Catching the *Clues,* Changing the Course of Lysosomal Storage Disorders Illuminating the Complex Pathways of Rare Disease with Fabry Disease and Alpha-Mannosidosis in Focus

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Welcome to the Chiesi symposium. The title of this symposium, Catching *the Clues, Changing the Cause of Lysosomal Storage Disease: Illuminating Complex Pathway of Rare Disease with Fabry Disease, Alpha-Mannosidosis, in Focus.*

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I'm Dr. Eto from Tokyo, Japan, and the three distinguished speakers: Dr. Nicole Muschol from Germany, Eppendorf University. Professor Aguiar, the Portuguese, The Inborn Errors of Metabolism Reference Center, and also Professor Robert Hopkin, Cincinnati Children's Hospital, United States.

The purpose of this symposium: Explore the patient journey across the LSD continuum, focusing on the unmet needs and diagnosis, and treatment initiation, and long-term management, and utilize case-based discussion focused on Alpha-mannosidosis, Fabry disease to highlight disease-specific challenges. Access where challenge persist in patient journey, and where tailored intervention can improve outcomes.

Introduction of LSD patient journey with a spotlight on Fabry disease, Alpha-mannosidosis. Challenge to the diagnosis and then treatment and monitoring. Common LSD challenges over the patient journey, as shown here, and at least more than 70 different lysosomal disease known. Incidence is about 1:5,000-1:8,000 in newborn. In the literature, much higher incidence.

Multi-organ manifestation in many organ involved, and clinical heterogeneity are very complicated. The new screen method has been established already. Identify patient presymptomatically. That important by the newborn screening, something like that, early treatment essential. After the diagnosis treatment start, early and the presymptomatic treatment initiation, and usually delayed diagnosis, delayed treatment. Perceived burden of treatment may delay treatment start in patient milder form. Milder form is very difficult in the many cases, and particularly for Fabry disease also.

After the treatment start and then monitoring, as you know, we discussed about the monitoring rely on the combination of clinical assessment, laboratory test, biomarkers, and imaging, and several other factors. Biomarkers and ADA drug assay lack standardization. Actually, the Alpha, and Beta, or [inaudible 00:03:19] Fabry disease, different ADA-titled measurement. Also, the patient experience between clinical visit, ERT infusion is under-reported.

We discuss today two topics, two disease. Alpha-mannosidosis is very rare. In Japan, only few cases, and caused by the deficiency of Alpha-mannosidase, an accumulation of mannose-rich oligosaccharides and inheritance of autosomal-recessive. Age of onset is a very early period and younger period, adult period. Incidence approximately is very rare, 1:500,000.

There are diseases we don't know exactly. If you have a treatment, maybe your incidence is much increased, and severe or attenuated [inaudible 00:04:09]. Alpha-mannosidosis is still a new disorder, and must differentiate from Mucopolysaccharidosis.

On the other hand, the Fabry disease I think is very common. There are many discussion already in the past 20 years. Deficiency of a-Gal A, accumulation of $Gb3^5$-- or Lyso-Gb3, many other glycoprotein, which a terminal of a-Gal A, and X-chromosome. This is very important X-chromosomal inheritance. In case of this, and usually, female does not affect, but in case of Fabry, more of female also involved.

First symptom, imagine at any age. Then incidence about 1:40,000-1:60,000. But depending on the country, as you know, classical form, about 1:40,000. Recently, after the newborn screening, late onset, very high incidence. About 90% of it—actually, we carried out a newborn screening in Japan—90% are late onset. But the clinical variety, so many clinical varieties, so incidents here, 1:3,000-1:4,000, something like that. Now, using the Alpha-mannosidosis and Fabry disease as an illustrative example, we will explore these disorders. First, I would like to introduce first speaker, Dr. Nicole Muschol.

Dr Nicole Muschol

What I'm going to do with you now is to look at the diagnosis of these rare lysosomal storage disorders. We've already heard from Professor Eto, that we are talking about multi-organ disorders. In Alpha-mannosidosis, you have mainly involvement of the cognitive function. You have cognitive impairment. You might have behavioral issues later on in life, also psychiatric manifestations. Very typical is also hearing impairment. Patients usually have immunofunction impairment, so they have an immunodeficiency. You have muscle involvement. These are the main features.

You have to think about Alpha-mannosidosis as a disease with a spectrum from severely-affected infants to manifestations in children and also adolescents. Fabry disease, on the other hand, we already heard in the introduction, there is late onset disease and there's classical disease. The main manifestations are neurological manifestations, either affecting the central nervous system, for example, with strokes, or the peripheral system with neuropathic pain, the typical acroparesthesia.

You might have fatigue in these patients. There is cardiac involvement, mainly the left ventricular hypertrophy, and there is chronic kidney disease, and the first sign is albuminuria. It's important to recognize that you have an eye involvement, cornea verticillata. This is important in terms of making the diagnosis. Also, angiokeratomas as a skin manifestation.

Looking at the diagnosis of these disorders, in Alpha-mannosidosis and Fabry disease as well, is of course, the clinical suspicion as a first hint for the disease. What do we do when we have this suspicion? We can screen for oligosaccharides in urine as a screening test, and we can look at the Alpha-mannosidase activity. Then the diagnosis is confirmed by genetic testing.

In Fabry disease, it's a bit more difficult because early symptoms can be very unspecific, like GI symptoms or the neuropathic pain. You might need organ checkups to identify organ manifestations. Fabry disease is an ex-linked disorder, so it is also important to look at the family history in this disease.

How do we diagnose the patients? We look at enzyme activity again of alpha-galactosidase A. Note that women might have a normal activity, and therefore, you need to do further testing, even if activity is normal. This is why we look at biomarkers. Lyso-Gb3 is the typical biomarker, and we always do genetic testing in these patients.

My main piece I want to share with you is basically two cases where we want to look at how patients made the diagnosis. The first patient is a woman, now 35 years of age, who was or is the first child of nonconsanguineous German parents, and she had an uneventful pregnancy and delivery. Then, mom stated basically from really early on, just a few weeks, she was permanently sick. She had ENT infections, but also bronchitis, was hospitalized with bronchitis.

Early development was normal. She was able to sit independently at 6 months of age, walking a bit later, independent, walking with 18 months of age, so borderline. But then she had a speech delay. She only spoke first words at 20 months. But nobody really wondered because she had all these ENT infections and glue ear, and then she was scheduled for ENT surgery at 23 months of age. This is when the ENT Department ordered for a pediatric consultation. She was seen in the University Center Pediatric Department.

When she was seen in the Pediatric Department, it was noted that she had these coarse facial features and a short neck very MPS-like. Everybody thought this could be some form of Mucopolysaccharidosis. But there were no skin abnormalities, no joint contractures. She had a systolic murmur, but no organ enlargement. The psychomotor development at this stage was documented as not clearly abnormal. They carried out a couple of tests, routine blood and also urinary glycosaminoglycans with suspicion of MPS, but everything came back normal.

They had a cardiac echo that showed a small ASD II. There was an abdominal ultrasound with a slightly enlarged liver and spleen. There was an ophthalmic consultation. No corneal clouding was found. Then they did extensive… I mean, it's quite a while ago, extensive X-rays of the head, of the thorax, of the spine, hips, hand. And the radiologist had this suspicion of a bone dysplasia.

This triggered basically extensive enzymatic testing for several MPS disorders: MPS I, II—more in males, actually—MPS III A-D, IVB, VI, VII, also ML and MSD, but everything was normal. Then they carried out another screening test. They did a blood smear and found vacualized lymphocytes, as a suspicion, giving for a lysosomal disorder.

What happened to our patient? At that time, that's quite a while ago, they didn't have a clue what to do. They decided to watch and wait and do annual follow-ups. Then she had a persistent speech delay. So also, grommets didn't improve anything when she was 3 and 4 years old. When she was five, the diagnosis of a sensory neural hearing impairment was made, and she got hearing aids fitted, so quite late. She developed problems with her fine motor function and also coordination. Also, it was noted that she had an enlarged head circumference. Head circumference was normal at birth, but was then plus two standard deviations.

The diagnosis was made after several rounds of urine screenings and enzymatic testing batteries, and she had Alpha-Mannosidase deficiency and was diagnosed with Alpha-mannosidosis at 7 years of age. What's interesting about this case is that she really had features of MPS, especially the facial features, and that's important for your differential diagnosis in MPS patients, maybe.

The second case I would like to share with you is also quite interesting, I find, because we made the diagnosis when the patient was 40 years old, although he had symptoms before. So what happened? He was a bit premature, not too bad, uneventful delivery. He had neonatal jaundice, but then he basically had frequent infections. Again, we had pulmonary infections, ENT infections. He underwent recurrent ENT surgeries. His motor development was basically a normal, but he had a speech delay and also was diagnosed with hearing impairment and got hearing aids fitted.

In school age, it became apparent that he had learning difficulties. That was stable for quite a while. That was actually primary school, and he also had behavioral issues. He had severe anxiety. He was a bit hyperactive and also displayed other behavioral things. This led to the fact that he underwent extensive metabolic testing when he was 10 years old.

They also found vacualized lymphocytes, and there was a suspicion for a lysosomal disorder, and he had slightly increased glycosaminoglycans in urine as well. But at this time, the family got really traumatized through all these investigations that were carried out. And also, he underwent either a skin biopsy or muscle biopsy—I'm not 100% sure—and had wound healing problems, so they decided not to go back to the clinic and just live their life like the child was.

When he was 40 years old, the family had noted that he had regressed in cognitive as well as motor function. He also had visual deterioration. This is basically where they decided to come to our lysosomal outpatient clinic to present him with a not yet diagnosed MPS disorder.

We found a patient with an angular facial features. We looked at pictures from earlier on where he was a handsome young man, so that was something that developed the last years. He had fleshy earlobes and abnormal helix. He was able to communicate with us in short sentences. His speech was a bit blurry. He was able to follow instructions. He was able to walk independently, but had a broad and unsteady gait. And first of all, we thought that was related to the vision problems, but it turned out he had ataxia. Also, from the skeletal system, he had a long and narrow chest, kyphosis and scoliosis, but no joint contractures.

In this case, we have Alpha-mannosidosis again. Routine blood and urinary GAG were normal. He had an enzymatic panel for MPS disorders that came back normal, but Alpha-Mannosidase activity was significantly reduced and oligosaccharides pattern in urine, abnormal and consistent with Alpha-mannosidosis.

We did a cognitive test in this patient, and he had an age equivalent of a six-year-old child at that time. Echo and ultrasound of the abdominal organs were normal, and he had progressed macular atrophy. This diagnosis was made at 40 years of age in this patient. I think the hint is the late regression, and we actually have a few patients with Alpha-mannosidosis who regressed between their 30s and 40s. This is a bit different in MPS disorders, maybe as a clue.

What are the red flags for the diagnosis? We went through this before. Cognitive impairment is one. The skeletal abnormalities. So this is data of 111 patients that were looked at. The coarse features, but you see not in our patient diagnosis in adult life. Hearing loss is an important one, but when you look at these numbers, you have to take into account that some symptoms only occur… Like ataxia, is quite common in the adult population. So you can't say, "Oh, this is a rare symptom of Alpha-mannosidosis."

In summary, it is challenging to diagnose these very rare lysosomal disorders due to their rarity, due to their clinical heterogeneity, because early symptoms might be unspecific. We need to work on awareness of these diseases, and we need to motivate general pediatricians to refer these patients to specialized centers, and also we need to work on the availability of testing possibilities like enzymatic and genetic testing. This is where I hand over to Patrício on treatment.

Professor Patrício Aguiar

I will speak about treatment initiation. In this patient journey, we need to move on from the diagnosis to the treatment initiation. When we think about treatment initiation in patients with lysosomal storage disorders, we need to think that we have some challenges in our face. So guidelines.

Guidelines, they can be a driver. They facilitate treatment initiation. Also, they can be barriers because if the treatment initiation criteria are very strict, they can serve as a barrier to treatment initiation. Moreover, we have lack of validated biomarkers of treatment response, of prognosis of each individual patient.

Moreover, we have to have individualized treatment objectives. As we understood before, we have a clinical phenotype, a wide spectrum of clinical phenotype, so each patient needs to have an individualized objective of treatment according to his phenotype and his disease stage. Moreover, we have some patients that are at high risk of infusion-associated reactions.

In Alpha-Mannosidosis and in Fabry disease, we have available treatments for Alpha-Mannosidosis enzyme replacement therapy and for Fabry disease enzyme replacement therapy, as well as Chaperone's therapy.

Let's move to the first case report. We have a 21 years old male, and he has complained since he was 8 years old about pain in the extremities, in hands and feet, about braille crisis and abdominal pain. He was mass diagnosis as having rheumatic fever or other rheumatologic disorder, and he was medicated with penicillin or other painkillers or anticonvulsants, but without improvement.

When he was 21 years old, he was observed by a dermatologist who were able to identify Angiokeratomas, and then he was referred to our clinic. In our clinic, we are also able to identify hypohidrosis, cornea vertisilium, and also a slight left auditory deficit. Then we proceed with the Fabry disease diagnosis in mind, and we were able to show that he has almost no activity of alpha-galactosidase A in local sites.

We were able to show a pathogenic variant in GLA gene and also a plasma lyso-gb3 very high in this patient. Then we move to further investigations with an ECG showing a full touch criteria of left ventricle hypertrophy and short PR interval. An echocardiogram only with slight changes in global longitudinal strains. The brain MRI was normal as well as heart MRI, and the kidney function was normal, but with a slight increase in albuminuria and proteinuria.

In this classical the affected male with Fabry disease, we want to start enzyme replacement therapy or other treatment for direct to Fabry disease. We can identify the patients at high risk of anti-drug antibodies, because we have several evidence in the literature showing what patients are at high risk of this type of anti-drug antibodies.

First, patients with higher values of plasmolysed OGB3, the most severely affected classical males with higher values of plasmolysed OGB3, they are more prone to develop anti-drug antibodies. Moreover, patients with non-SAS frameshift variants, they are more prone to develop anti-drug antibodies, as well as patients the starting treatment with agalsidase beta. But there is also a clear relationship between the development of anti-drug antibodies and diffusion-associated reactions.

We know that almost 90% of the patients with infusion-associated reaction, they have anti-drug antibodies. In this case report, I want to highlight that this patient has several features that are associated with increased risk of infusion-associated reactions, namely a classical phenotype, very high LysOGB3 values, and a male sex. It's important to take this into account when we want to start treatment in this patient.

Then we want to move to the second case, a 46-year-old female. He has no symptoms, and he was identified as having Fabry disease in the setting of a family screening. He has a relative, a male, which was identified as having a Fabry disease, classical phenotype, and she has the same variant of the effect, a relative, and a slight decrease in alpha-gala activity in local sites.

We perform all the investigations, the panel of exams, with the echo showing only a mild left atrium enlargement, a cardiac MRI showing low T1, but a normal head MRI, no complaints in the peripheral nervous system. The audio gram was normal. He presents with coronary fertility later, according to the classical phenotype in our family. No angiokeratoma, plasmolysed OGB3 within the range of females with classic phenotype, slightly above 10 nanomoles per liter, and the kidney function was normal.

Here we have the European guidelines, but they mirror most of the guidelines. In females and males with late onset phenotype, we should wait until organ involvement appearance to start treatment. Regarding the treatment initiation criteria in these guidelines, we have the presence of white metal lesions, TIA or strokes, also GI symptoms, kidney involvement with micro-albuminuria, proteinuria or regional insufficiency, heart involvement with increasing in left ventral we call hypertrophy or arrhythmias, and also neuropathic pain.

But nowadays, we have evidence that earlier treatment allows us to achieve better outcomes. We know that patients starting very early treatment earlier than 25 years of age, male, classically affected males, they tend to have a lower value of plasmolysed-GB3 under treatment than the patient starting treatment later after 25 years of age.

We also know that patients starting treatment before 18 years of age, they tend to have better outcomes in terms of kidney and heart function during the follow-up in comparison of patients starting later, mainly patients starting treatment after 13 years of age. These are data from classically affected males. But we have the guidelines in place. In the patients starting per guidelines, they can achieve the better outcomes or not.

As we said, we need to have in terms of the kidney, signs of kidney involvement like albuminuria or renal insufficiency. But we know that patients with renal insufficiency, like patients with a EgFR below 60, they tend to have a higher risk of very associated clinically fats. They seem to be late to start treatment because they do not achieve the better outcomes.

This is also true for the heart. If we wait until we have cardiac hypertrophy with a maximum wall thickness of more than 12 millimeters, we have these patients having higher risks of having an event during treatment. It seems that the guidelines treat patients a little bit later than they can be treated to achieve the better outcomes.

Also, the presence of an event before an enzyme replacement therapy is associated with worst outcomes during treatment. As main take-on messages, I would like to highlight that diagnostic delay and misdiagnosis are the most important barriers to timeline treatment initiation. That we need to identify patients at high risk on fusion-associated reaction and then to drug antibodies because we need to optimize treatment strategies in these patients, mainly in classically-affected males.

We know that there is emerging evidence suggesting that earlier treatment strategy may benefit some patients while delaying until guideline-based criteria may affect long treatment outcomes. But we need to have better biomarkers in order to assess the prognosis of each individual patient and to understand what is the treatment response, because we know that we are late, but we don't have very good biomarkers in order to understand if we need to start treatment before. I will hand over to the next presentation. Thank you.

Dr Robert Hopkin

I get to tell you what to do after you've started your patient. I get monitoring, which sounds boring, but it's really important. We do have monitoring guidelines for both of these diseases, disease. Alpha-mannosidosis guideline has just been published in 2024. It's a very rare disease, so there's a lot less detail going on, and we need to collect more data, which means we need you to monitor those patients, particularly closely, so we can update the guidelines effectively.

Fiber disease, we have had guidelines since the early 2000s, and they have been updated several times. We have broader recognition, but we still have underutilization of the guidelines, and many practitioners are unaware of some of the current recommendations.

Consensus statements for Alpha-Mannosidosis. There are about 60 best practice statements noted. Patients should be monitored closely for changes in cognitive impairment, changes in behavior, increased evidence sense of balance problems, ataxia, or increasing levels of immune dysfunction, and things need to be done and can be done to address those issues.

The other thing that's complicated with them, it means that there's more than one treatment option. If somebody has opted for monitoring versus treatment, what should you do differently with the patient as far as the monitoring that you go. My recommendation is that that should be the same. You don't want to space out your testing because you're not giving a drug and then miss progression of the disease.

Some kids will have stem cell transplant, which does improve outcomes for this disease, but the monitoring that they need is going to be different because you have to monitor the stability of the transplant. We need a holistic approach that is tailored to the current needs of the patient. We need to know how the patients are doing, both with the common and the less common manifestations. We need to monitor these children and follow them regularly.

Guidelines for Fabry disease, this is one of the more comprehensive guidelines, but there are several that are available now. They are all very similar in most ways, but do have some differences. What do we look at? This is clearly a multi-system disease. You need to update on how the patient is doing by doing a physical exam and getting a good history, updating family history with every encounter.

We also need to monitor changes in renal function, heart function, cerebrovascular manifestations, pain, etc. I Ideally, we will do this without waiting for the patient to be doing worse, because a lot of times, reversibility is not very good if you wait until you have signs of permanent damage.

Paying attention to subtle changes in things like kidney and cardiac function is important. We need better tools for GI monitoring, but definitely ask. If somebody gives you a hint that there's a problem, ask the follow-up questions. Anti-drug antibodies have been mentioned already. These do change with time. They are associated with an increased risk for infusion reactions and for decreased impact of the drugs. We tend to think of anti-drug antibodies as being just a plus or minus thing.

But we have to remember, there are IgM, IgG, IgA, and IgE antibodies that have different implications. Furthermore, the IgG antibodies have subtypes, and those also have different risk factors for the degree of risk for infusion reactions and the severity and chronicity of the infusion reactions. It's good to monitor the antibody levels, including down to the level of some of the details of the antibody types if that's available.

Now, if you think that your patients are going to tell you how they're doing, as you can see from this slide, about half of the time you will be right. They will tell you if there's been a change, but you'll be wrong half the time. Which means of the people who are experiencing breakthrough symptoms between infusions, only half of those are going to tell you that unless you specifically ask them. Ask the questions.

Now, if a female patient, she is in generally good health, has a confirmed diagnosis of Fabry disease, a demanding work and social life, and she is on treatment with ERT. She is tolerating the treatment well, but her reason to go on treatment was to preserve her ability to have this active life, keep up on her work, and have energy for her friends. But the last 4-5 days between each infusion, she has increasing symptoms of fatigue, daytime sleepiness, dizziness, and worsening pain.

You have a patient with breakthrough symptoms, and you want to know what to do about it. Most people will try to treat the symptomatic things with medications. It is clearly something that's difficult to manage. Less people are admitting to them, but I suspect that they are more frequent, maybe not in this group, but in general, than we would like to think.

Now, let's go to the next one. Another female patient, 35 years old, has been receiving ERT for a couple of years, has a reasonably short infusion time, but for the rest of the day, on the day on the day of the infusions and for the next day, she has fatigue and dizziness. She's on premedications. She started off without any premedications, but premedications were added to see if that would help to reduce these symptoms. But she reports no change in that.

The diagnosis is classic Fabry disease in this patient. How would you manage this? Would you use ADHD treatments, steroids, discontinue antihistamines, add other drugs, change the infusions, et cetera? We

have more than one option for treatment. Trying a different treatment would be good. For this particular patient, in my opinion, one of the things I would definitely do is discontinue the antihistamine because it's not doing any good. It didn't help.

Then the other things, it depends. For example, if I have a patient who has severe daytime sleepiness or severe fatigue, I'm going to want to treat that. If I think that that is due to the Fabry disease. In this context, it's only related to the treatment. I don't know if I'm going to treat that with a separate medication or try to adjust the treatment. We have a patient here. I'm not going to give you a final answer on what to do, but I will tell you that we need to pay attention to what the patients are telling us.

We also need to pay attention to what the patients aren't telling us, and we want to know if there are changes before the patient knows that there are changes if possible, because that gives us the best opportunities to optimize the patient's outcome.

Conclusions. We need a patient-focused approach monitoring. We need to assess quality of life. We need open communication, asking specific questions, and if they give positive answers, following up with those specific questions. We need to consider symptoms that the patients might be concerned about, and we need to order the testing that is recommended for the monitoring and additional testing as indicated. Now we'll turn the time back over to Dr. Eto.

Okay, thank you very much. Three speakers, distinguished speakers. We learned the Alpha-Mannosidosis and also the Fabry disease. This is a take-home message diagnosis. The Fabry disease benefit from family tree analysis. I think this is important, you know already. Also, the diagnosis by DBS, a newborn screening in Japan, Taiwan, and also Italy, US. Now expanding in many countries and on screen give us a more important message to you. Alpha-mannosidosis dose is very rare. But once you notice this disorders, maybe you include the enzyme assay panel in the lysosomal disease to detect Alpha-Mannosidosis deficiency.

Professor Yoshikatsu Eto

This is a difficult diagnosis because it's not include the test panel. Alpha-mannosidosis dose must be differentiated from the NPS. If you have a NPS patient, you must have assay. Alpha-Mannosidosis enzyme assay. Diagnosis made by EZD by the DBS leukocyte and also skin fibroblasts. Greater awareness, Alpha-Mannosidosis, also beta also. But you must notice about these disorders.

Then treatments that, for every patient, we treated in Japan 100, 1,000, almost 500, maybe number second in the country in the world. We treated the ERT, Alpha, Beta, and biosimilar and chaperone

therapy. Treatment guideline in late onset, very difficult. We have diverse clinical spectrum in late onset after newborn screening. Some patients, no clinical symptom, almost normal, and sometimes you find out [inaudible 00:38:28].

You cannot identify that this mutation is symptomatic or not. So this is a difficult point. It's a huge problem, huge task forces. Alpha-mannosidosis, few cases, as we mentioned, reported. And the ERT is not yet approved in Japan. But once you find out that this enzyme therapy approved, you will find out more patients. Education and also education to the physician is very important, and so they only approve in the US and EU. So diagnostic delays, hinder timely treatment. So after the treatment and monitoring is important and also incorporate the PRO and individual ERT management based on the patient and drug characteristic.

Also, antibody formation, still, we are discussing. And how do you monitor the antibody, and how do you assay... Assay method is different in each company. So antibody titer, how do you moderate this antibody? And antibody also produce the IRR and some other things. And Alpha-mannosidosis monitoring, less common. But anyhow, diagnosis, very important. Highly treatment, important. So a patient-centered approach to critical improved long-term outcome.

Now, we don't have enough time, but we start the question, Q&A session. Do you have any questions to the speakers? Dr. Hopkins, do you think a symptom worsening between infusion is due to the short half life of ERT?

Dr Robert Hopkin

Symptoms worsening between infusions, we don't know what causes that. We do know that it's a commonly reported thing, and it could be the short half life because the drugs are eliminated, the enzyme activity is dwindling, but that has not been adequately studied to say definitively what's causing it. We need a lot more information.

Professor Yoshikatsu Eto

At what frequency do you monitor for ADAs?

Professor Patrício Aguiar

I think that the frequency of monitoring, it depends on the phenotype, the sex of the patient. In classically-affected males, of course, we measure it at baseline and thereafter, every 3 months, at baseline, 8 months, 6 months, and every 6 months thereafter. However, in the other patients, like in females or late onset males, the risk of anti-drug antibodies is quite lower. We can measure them in a longer period or

even don't measure them instead until we have infusion-associated reactions. If we have infusion-associated reactions, we need to assess them even if the patient is late onset male or a female with Fabry disease.

Professor Yoshikatsu Eto

What's the point to give a diagnosis Alpha-mannosidosis very, very rare. Are there any difference in clinical pictures? I mean, particularly the schilder problems, in different from the NPS. What do you think about this kind of the matters?

Dr Nicole Muschol

So first question, maybe the point of diagnosing is being able to treat them. There is ERT available, there's HSCT available, there is HSCT to salvage the central nervous system. If you can diagnose them very early and maybe treat them early, so these are the considerations. And there are differences between MPS and Alpha-mannosidosis.

You also have [inaudible 00:42:26] changes, but you have the hip disease in Alpha-mannosidosis, but you don't have joint contractures like in MPS diseases, for example. That's a bit different. You do have scoliosis, kyphosis, but they aren't as progressive in Alpha-mannosidosis, either as in MPS diseases like MPS 1 or 6.

Professor Yoshikatsu Eto

What is the biggest barrier to see today in transitioning Alpha-mannosidosis patients from the bed to the adult care, the regional that are transitioning well?

Dr Nicole Muschol

We don't do transitioning to adult care. I unfortunately have to state. So I think that you have patients with cognitive impairment. We usually have the parents accompanying them. But in our center, we never transition. We transition that subdiscipline, so they go into adult cardiac care when they have cardiac manifestations, for example, but we still see them in the pediatric department. I think this is very, very country-specific question. Some countries transition, like in the UK, you are transitioned to adult care all the time, or in Portugal, I guess, Patricio, is the same. You get transitioned. You're probably seeing there.

Dr Robert Hopkin

And in the US, it depends on where you live, what transition you get. At my institution, we don't transition, but in some places they do.

Professor Yoshikatsu Eto

With the treatment, is there any exploration of newborn screening or Alpha-mannosidosis. This could help identify attenuated condition or severe condition.

Dr Robert Hopkin

There is attenuated and severe disease for this, and so you would want to account for that. Newborn screening is valuable if earlier treatment improves outcomes, and there is already evidence enough to say that earlier initiation of treatment does, in fact, improve outcomes because it helps preserve mobility, decreases progression of the ataxia, and can improve the immune system.

Dr Nicole Muschol

I really think there is no attenuated added Alpha-mannosidosis, so you have cognitive impairment. We have lots of these patients who really regress in adult life. I mentioned that in our case between 30s and 40s, so I'd be careful to call that attenuated. Of course, it's different than the early onset, very severe ones, but still.

Professor Yoshikatsu Eto

When patients have IRR, could you consider switch to oral therapy?

Professor Patrício Aguiar

In patients with Fabry disease, the patient presenting infusion-associated reaction, we can switch to oral therapy, but if there is an amenable variant, because most of the patients, classically-affected males, the patients that have more infusion-associated reactions, most of them are not amenable to chaperone therapy. It depends on the amenability. But if the patient is amenable, we can try because the patient will not have infusion-associated reaction.

Professor Yoshikatsu Eto

What is the optimal monitoring for the adult woman with late onset Fabry disease?

Dr Robert Hopkin

The females with late onset Fabry disease should be monitored as regularly as if they were any other form of Fabry disease, and they should be monitored whether or not they currently are qualified for treatment. That doesn't mean all of them will need treatment, but I have had experience where women decided they weren't going to be monitored and came back with advanced heart failure because they don't usually get pain. They don't have some of the other typical findings of Fabry disease, but they are at risk for slowly progressive heart and kidney disease. And if we aren't monitoring it, we're going to miss that and miss the window of opportunity where we could help these patients.

Professor Yoshikatsu Eto

Okay. Thank you very much indeed, all the audience. Thank you very much to participate in this symposium. Thank you.