Ozlem Goker-Alpan:

Good afternoon and welcome to a new CME series on lysosomal disorders. Aware this season that we'll be approaching to the lysosomal disorders in a systems approach through the organ systems, where we invite a subspecialist to discuss different disorders through an organ.

For today's talk, we invited Dr. Walla Al-Hertani from Boston Children's Hospital to start with a wholesome approach, that she's going to be talking about the multi-team approach to lysosomal disorders.

As a brief intro for this topic, I actually gathered some slides just want to remind you what the lysosomal disorders are and how we manage them in a multi-system way.

So lysosomal storage disorders, while they're rare individually, honestly, they are common disorders in a collective way. So the incidence is almost one in 5,000 births. So every half an hour a baby with a lysosomal disorder is born. However, most lysosomal disorders, especially the ones that are recognized later on, such as the adult or juvenile, or later juvenile subtypes, actually miss the diagnosis early on. As I said, the LSDs can present during early infancy, childhood, and adulthood.

Lysosomal storage disorders, even though there may be one system predilection, such as the hematopoietic system in Gaucher disease or cardiovascular and vascular system in Fabry disease, they are truly multisystemic disorders, such that requires a complete clinical examination that we deem to be head-to-toe. A neurologic exam and also a gait exam is an essential part of the evaluation of a patient.

It is important to know that there are specific therapies that exist for some lysosomal disorders, and the number is increasing with each day. Thisrequires a change in the course, how we care of the patients and how we design the multi-team approach to these patients. As we know that there is a disease spectrum in lysosomal storage diseases, there are purely neurological forms such as the Sanfilippo disorder. There are also peripheral forms such as in late-onset Pompe disease.

This is a slide from the 1990s. The reason I want to give you this as an example because truly the landscape of lysosomal disorders in the clinic is changing. So, as you see, this is the Australian data where the most load of lysosomal clinic actually comes from the clinical recognizable patients by phenotypes, such as the MPSs or severe neurological phenotypes such as Krabbe disease or GM2.

However, with the advent of genomic and genetics approaches, now we have less recognized presentations and especially more adult type patients exist in our portfolio in the lysosomal clinic, and also which is also important because more therapies are being introduced.

So there are pros and cons of a comprehensive or a multidisciplinary approach to a patient with lysosomal disorders. You can ask why there are cons because it is a pro thing. Is that right? Obviously such an approach will allow for early detection and management of complication and initiation of specific therapies, and also the introduction of new therapeutic modalities, because it would be easier or allow the team to select the patients for this upcoming clinical trials.

Also, this will allow the team to offer psychosocial support and better quality of life to the patient, and also, which is important, transition and long-term care of these patients, especially from the pediatric to adolescent clinics, to young adulthood and later on.

However, what a multispecialty clinic could also jeopardize or have challenges, obviously the resource allocation, coordination among different specialties, and access to expertise, which is I think the most important thing here because we don't have enough experts in the field to separate the knowledge and education. This is why we're doing this series actually.

And also coordination and communication. And also offering such a care, even though it had all the good intentions, may lead, inadvertently, to fragmented healthcare systems because the patients will get shuffled to one place to another without a leading team. So obviously there needs to be a limited awareness and education.

With that said, I would like to invite Dr. Al-Hertani, who holds combined honors in Biology and Biochemistry degree from Dalhousie University from Halifax, Canada. She received her Doctor of Medicine degree in 2005, and she got further trained in residency in medical genetics and also in medical biochemical genetics. She held various academic appointments at human genetics, pediatric and medical genetics at McGill and University of Calgary.

To the United State's luck, she decided to move from the border to Boston Children's, where she holds an assistant professorship title. She's the co-director of the lysosomal clinic. She also actually runs a clinic at Brigham and Women. Walla, I would like to invite you to present your talk on challenges in the current care models for lysosomal disorders.

Walla Al-Hertani:

Thank you very much, Dr. Goker-Alpan, for this fantastic introduction and also for your very kind invitation. I'm just going to share my screen.

Thank you for everyone in attendance today. I think some of you may have heard some of the content that I will discuss today. But I do feel this is a very important topic. Thank you, Dr. Goker-Alpan, for bringing this up as a discussion that should be had in a wider arena. Let's see. So these are my disclosures.

So today really the purpose of this talk is to take a bird's eye view of the care models that we have in place that will apply to lysosomal disorders and inborn errors of metabolism, and how precision medicine fits in. And are the care models that we currently have keeping up with the advancement in precision medicine? There's a lot of advancement happening with therapies, but I'm not sure the care models are actually keeping up.

The infrastructure for these care models is pretty significant, and making changes is a huge task to tackle. So we really need to start thinking about these things now for the future of our patients and the care that we offer our patients.

I will also like to cover access to adult care and transition to adult care as a subarea of multidisciplinary care. Then I would like to open it up at the end in the discussion for ideas from the audience on how can we make a shift in these care models.

But I always like to do a brief introduction about precision medicine because it's so important for lysosomal disorders and inborn errors of metabolism. So there was a precision medicine initiative put in place January 2015, and it was launched to accelerate the understanding of individual variability and effect on disease onset, progression, prevention, and treatment.

There are three arms to this initiative, discovering new biomarkers predictive of future disease risk, and also extremely important for clinical development of newer therapies, discovering determinants of individual variation in response to those therapies, and then enabling targeted clinical trials with rich clinical data.

Although one may think that precision medicine is a relatively new term in medicine, it's really not. The founding father, as we like to call him, of inborn errors of metabolism, Sir Archibald Garrod, was the first to describe the idea of biochemical individuality in health and disease. In a manuscript in 1902 where he discussed the incidence of alkaptonuria, another rare disease/inborn error of metabolism, he commented that the thought naturally presents itself that these conditions, alkaptonuria, albinism,

cystinuria, are all mere extreme examples of variations of chemical behavior. Just like there are two individuals of a species who are not identical in bodily structure, neither are the chemical processes.

So, really, there are many types, and this can be an entire talk by itself on precision medicine, but I really see inborn errors of metabolism as a perfect subset of conditions for precision medicine. Why is that? Inborn errors of metabolism are a subset of genetic, clinical genetic, conditions. They can be rare or ultra rare. The underlying defect typically is a deficiency of an enzyme, a deficiency of a co-factor, leading to some sort of toxicity, leading to cell death, or leading to the inability to generate energy, which is needed for bodily function.

This is just a diagram to show you all the biochemical reactions and how intricate these reactions are and how intertwined they are. And so, you can imagine, if we simplified it down to a schematic like this, if an enzyme is not working, the substrate increased, there are downstream effects of this substrate accumulating, including toxicity. Then not being able to generate a product that is needed for the multitude of reactions is also challenging and problematic.

Sometimes it's not the enzyme, sometimes it's a co-factor that is missing, but this is really the basic framework behind inborn errors of metabolism.

So, as you can see, they lend themselves very well to precision medicine, because just looking at that very simple diagram, you can think of different ways to develop therapies. In fact, this has been the basis for many of the therapies that we have right now. So replacing the missing enzyme. We have multiple types of enzyme replacement therapy. Removing or scavenging toxic substrates. We do have examples of that. We're providing the missing product or providing the missing co-factor.

So what these treatments have done for, I would say ... I'm lumping here lysosomal disorders and inborn errors of metabolism ... multiple decades now is they've improved survival significantly and they've improved outcomes. But we know they're not curative. We also know that many of these therapies, whether they're dietary, oral, repeated enzyme infusions, require a lifelong compliance, and this is something that is quite difficult to achieve for our patients.

So, as many of you know in the audience, there are multiple new types of therapies that are coming down the pipeline that will even, again, change the natural history of these disorders.

So, as I said, inborn errors of metabolism are a subset of clinical genetic. Lysosomal disorders are a subset of inborn errors of metabolism. There's about 70 monogenic conditions. They're individually rare, but with the incidence that Dr. Goker-Alpan mentioned, they're not that rare.

There are many different ways you can develop a lysosomal disorder. It could be a lysosomal enzyme deficiency. I Could be an impairment in membrane-associated protein, defect in enzyme activators, or modifiers that alter the lysosomal function. We typically categorize the lysosomal disorders in categories such as mucolipidoses, mucopolysaccharidoses, sphingolipidoses, as this schematic shows here.

So, as Dr. Goker-Alpan mentioned, lysosomal disorders as a group affect nearly every organ and every system. They are multisystem conditions and, therefore, when you are caring for a patient, you have to think in a systematic fashion. Depending on where you are on the phenotypic spectrum, because this is something else that we see quite commonly with lysosomal disorders, is the condition the phenotype is on a spectrum, you can have symptoms varying from relatively mild somatic symptoms to severe somatic with rapidly progressive neurological manifestations.

For example, I'm just going to pick the sphingolipidoses, and Gaucher disease as an example of sphingolipidoses. Everyone knows in the audience that Gaucher disease is a multisystem disorder. Some of the main features include hepatosplenomegaly, anemia, thrombocytopenia, bone disease, bone crises. Onset can happen in the first or second decade, but may present any time between infancy and adulthood.

We have this classical categorization of Gaucher disease of non-neuronopathic type 1 versus neuronopathic type 2 and type 3. But in reality it's really a continuum and, in fact, patients with type 1 also manifest certain neurological findings, as well as the increased risk for Parkinson's disease and Lewy body dementia in patients with type 1, as well as carriers of Gaucher disease.

So just looking at this schematic very quickly, it shows you some of the organs that are involved in Gaucher disease. Very quickly you realize, if you are a geneticist or a metabolism physician, that your patient needs to see a hematologist. Your patient is going to need to see an orthopedic surgeon. You're going to need to collaborate with your radiologist. You may need to see gastroenterology to look at the liver. It's not mentioned here, but there are liver manifestations outside of hepatomegaly in Gaucher disease. So very quickly, if you look at every condition, you can determine that you're going to need help from multiple specialties.

This is just one final slide that I wanted to talk about before moving on to the challenges. The majority of drug development in inborn errors of metabolism has really been focused on lysosomal disorders. So lysosomal disorders as a field have laid the framework for drug development and therapies that are life-changing, which is really fantastic. The therapies that we have currently, enzyme replacement therapy, small molecule substrate reduction therapy, and of course hematopoietic stem cell transplant.

But there are lots of therapies coming down the pipeline. There are lots of clinical trials that are happening at your site and many other sites, including, for example, second-generation ERT that is able to bypass the blood-brain barrier, an obstacle that we face with the first generation, intrathecal, intracerebroventricular delivery of ERT, combining ERT and small molecule therapies, and of course ... I think, in 2020, there were at least 35 clinical trials for gene therapy in lysosomal disorders. I'm sure the number is much, much higher now.

So the reason I wanted to talk about this is this shows you that the advancement is happening at a fantastic rate. If it could be faster, that would be even better for the care of our patients. But I don't think that the care model that is being carried out in clinic or in hospitals or in centers is really keeping up with the advancement of therapies. This is why I think it's important to have this discussion.

So I broke down the challenges into four categories, and I'd like to go through one-by-one. So this is the challenge that we talk about the most. So the diagnostic odyssey, the delayed diagnosis. Why does this happen? Most of the patients and families, their first point of contact is either their primary care provider or a non-lysosomal specialist.

So that specialist or primary care provider has to think about lysosomal disorders to refer the patients and their families to the right center and the right specialists, and it takes time before this happens, and this is part of the diagnostic odyssey, as I'm sure you've heard many stories along those lines.

Another obstacle for delayed diagnosis is urban versus rural centers. Most large tertiary care specialty centers are in urban areas. The rural areas don't have as much access and, therefore, having a referral to go to an urban center does take time and may not be as timely as if you lived in an urban center.

Atypical adult presentation. This is definitely an issue with the later onset presentations for some of the lysosomal disorders. The patients are underdiagnosed. So they also have their diagnostic odyssey. Because typically those presentations can be on the milder end, that diagnostic odyssey can be significant, multi-decade diagnostic odyssey.

Then of course if there was equal access to genetic and biochemical testing across the board at every center, that would be a game-changer. But that is not the case. Not only is access to genetic and biochemical testing not equally available at every center, but also there is the obstacle of insurance, and not every insurance would facilitate the patient to access this type of testing, which, again, further delays diagnosis.

Another challenge that I'm seeing more and more frequently being a physician working in a large center in Boston and seeing patients from many areas outside actually the Greater Boston Area, including Maine, New Hampshire, Rhode Island, and this is actually even accentuated even further by newborn screening where we're now able to, which is great, identify patients as infants with lysosomal disorders like, for example, Pompe disease and identifying a patient with infantile onset Pompe disease.

But I have patients who live six to eight hours away, and once the diagnosis is made, they have to go to an infusion center for their ERT. They have to drive every week or every two weeks, depending on the ERT and the diagnosis, six to eight hours to come to the infusion center. There is a financial cost to that. There is a time cost. There is a significant burden on the family, especially if there are multiple other children.

Unfortunately, this does lead to compliance issues and will impact outcome. So although this is not discussed as much because it varies between state-to-state and region-to-region, but this is a major challenge that I'm seeing in multiple patients at my center at the moment.

This next challenge, I want to spend a little bit more time on, which is there are two type of adult patients. There are the adult patients who are identified as pediatric patients, and then they were in pediatric care until they reached 18 years of age, and then they need adult care. Then there are the adult patients who present as adults because they have adult onset conditions. I will talk about both.

What we do know, as I mentioned, the availability of therapy and the types of therapies we have available have changed the natural history of rare diseases like inborn errors and lysosomal disorders. So 90% of patients now survive past 20 years of age, and 50% of those patients are adults.

So although 50% of our patient population are adults, we actually are taking care of the adult patients in pediatric centers. So this is problematic because pediatric phenotypes are more understood than adult phenotypes, the complexity of adult care ... Because then there are other elements and caveats that you have to add when someone is an adult that you don't think about in pediatrics. If you continue to care for adult patients in a pediatric setting, I'm not sure that that is the most optimal way to do it. But this is all historical.

So historically most patients with rare diseases were pediatric patients. So the pediatricians had the most experience, and this field was under the purview of pediatricians, which also led to adult physicians having very limited familiarity either with the diagnosis or with the management.

But I gave one example, and I'll talk about another example in a minute. When you have complex conditions in adults, as well as just regular age-related health problems on top, I'm not sure that the pediatric center is the place to be for the most optimal care for our adult patients, and we need to have expert adult providers.

I came across actually these two surveys, very similar surveys of metabolism physicians. One survey was in the US and another survey was in Europe. The survey was really trying to elicit more information about how is the care provided in those different regions in the world.

Interestingly, 98.9% of US physicians said that they, metabolic physicians or lysosomal physicians, take care of both pediatric and adult patients in pediatric settings versus 84% of European physicians. European centers were more likely to have separate adult metabolic clinic and they were more likely to have specializations. So a lysosomal clinic, small molecule clinic, so on and so forth. In contrast, in the US, adults, as I said, predominantly receive care in pediatric clinic, and they're predominantly not as specialized and tend to have limited access to adult care.

Many tertiary US pediatric hospitals are standalone institutions and unaffiliated with any local adult institution. So you can very quickly imagine what kind of obstacles our patients face, especially as they enter adulthood or as adults, as they continue to come to a pediatric setting for their care.

If we thought about the other angle, adult hospitals that are not affiliated with pediatric institutions, for the most part, typically don't have genetic, metabolic, or lysosomal specialists, and they may not even have some of the ... Let's not talk about the complex therapies, but even the more simpler therapies for metabolic disorders and lysosomal disorders.

So I don't think there's one system. I think Dr. Goker-Alpan mentioned this a little bit earlier. There is no one perfect system at the moment. Both models can result in care fragmentation and, specifically when we're talking about adults, prevent the adults from receiving ... So adults meaning older pediatric patients who have been under care in a pediatric setting and then getting older and transitioning to an adult setting, they're not really getting the necessary multidisciplinary care that they need.

So what about access to multidisciplinary care, both in pediatric and adult setting for patients with lysosomal disorders? This is the next challenge that I'm seeing quite frequently. So when I say access to multi-D care, I mean I gave the example of Gaucher. You're going to need orthopedics, you're going to need neurology, you're going to need gastroenterology, you're going to need hematology. Do you have access to all those specialists within one center?

Typically, in larger academic centers, yes. But as not every center is a large academic center, patients who go to smaller centers may not have that access. So what that means is now they have to travel for their care to other centers. Then there has to be some sort of continuity of care and flow of information from the various centers back to the supervising rare disease physician to make sure that the plan is being followed for the patient most appropriately. Most of them, even in the larger pediatric settings or in the smaller settings, there is really insufficient adult multi-D care.

So let's, for example, look at MPS. There was this really nice table summarizing all the different specialists that you need for the care of all the types of MPS. In fact, the table is pretty extensive, but I noticed that there were no genetic counselors. I feel like you need prenatal genetic counselors, lysosomal genetic counselors. You need obstetrics-gynecology. That was not in this list.

But you can see in the list that it's an extensive number of specialists that are needed for the care of the patients. And so, if you are not in a center where you can easily access those specialists, then that means that you have to travel, you have to find the time, you have to find the money, and then there has to be some sort of coordination with the primary center.

In addition, most of the lysosomal disorder physicians now have a lot of experience with enzyme replacement therapy, how to deal with infusion-associated reactions. We need that kind of expertise for gene therapy. So as we are moving closer and closer to gene therapy, we need experts in gene therapy who are also caring for our patients. I'm not just talking medical doctors, I'm talking nursing, I'm talking all allied health professionals, and we're not really anywhere close to that at this point. But this is just to illustrate if we want to really provide precision medicine for lysosomal disorders, we have to start thinking about these things.

So with very few exceptions, in general, lysosomal clinics are run by metabolic docs who are pediatricians and standalone pediatric centers. What they do is they refer the patient. You need specialty X, you get referred to that specialist. Those lysosomal clinics are within metabolism units, which are within genetics divisions and departments.

So you tend to find that in larger centers. This is not necessarily the case in more rural areas or smaller centers. Even if you have a pediatric patient, being in a small center, again, presents the issue of not all the specialists are available to your patient, which your patient again will need to travel.

There is definitely a lack of adult care infrastructure within the pediatric centers, and raises many, many challenges. For me, I see this quite often being at a pediatric center, it is most accentuated when my patients need psychiatric care, obstetric care, or gynecological care, which is definitely something I

cannot provide at a pediatric center, and very difficult to access, especially if your patient is admitted at other adult center. You have to wait till your patient is an outpatient, and then you refer them. Really not an ideal way to deliver care.

In addition to that, due to workforce changes post-pandemic, reduced human resources and other resources, pediatric hospitals now are moving more and more towards incorporating age limits. So what's happening is now you're going to have to refer your patient to an adult center for various systems, and there's no integration of the electronic health records. That can be very problematic, as I mentioned, for continuity of care.

In addition, you have the lack of awareness. So if I wanted to send my patient to an adult orthopedic surgeon for a hip replacement or a knee replacement, there are very few adult orthopedic surgeons who can see my patient, who have the experience of lysosomal disorders or MPS, for example.

So not only do you have the physical center separation, the electronic health record separation, you have the lack of the knowledge. Then you yourself, as someone who has this knowledge and trying to create this surveillance plan for your patient and give them the best outcome, have to do this extensive communication and collaboration with all of these providers, which in itself requires infrastructure and processes, which most of the time are not in place.

So I think I'm really trying to show some of the obstacles that I'm facing with my patients, be it pediatric patients or adult patients.

There are some other care models. So I mentioned the more common care models. There are some other care models. For example, expert pediatric center with an official affiliation with an expert adult center, with established transition processes for the patients starting at the age of 16. There is a specific process until the patient is 18, where they're completely transitioned over to the adult center, with electronic health records easily moving with the patient. There is continuity of care, and the providers, because they're at affiliated centers, are in very close communication with each other.

There are also a few examples of standalone lysosomal centers that provide whole-person care across the lifespan. I feel that does give you the best outcome and would be the best model going forward. But, of course, there are all kinds of things that one has to think about if we wanted to have that model countrywide.

So I have questions more than I have answers. How can access to multidisciplinary care to both our pediatric and adult patients be improved? I will ask the audience for ideas. How can we provide better transition processes, as well as increase the knowledge for adult onset conditions with adult providers, so the care does not have to always be in a pediatric center, which is not age-appropriate for an adult patient?

So in my opinion, I think there are multiple things to think about. First is education. I know we've been talking about this. We've been talking with our industry colleagues about education of providers, but I feel the education is not just education of providers in practice right now, but has to start early on and has to start in medical school, in residency, and not just trying to catch very busy providers to give them information. So that's going to be an essential part of the solution and requires collaboration with medical schools, deans of medical schools, so on and so forth, department heads.

We also need frameworks. We need processes. Currently, as many of you know, every center has a slightly different framework, different process. Patients get different types of care depending on where they go. Ideally, this needs to be streamlined a little bit.

I don't think single universities or single centers can do this alone. I think it has to be a wider collaboration. Maybe it even has to come from a governmental level, like a state-level support, funding, obviously, and collaborations.

I think those are the categories where I feel the innovation is going to come from to change the care model that is available right now. There is definitely an urgency to change it. I don't see how we can continue with the current care model and have five or six types of gene therapy available for treatment, but still be caring for the patients using a model that is a few decades old.

So I'd love to hear from the audience. I think there may be questions.

Q&A

Ozlem Goker-Alpan:

Yes, there are a few comments and questions. Before I start actually reading the questions and comments verbatim, how we started about 10 years ago now as a standalone center, which is probably one of a kind in the US, if not in the world, with an aim actually to provide easy access to expertise without the convolution of the whole system.

Truly, the system does not allow this kind of approach because the patients are so complex. The families are most often neglected and the expertise is lacking. And so, this really doesn't work with the current practice of spending 15 minutes with the patient and looking and writing your note most of the time.

This is what we try to provide. However, then we face with the education issues, and then the funding issues. The reason is mostly, as you said, it probably needs to be taken at a state, maybe a federal level. But we know that most grants actually go to this very large academic centers for, quote-by-quote, rare disease or the donations, and academic center will pick and choose what their interest is, to put them from level A to level B. It is not necessary what the patients need.

So these are actually some of the issues that we need to start talking about, and about the expertise, too. Expertise, fortunately and unfortunately, requires numbers. So basically I understand each university, academic center, large hospital can be, quote-by-quote, centers of excellence in one or two, three patients. However, truly like the surgery for Gaucher disease. Is that right?

Now we don't have too much surgeons to deal with this issue. And so, we have less and less surgeons that are indeed experts to deal with the bone issues in an older patient that requires a repeat hip surgery. Then this requires patients traveling and actually going to uncharted territories, which occasionally is a must. Like for the MPS, is we know that one hospital is the hospital of orthopedic care for the MPS patients. Literally, I would rather refer my patients to that place rather than trying and error for something that is so rare.

I mean I'm going to give myself as an example. My child requires splenectomy, and splenectomy is not something done very often right now. And so, we had to travel out of state, stayed at a hotel, and then we had to come back while he was actually still sick because we had to attend our affairs. So, unfortunately, there will be issues.

But I'm going to start reading the questions because there are really some interesting comments and questions here. First, this is coming from a family, I believe. So I'm going to read verbatim just so that the others can hear that, too. "So based on our lived experience of 19 years with ASMD, which is Niemann-Pick A/B, the concept of the center of excellence for disease-specific care is working against our ability to access quality sustainable care rather than for it. I would love to see efforts to de-emphasize the pressure we are put under to seek care at these centers."

So basically they're giving a standing ovation to you. So how would you comment on that? I mean obviously we need centers of excellence, but how we can actually get this into the community and then try to be more approachable to the patients?

Walla Al-Hertani:

Thank you so much Dr. Goker-Alpan. Thank you so much, Karen. I mean you're absolutely right. I would love nothing else than to have my patients get local care. I'm constantly thinking about this issue because it's just not sustainable to drive six to eight hours to get an infusion of an enzyme, and then do it again next week and then doing again next week. There are multiple children, there are large families, people have jobs. I have patients who can't afford parking or the car breaks down in the middle of the drive to the infusion center.

We need infrastructure to have this care locally. Like myself as a physician, I don't really have any power to make this change, but maybe we need to start lobbying state governments. Why are there states that don't have this care? Can they fund care like this? The larger centers, at least for myself, I would be more than happy to support other centers to have this care locally for the benefit of my patient.

I don't want to see patients suffering just to get care. It doesn't really make a lot of sense. But that requires big change and requires highlighting these issues at a higher level, at a national level. Maybe this is something that the National Organization for Rare Disorders would take on, lobbying governments and so on and so forth. But I absolutely agree with you.

Ozlem Goker-Alpan:

Yeah. So another question is about guidelines that promote the concept of the team approach care, but that is simply not practical outside a rare disease. We're coming to the centers of excellence. Is this concept in need of changing? If so, how? So basically that is what we discussed a little bit earlier - the community and what might be the other steps.

Walla Al-Hertani:

I think it is definitely not practical. I like the idea of the whole-person care within one center, because the idea of having a specialty rare disease center is great, but we are forgetting the geography. When you're dealing with large countries and lots of rural areas and many patients who just are unable to access, it doesn't really make sense, because it puts the burden on the families and the patients that ...

I have families, for example, who had to leave their job. They don't have the financial means to do that, but they have to, just so that they can go to their infusion. This is not sustainable. And they have multiple children with the same lysosomal disorder. Again, we need education, we need framework, we need funding, and we need that care available in multiple smaller centers so the patients can access it locally.

Ozlem Goker-Alpan:

Speaking of travel. Let's talk about gene therapy. Obviously gene therapy, I mean it's still at the dawn of its time. It is very early, but it is not going to be administered at a local hospital. So basically there are so many things as we go by that needs to be followed and be vigilant and follow the complications, not even the administration. So can we ever circumvent the patients ever traveling? I'm going to tell how we do our model.

So basically we require to see the patients at some point, but we also team up with the local doctor, either a pediatrician or internist, or whoever is giving a wholesome care to the patient. Then we help with the complicated things like having your prior authorization for enzyme therapy or arranging for these complex procedures.

Some of them actually require coming to our site. Like I'm going to give a very simple example. MRIs, there are certain views of the MRIs that need to be done, and certain measurements, like in heart MRIs.

They do an MRI, but I don't have that result from a local center. So basically there is something ... The whole procedure goes in vain because this is not the information I require. Similarly, some finesse things like in looking at the bones of a Gaucher patient could be missed by the local radiologist.

So still either for technical procedures that require expertise on the issue, or the expert care, unfortunately, is not widespread and will never be widespread actually. So there is going to be some give and take in the whole situation.

Walla Al-Hertani:

I have a few words on this workforce issue. There are less and less people, medical students or residents, going into rare disease, going into lysosomal disorders. So we don't even have enough providers for the future. If those who are in the field are concentrated in certain areas, this further accentuates the problem.

Can we have training for primary care providers? Can there be some sort of course ... They would not be rare disease experts, but at least learn a few of the ins and outs, so they can provide some of that care closer to the patient? Maybe that's a model to look at. I know that there are a couple of places where this was done. But this is a real significant issue.

With regards to the telehealth, I mean we had this experiment with telehealth for two years during COVID. I converted overnight to 100% telehealth, and I see patients across all conditions, not just lysosomal.

While telehealth is great, you cannot examine the patient effectively. I have a patient with neuronopathic ASMD deficiency. I could not see the extent to the worsening of the contractures until I saw my patient in person. This is the problem with telehealth.

So depending on the type of disorder and the severity of disease, telehealth can be great. But if you need to do a physical exam, it's really quite problematic.

Ozlem Goker-Alpan:

Which is usually the case. Obviously telehealth is a structured visit, the reason is you're doing virtual and you cannot observe every single thing, because the whole evaluation is not only limited to the exam. I mean you go into the room and you start listening how the patient talks, how the patient acts, and if their accessory muscles are moving for muscle disorders so and so forth.

I mean the exam doesn't start actually in the exam room. The exam starts as you enter the room. I mean you look at the face. You recognize some of the things even before you examine the patient.

So the telehealth takes away that opportunity. I mean you can obviously observe some of the things but not to the whole. Also, you need to cover so many things in a certain period of time, which is not possible with telehealth.

I see patients that are referred, quote-by-quote, by ataxia and diagnosis of ... Differential diagnose ataxia through telehealth, which I think is not possible. Similarly, I have seen patients coming with a very complex disorder and just being evaluated by telehealth, and obviously they need a whole head-to-toe approach and evaluation.

So telehealth is good as far as the approachability, but it gets very limited due to the complexity of the disorders. Especially with the neuronopathic form. So we use telehealth usually to disclose results. So you're still face-to-face and the patient doesn't need to come to the clinic. But we can still offer ... Review the labs, show the results, compare the previous results, even show them x-rays.

So there is a great opportunity as far as what we can share without requiring the patient to come into the clinic. But, obviously, I mean it gets quite limited for the complexity of the disorders that we deal with.

Walla Al-Hertani:

I think there's an interesting question by Rita. "With all the mergers of larger hospitals buying all the local regional center, can a network be formed to enable expansion of services?"

I think this is actually a really interesting concept, Rita, and I wonder the same, as long as the regional centers that are being acquired by the larger hospitals are making services available for rare disease patients, because sometimes they will acquire them and they will assign, "Oh, this is going to be an outpatient radiology center." So as long as there is going to be actually access to rare disease care, I think that's a very interesting idea.

I think we have something similar in Boston, but it's really still not extensive enough, especially when I'm trying to provide care to other states like Maine or New Hampshire. It's really quite a struggle.

Ozlem Goker-Alpan:

There may be one side. I feel like Debbie Downer here, but when these mergers happen, actually that happens mostly in individual practices, in the private settings. Usually either the venture capitalists or larger hospital systems purchase those practices. Obviously these larger systems, they do have their own ... How they run the things. So basically this takes the freedom out of this local center, how they would accept the patients. I'll give an example for us.

So basically we accept the patients with no strings attached, meaning whether they have insurance, they don't have insurance, they're coming elsewhere, so and so forth. So basically our main attitude is to provide care, if it needed. But obviously if we were to be bound by a system, then I am sure I would be required to ask what their insurance is.

We know that even for the clinical trials, most centers that run very complicated clinical trials, which they're no cost to them because they're all contracted, sponsored studies, but they still require the patient having an insurance that is accepted by the system for the incidentals. The reason is things happen.

Obviously this becomes a big issue. I wanted to refer a patient for gene therapy and the patient did not have appropriate insurance. We couldn't find a place because the main centers that were offering was not taking the insurance of this patient. So that was a big issue for us.

Walla Al-Hertani:

That's actually a really good point, Dr. Goker-Alpan, about insurance. This is why I think maybe there needs to be some lobbying done at the state or at the governmental level, because there is definitely unequal access to patients based on insurance. As someone who's practiced a lot longer in the Canadian system, it's very unusual for me, but it's a real issue that I see happening all the time.

I don't have really, again, resolution as a physician. That has to come from higher leadership. But maybe something else to put on our wish lists for how we can change the system going forward is by involving state governments more and more.

Ozlem Goker-Alpan:

All right. I guess there is one last question. So it's talking about the larger systems. So I'm trying to read it. "It seems as if many times when large system acquire a small regional hospital, one of the first things

to be discontinued are the pediatric services." I truly agree with that, and also complex care services, because these ... Like genetics. Actually, I'm going to give an example.

The reason is what we deal with are very expensive disorders, which not much income. So basically you have to devote your time and energy for a patient that needs care. However, the billing practices only allows this much.

So basically we're never profitable for a large system. That's why we got rid of almost immediately. Unless it's like Boston Children's or is a big, big reputable system that will just keep what we offer as ... Because it will bring them good reputation.

Walla Al-Hertani:

Yeah. I mean I don't know what to say. This happened in Boston very recently, actually. A large center just closed down their pediatric services, and all the pediatric services were moved to Boston Children. It's a real problem.

Ozlem Goker-Alpan:

Yeah. Okay. So maybe one last. Let me see, a comment here. So actually somebody is commenting. They say, "This is not unique to lysosomal disorders," and giving an example, the adult congenital heart disease. As the diseases are rare, two different establishment, different adult and pediatric, are needed. Are they cost effective? Like having a pediatric system versus an adult system such that are cost effective?

Walla Al-Hertani:

I don't know. I'm not sure. Actually, this is a good question. You're right, it's not unique to lysosomal disorders. One thought which I think is more facilitated in the US versus Europe and Canada is whether you have providers who are both pediatric and adult trained who can provide care for both. But, again, that doesn't solve the problem of the different institutions with the different infrastructure. So that's a good question. I don't know.

Ozlem Goker-Alpan:

Yeah, exactly. I mean different countries have different systems. So we know UK has an adult and pediatric, and there's a transition team. I know in Germany, there are some centers. There are [inaudible 00:54:06] lysosomal, and they will take care of both adults and children. I guess there is not one easy answer to this. Similarly is the expertise and also the training and education.

I believe this concludes our session today. Thank you for attending. We thank Dr. Walla Al-Hertani for this wonderful presentation. But not only for the presentation, for this very lively and very timely discussion that opens actually more questions than answers. So we definitely need to more discuss on this subject and maybe have a whole symposium on it.

So while we are closing, we thank to all our supporters for this continuing medical education program, and we will invite you to the next one in a few months. Thank you.