch, MSPAS, PA-C: Thank you so much, Dr. Burton, for a wonderful introduction on alpha-mannosidosis and diagnosis. I will continue by talking about implementation and monitoring, talking about the standard of care treatment for patients with alpha-mannosidosis.

As we know, there are several options available for disease-directed treatments for alpha-mannosidosis. We'll start by talking about enzyme replacement therapy or ERT. Velmanase alfa is the only FDA-approved therapy for alpha-mannosidosis and is regarded as a standard of treatment for patients with alpha-mannosidosis. It addresses noncentral nervous system symptoms of alpha-mannosidosis and is generally accepted to be well tolerated. Notable biochemical and functional improvements were covered in clinical trial results for this ERT and we will talk about these at later slides. As with most treatments and intervention, early initiation may lead to better clinical outcomes and it's important to consider enzyme replacement therapy, implementation early in the disease course, where this is possible.

Looking at hematopoietic stem cell transplant or HSCT, this has long been used for preservation of neurocognitive function and prevention of early death in patients with severe alpha-mannosidosis. There are better outcomes noted that are achieved by performing HSCT early and before complications of alpha-mannosidosis arise. Morbidity and mortality associated with HSCT must also be balanced against the benefits of this. And looking at also the patients' access to these therapies and sites of care, there can be many challenges for both patients and caregivers for both of these treatments.

Looking at the mechanism of action and the indications for velmanase alfa, we know that this enzyme replacement therapy is a human recombinant form of the lysosomal enzyme alpha-mannosidase. This helps provide an exogenous source of the missing enzyme and helps catalyze degradation of those mannose-containing oligosaccharides in the lysosomes. This enzyme is directly transported into the lysosomes where it's thought to exert this activity. Velmanase alfa is indicated for the treatment of, again, those noncentral nervous system manifestations in alpha-mannosidosis in both pediatric and adult patients.

The recommended dosage of this enzyme replacement therapy is 1 mg/kg of a patient's actual body weight. As a patient grows over time, this dose that they're administered changes as well. Velmanase alfa is administered once every week as an intravenous infusion, either through peripheral access or central access like with a port. If 1 or more days of this treatment are missed, it's important to restart the treatment as soon as possible as long as you're within those 3 days from the next scheduled dose. If you're within those next 3 days from the next scheduled dose, you're only supposed to give that next dose per the schedule.

The most common adverse events reported in clinical trials in patients, with an incidence of greater than 20%, included hypersensitivity reactions, including anaphylaxis, pyrexia, headache and arthralgia. Velmanase alfa administration may cause severe infusion-associated reactions and patients should be monitored accordingly. When looking at velmanase alfa use in females of reproductive potential, it was noted that this enzyme replacement may cause fetal harm; therefore, effective contraception during treatment and for 14 days after the last dose, if discontinued, is required. There are no listed contraindications to velmanase alfa at this time.

Taking a look at the pivotal trial data for the enzyme replacement therapy velmanase alfa, we look at the rhLAMAN-05, a phase 3 clinical trial that took place over 52 weeks. This was a double-blind, placebo-controlled trial in patients with alpha-mannosidosis. Twenty-five patients with alpha-mannosidosis were put into either a treatment arm or a placebo arm for the first 12 months. And then our serum-oligosaccharides and the 3-minute stair climb test were evaluated in these patients.

Looking at the serum-oligosaccharides on the right-hand side of this slide, you can see the blue representing the treatment arm with velmanase alfa patients and the orange line representing the patients who were receiving the placebo drug. For the individuals receiving velmanase alfa, a 77.6% decrease in the serum-oligosaccharides were noted over time. In those first 12 months for the placebo arm, only a 24.1% decrease was noted. When then switched over to the active-only extension, meaning all patients were then receiving active velmanase alfa, regardless of whether they had received the velmanase alfa or placebo in the previous arm, it was noted that continued decreases in the serum-oligosaccharides of the patients receiving velmanase alfa at 62.9% decrease by the end of this follow-up was noted for the patients. For those individuals who had been receiving placebo, an additional decrease down to 55.7% of baseline was noted once placed on velmanase alfa.

Looking at the 3-minute stair climb testing results, in that beginning arm where patients were either placed on the velmanase alfa or the placebo drug, 0.5% improvement was noted in the patients receiving velmanase alfa on their 3-minute stair climb test results. Whereas a decrease of 3.6% from baseline was noted in the placebo arm in that first 12 months. After switching over to active drug for all individuals, an overall 3.9% from baseline change of improvement in the 3-minute stair climb test was noted for the individuals who had been receiving velmanase alfa from the start. 9.0% improvement from baseline was noted in the patients who had previously been on placebo.

Additional long-term data looking at the rhLAMAN-07 and rhLAMA-09 phase 3b trials in a pooled analysis looked at 16 patients who had previously completed the velmanase alfa trials and 5 enzyme replacement therapy-naive patients or treatment-naive. We looked at both patients who were pediatric and adult, annotated over here as green, less than 18 years of age, and blue, greater than or equal to 18 years of age. What we can see in the serum-oligosaccharide percent change for individuals was that there was a sustained serum-oligosaccharide clearance and, when looking at serum IgG, or the immunoglobulins related to immune system function, there was an increase noted as well. Overall, treatment was noted to be well tolerated and a majority of adverse events to velmanase alfa were of mild-to-moderate intensity.

Additional long-term data monitoring motor status with 6-minute walk test and 3-minute stair climbs in patients who were followed up for up to 12 years, we saw that in 14 pediatric patients, the 6-minute walk test distance was increased or stabilized and they also performed better in 3-minute stair climb testing results. In 7 adult patients, the 6-minute walk test distance was stabilized or even slightly decreased.

Looking again at the 2024 Global Delphi Consensus Recommendations, treatment-related follow-up care, as related to enzyme replacement therapy, has particular recommendations for monitoring. Specifically, what we're looking at is related to serum urine oligosaccharide levels, antibody titers, infusion-related reactions, and comprehensive symptom-based monitoring. In any individual starting treatment with enzyme replacement therapy, it's important to obtain a baseline serum or urine oligosaccharide level, obtain these levels after receiving enzyme replacement therapy and then monitor these levels every 6 to 12 months. Antibody titers should also be tested every 6 to 12 months for any patient receiving enzyme replacement therapy, and also as clinically indicated for any patients who receive or start to develop infusion-related reactions or have insufficient clinical response, such as maintaining high oligosaccharide levels.

Administration of premedication and slowing the rate of enzyme replacement therapy infusions should also be considered if a patient has a high risk of developing infusion-related reactions. And a patient should be monitored at every infusion, pre, post and during those infusions, for any related reactions that may be occurring. Annual comprehensive symptom-based monitoring should also be performed for patients with alpha-mannosidosis.

Barbara Burton, MD: That was a great summary and I'm so glad you emphasized the importance of monitoring efficacy by measuring the oligosaccharides and also of tracking antibody titers in our patients. I think it's so important.

Now I'd like to pivot a little bit and talk about considerations for the use of hematopoietic stem cell transplantation, or HSCT, in alpha-mannosidosis. As you mentioned, this has historically been used and has been used for several decades and we know that it can improve neurologic and systemic symptoms and reduce disease severity. However,

HSCT is associated with significant morbidity and mortality risks, and so this is a decision that has to be made very carefully and is one that needs to be appropriate for the individual patient that you're seeing. It may not be an appropriate treatment option for all patients. In addition, patients and caregivers may have difficulty, in some locations, accessing transplant centers that have experience in treating patients with rare disease, like the glycoproteinoses, such as alpha-mannosidosis.

There are several series in the literature that describe the outcome in patients treated with transplantation. One of these, published in 2025, described 21 children with alpha-mannosidosis who were diagnosed and transplanted at a median age of 3.9 years. There was primary engraftment in 17 of the 21, with 4 requiring a second transplant. The outcomes suggested what we would expect, which is higher levels of functioning in those patients who were treated earlier.

A second series describes 17 patients who received transplant later, at a median age of 5.5 years. They showed stabilization or improvement in skeletal abnormalities, improvement in hearing in some, and improvements in activities of daily living in some patients as well. We know that we also can see stabilization of development and prevention of the progressive neuromotor degeneration that we see in the severe phenotype.

Delphi recommendations did address treatment-related follow-up care, again going back to the 2024 Global Delphi process, and one of the areas that were addressed was post-HSCT monitoring. This should include, just as was the case for velmanase alfa, assessment of serum and/or urine oligosaccharides, as well as alpha-mannosidase enzyme levels, both pre- and post-HSCT. Patients who have HSCT also need to continue to have comprehensive symptom-based evaluations. This should be done every 12 months in these patients. And of course we need to have monitoring of engraftment and HSCT-related complications which will typically be directed by the hematology or transplant team.

Now, there is the potential for combining ERT and HSCT, although limited data are available at present on this combination approach. Certainly, bridge therapy may be utilized just as we commonly do it with conditions like MPS-1. In other words, treating the patient with ERT leading up to HSCT, and in the peritransplant phase, until there is restoration of circulating leukocyte alpha-mannosidase activity. There is 1 published case in which such therapy was utilized, and findings 3 years post-HSCT suggest that that early combined intervention may reduce disease progression and urine and/or plasma oligosaccharides.

At this point, I'd like to continue my case vignette of the patient I introduced you to early in the program. This patient did undergo HSCT at 17 months of age with his HLA-identical mother as a donor. You'll recall that he had a very severe phenotype. He had the type 3 phenotype with presentation in the first year of life. The patient became fully engrafted post-transplant and had no acute graft-vs-host disease, but did develop complication of chronic GVHD with skin, eye and mucosal involvement. Over time, other medical issues that were observed in the patient include chronic otitis media with ear tube placement at 4 years of age, multiple dental caries requiring restorations under general anesthesia, and developmental delay with some problematic behavioral issues.

Over time, the behavioral issues certainly improved and really resolved. The patient continued to have mild-to-moderate intellectual disability, but stable with no regression over time. At 19 years of age, he started on ERT. This was prompted by the fact that he was having some mobility issues, limiting his ability to walk more than a block. He also was having some joint pain and arthritis, which is common, of course, in our older patients. And following the initiation of ERT, he had improvements in joint pain and improved mobility. The patient always had had normal immunoglobulins and this remained unchanged. He also has mild hearing loss.

Just to summarize what both Laura and I have discussed with regard to treatment, we see that there are 2 treatments utilized for alpha-mannosidosis, ERT with velmanase alfa and HSCT. ERT has been evaluated in multiple phase 3 trials. HSCT has been evaluated in observational studies and case reports. And we know that treatment-related follow-up and monitoring with ERT and HSCT, regardless of which is utilized, is really essential. We have limited data available, currently, regarding the combination or sequential use of ERT and HSCT.

Laura Buch, MSPAS, PA-C: Thank you, Dr. Burton, again for following up on our case vignette and for giving a really great example of how that marriage between enzyme replacement therapy and hematopoietic stem cell transplant has been a part of your patient's care. I think

we'll continue to probably see a trend of that as we move forward in the management of these patients, identifying them earlier and younger, hopefully, with more expansive genetic testing opportunities available and really giving the best treatment options to those patients in each case and looking at them each as individuals.

PATIENT-CENTERED HOLISTIC CARE

Laura Buch, MSPAS, PA-C: Next we'll talk about patient-centered holistic care speaking about, again, the Global Delphi Consensus Recommendations from 2024 regarding their key area 3-treatment-related follow-up care for supportive care-related monitoring and integrated care coordination.

We've seen how important it is that patients with alpha-mannosidosis receive a multitude of care from multiple different settings and specialists. Looking at individuals with alpha-mannosidosis who are on supportive care only for their treatment, these individuals should be monitored every 6 to 12 months for symptom-based assessments. According to the Global Delphi Consensus Recommendations in 2024, there should also be an integrated care coordination for patients with alpha-mannosidosis, looking at having long-term multidisciplinary care teams that include not only a specialist in alpha-mannosidosis, such as a geneticist or a metabolic specialist, but also a group of specialists including, but certainly not limited to, audiologists to evaluate hearing, otolaryngologists to care for ENT complications, cardiologists to monitor heart and cardiac care, ophthalmologists to evaluate for vision, orthopedic specialists to help evaluate patients for skeletal involvement and progression, pediatricians for young children, and then, also, as individuals age, we look at adult care, so primary care and family medicine, physiotherapists, occupational therapists to help monitor motor status changes, pulmonologists for breathing and lung function and, of course, social and family therapists for the individuals who are caring for these patients with alpha-mannosidosis. Psychologists will be very helpful for individuals with psychiatric concerns, imaging specialists for interpretation of possible findings related to alpha-mannosidosis and, of course, speech and language therapists to help with communication over time.

Where it's possible, patients with alpha-mannosidosis should be seen through a multidisciplinary care clinic to allow for this coordination, and reduction of the burden on patients and their caregivers going to all of these different specialists. When this is not possible, a social worker or a case worker should be offered to—or assigned to—the family to help in the navigation of this complex care.

We see, though, many barriers to this interprofessional and multidisciplinary collaboration. Not only are there financial burdens on families and institutions, but access to the use of a case worker or social worker may be challenging in many areas and practices. For many specialists, there's a lack of time and resources and, depending on the region or practice that a patient is being seen through, there may be specific challenges to each of those sites of care. However, despite all of these challenges, coordinated patient care may be helpful to improving patient-centered care over the long term even though these immediate gains may not be evident right away.

Returning to our 2024 Delphi Consensus Recommendations, we'll now take a look at key area 2, looking at routine follow-up care. We'll see that muscular or motor function monitoring is very important at every visit, or at least annually, including neurologic examinations, looking at balance and coordination, and also taking patient-reported assessments. Specifically, we also want to take a look at motor function assessments every 6 to 12 months in pediatric patients, yearly in adults, depending on their ability, since younger patients may not be able to comply with the directions for some of these assessments, like a 6-minute walk test. Assessments and follow-up with physical or occupational therapy, as needed, is also helpful.

Monitoring for skeletal abnormalities, at least annually, and referring to orthopedic specialists if surgical or other specific interventions are needed, is critical. Looking at skeletal imaging and bone density tests in adults, physiotherapy tests can also be performed as needed or based on disease severity and age of the patient. Monitoring for any cognitive function testing or changes with delays or declines, over time, we want to conduct cognitive function assessments annually in pediatric patients and look at formal assessments at periods of key transitions, like changes in environment or other disease progression. Referral to any specialist, as needed, or based on clinical assessments, may be offered to patients.

For behavioral and psychiatric manifestations, monitoring of these problems and looking at a patient history on symptom-based screening every 1 to 2 years is very helpful, in addition to referrals to specialists, like psychiatrists or psychologists, as needed. When evaluating for central nervous system manifestations, we want to look for any potential symptoms and perform a physical and neurologic exam every 6 months for patients less than 4 years of age,

or annually for patients 4 years of age or older. Brain imaging is also helpful, when needed.

For hearing loss, standard audiometry assessment should be performed every 1 to 2 years, and, in pediatric patients with hearing aids, we should be monitoring them at least every 6 to 12 months, and having an otoscopic evaluation at least every year. For biochemical assays, annual lab assessments, such as those that screen for liver and kidney issues, blood glucose levels, fluid and electrolyte imbalances, and blood counts, are very helpful.

For pulmonary function, assessing this function regularly and conducting yearly pulmonary function tests in patients able to complete testing can be impactful. Monitoring for signs of respiratory difficulties and conducting additional workup, if needed, is also based on the patient. For cardiac function, individuals should be monitored for hypertension, cardiomyopathy and exercise intolerance, looking at these functional assessments every 2 to 3 years; and referring to cardiology if abnormalities are expected. For the ophthalmologic pathologies related to alpha-mannosidosis, monitoring of visual acuity and night acuity for myopia, hyperopia and other ophthalmic disorders is important. Ophthalmic evaluation, or an examination at least annually, or every 6 months if there's worsening pathology, for patients, can help detect these earlier on.

With immune function, monitoring of immunoglobulin levels and assessing for signs of immune dysfunction and infections can be life-saving. Conducting relevant laboratory assessments and encouraging routine vaccinations for all patients with alpha-mannosidosis is also important. Patient-reported outcomes or PROs where we're able to regularly monitor school and work performance, disease burden, quality of life, motor skills, cognitive skills and social competence, as well as caregiver quality of life and well-being, is helpful for the entire family. In addition to other manifestations for patients with alpha-mannosidosis, the Global Delphi Consensus from 2024 recommends monitoring for dental quality and incidence of dental caries, endocrine disorders, growth problems, and unusual behaviors or new symptoms, as clinically indicated.

Now that we've gotten a chance to take a look at many different aspects of alpha-mannosidosis, we can see how patient-centered holistic care is very important. This is critical follow-up for patients with alpha-mannosidosis and for any member of the interprofessional, multidisciplinary care team every step along the way is helpful. Follow-up monitoring includes not only routine examination and laboratory assessments of relevant body systems, but also there are many considerations for the interprofessional, multidisciplinary care team looking at not only the role of the pediatrician, but also the role of medical geneticists and the many other specialists who are involved in patients with alpha-mannosidosis care.

Barbara Burton, MD: That was a great summary of the complexity of the care required for patients with alpha-mannosidosis. Although the multidisciplinary care is really critical, I think you know well how challenging it is particularly in the United States where patients may travel a very long distance to get to their metabolic specialist or geneticist. They may get some of their care locally from specialists in the area. We really need to integrate what goes on in multiple different locations, in many cases, and I really feel like the critical element is that there's some one person who takes charge of coordinating all of that and making sure that everything happens that needs to happen. And that can be a genetic counselor or a nurse in the center; it can be the primary care physician, pediatrician or internist. Sometimes, unfortunately, it turns out it's the mother or the caregiver, which it shouldn't be, but I think that that critical care coordination is so very important because otherwise we have specialists just doing their own thing and we're not really overseeing the big picture. When we can't have a multidisciplinary clinic, which really often we can't because of all of these complicated factors of scheduling and distance and so forth, really that coordinator plays a very important role.

Laura Buch, MSPAS, PA-C: Absolutely! I completely agree, Dr. Burton. Every team needs a quarterback.

Barbara Burton, MD: Absolutely, or a general contractor of care, I say sometimes!