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Chairperson Perspective: Acromegaly Care: Individualized Diagnosis and Management Strategies

Announcer:
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Dr. Fleseriu:
Hello, this is CME on ReachMD, and I'm Dr. Maria Fleseriu, Professor of Medicine, Endocrinology, Diabetes and Clinical Nutrition, and Neurological Surgery, and the Director of the Pituitary Center at Oregon Health and Science University in Portland, Oregon. Today, I'll be highlighting the key messages presented at a Satellite Symposia at ENDO by Prova Education in San Francisco, California.

What is acromegaly? The disease of gross hormone excess. And the gross hormone excess, the majority of it comes from a pituitary adenoma and very, very rarely by an extra pituitary source, including some rare neuroendocrine tumor. Overall, 99% are pituitary adenoma. And there are several genetic syndromes that include also gross hormone excess, so I wanted you to keep in mind that, especially for MEN1 and McCune-Albright, patients have to be screened for acromegaly.

And you see here, several manifestations of patients with acromegaly, including 1 of our patients, which wanted to be included because she had a delayed diagnosis of more than 20 years. We can see enlargement of the hands. We can see sometimes enlargement of the heart, and also other complications, as you can see here.

The prevalence of the disease is between 3 and 4 cases per million, almost equal female to male. Though, it’s delayed diagnosis more in women. And in addition to what you've seen before with the tumor mass effect, the cardiovascular and cerebrovascular disease are significantly increased and are the main cause of mortality. And let's not forget about the reduced quality of life in these patients that we have to do something about it.

I said morbidity is high. So, in this study, we looked at an acromegaly cohort of over 1,000 patients and compared with control, almost 6,000 patients, and you can see visually, in blue, is the acromegaly cohort. Everything was higher than normal population. And keep in mind, some of these were much younger patients. And besides the hypopituitarism, which is expected because it's a pituitary tumor, everything else is not expected to be higher in acromegaly at the same age, compared with controls. Many patients, 89% in the acromegaly cohort, took more than 3 concomitant medications. So the treatment of these patients is very important, both for acromegaly and for comorbidities.

Why is it important to diagnose these patients earlier? And we have done some improvements over the last decade, but clearly not

enough because some patients can go undiagnosed for more than a decade. And the reason it's important is that the more delay, as you can see here from gray to a dark black, the risk of comorbidities is significantly higher if the patients were delayed. For example, more than 10 years, they had 1.5 higher risk of vertebral fractures. It's important to treat well but also to diagnose earlier.

Furthermore, it's important to treat at goal and normal IDF-1. This is the Swedish pituitary register, and you see the patients were not controlled. They had significant increased mortality, which goes down if they were controlled. Again, very important and you see here, very well in the Kaplan-Meyer curve, how the controlled have improved survival versus uncontrolled in here. And of course, no status or no follow-up, so that's another issue that we need to discuss about closely follow-up of all these patients.

Furthermore, women may have higher mortality risk. This is the data from South Korea. You see men higher in acromegaly, the mortality, but pretty close. But in women, you see clear difference between these lines and you see the hazard ratio was 2.17. So women will need even more attention to make sure they are controlled.

So, when we're asking patients how they're doing, especially for quality of life, which my passion is to have a patient-centered approach. Yes, there are many physical symptoms that we discussed earlier, many neuropsychological symptoms, several comorbidities, which some of them increase mortality, and also treatment side effects, so we should ask in detail, not just how are you doing? Does the treatment work well for you, for your schedule? Do you have any adverse effects? And there are several quality-of-life questionnaire.

Also, more recently, its data, which we knew in advance that there's a lot of arthritis, but look at this recent study. In Danish acromegaly patients in match very well, 1 to 100 with healthy control. This is osteoarthritis. This is joint replacement surgery. Keep in mind, these are patients who are young. Hip replacement surgery, and knee replacement surgery. So the arthritis is so severe that these younger patients will need replacement surgery in a lot of patients.

So how do we manage the acromegalic comorbidities? It's easy to say, these are the comorbidities, but do we have a way of finding out which ones are more frequent? Yes, by looking at these patients very closely. And we have recommended in the recent guidelines to check the baseline blood pressure, check for sleep apnea with scale or sleep study, preferably. Of course, check all the hormones, but that's not enough. And we do that very well, but if we're looking at the studies, there are a lot of other tests that we do not follow close enough.

So, for example, we need every year some cardiac testing. We need endocrine metabolic disorders also every year, and this I do. I check the hormones every year. For musculoskeletal disorders, we need DEXA every 2 to 3 years. But very important to look at vertebral morphometry because the bone has poor quality in acromegaly, and they have increased risk of vertebral fracture. And, of course, colonoscopy diagnosis in them every 10 years or earlier, if there are polyps. And we should look at quality of life in these patients.

So how can we improve the clinical detection? You see here, there are several pictures from many journals. And I have to tell you, these are, several of them, older, but we have seen patients presenting with severe acromegaly and very light real-life diagnosis, including with macroglossia, even last year, increased colon size, and somebody said colonoscopy, and of course, significant increase in height in younger kids, which everybody thinks that is puberty, and they do not get the proper checkout.

So how do we make the diagnosis? So, early diagnosis is important. IGF-1, if anybody—any clinician—has a suspicion of acromegaly, we should measure an IGF-1. If it's normal, it's probably excluding acromegaly with the exception of some false negative results, which are lower. If it's elevated, some patients will require OGTT with gross hormone. But we have mentioned in the most recent guidelines that if the IGF-1 is significantly elevated, and a patient has features of acromegaly, and if no concerns for diabetes, maybe we don't need that for diagnosis, and we can move on and actually do an MRI. And if the patient has a mass on the MRI, they can have treatment while waiting for the OGTT, because that's important information for physiology of gross hormone and also for diabetes.

Remember, just the GH is not good enough. This is normal population where it gets higher at night. That's why we tell the kids to go to sleep so they can grow, and they believe us or not. And then, in acromegaly it's just erratic secretion.

So once we have a somatotropin adenoma, we know that this is the diagnosis. But keep in mind that sometimes, as I mentioned earlier, it could be extrapolated acromegaly, and we have to look pretty much everywhere with CTs or other data scan.

How about treatment? So, we covered the importance of early diagnosis because of so many comorbidities. We briefly cover how we make the diagnosis, so now we know it's a pituitary adenoma. We know they need surgery. But if the surgical remission is not achieved, what do we have available after that? And we have several medications, and I will review them by groups.

First, somatostatin receptor ligands. Lanreotide and octreotide are available for a while now as an injectable form, and they're once a month and they, lanreotide and octreotide, are specifically for SST2.

And then pasireotide, also for SST5. We also have available oral octreotide, and I'm going to show you some data. If controlled or injectable, and if not controlled, some patients can switch to pasireotide. I use sometimes, pasireotide. In US, it's approved as first-line, too, for specific patients.

Cabergoline is not approved. It's used in patients, I use more in combination if the IGF-1 is really low on the high-normal range, so not low-abnormal, or as an add-on to SRLs. And then we have pegvisomant, which is a gross hormone receptor blocker. And if the tumor growth is not a concern, then the IGF-1 will be normal, and then we do not even measure the growth hormone.

So efficacy of the somatostatin receptor ligands. The control of GH and IGF-1 is between 50 and 66% with huge variation between studies, depending on patients, study design, if they had surgery or not. So if it's primary therapy and, importantly, because they work at the pituitary level, tumor shrinkage occurs in about 30% of patients. And in some, very significant tumor shrinkage. The problem is, we do not know exactly if they're going to shrink or not from the beginning.

Side effects are gastrointestinal, are mainly. That's what I tell the patient. You are going to have some, especially at the beginning, diarrhea and nausea, abdominal pain, some biliary tract abnormalities, glucose metabolism, and especially for pasireotide, it's higher. Injection site pain reaction, transient hair loss, and hypothyroidism. These are much, much lower.

The oral octreotide that has been recently approved maintained control of IGF-1 and GH with a placebo-controlled randomized trial. You see here, the drug, the octreotide is in black, and in gray is the placebo. And on the left, you have the response of patients responding as a percentage of biochemical response.

How about pegvisomant? Pegvisomant is a growth hormone receptor blocker, and this was the initial study. And what's interesting is that, as you can see, this is serum IGF-1 on the left, serum GH on the right. Ninety percent of patients normalize IGF-1. But keep in mind that this was a clinical trial. And we had, for several other medications including the somatostatin receptor ligand pasireotide that I have mentioned earlier, that if the dose is not properly up-titrated, you do not see response enough at the level you expect. So for example in this trial, this was 90%. More recent studies, it's 65%. So in real life, if you don't get to the right dose, you see less control. Same for short-term increase in tumor size. At 2 years, it was 3.2. And at the 9-year follow-up, we have recently published from a large trial across study, it was about 7.1. Again, these were more aggressive tumors, which some of them were on combination therapy.

So this has been a selection of the natural progression and not an effect of the drug itself. But patients will need MRI if they are on long-term medications, especially without somatostatin receptor ligands.

So the data society has established the term between the centers of excellence, and the treatment of acromegaly is best determined by a multidisciplinary team of experts within these structures. And it's very important because most of the patients have a large adenoma to begin with. They will need to see a neuropharmacologist. In addition to us and oncology to check all their hormone, they need to have a pathologist who is looking to see what type of tumor, densely granulated versus sparsely granulated, and then also to look at all comorbidities. And let's not forget, the good neuroradiologists, and the most important one, a good neurosurgeon. So that's very important. And in the case we have described, the patient would have had a potentially unnecessary craniotomy and, this is important, that having a second opinion with a specialized team, the patient ended up having the appropriate treatment and did not have craniotomy.

Future directions. We have several medical therapies in the pipeline. It's a monthly depot, subcutaneous injection of octreotide with the option of a pen, and also a single-dose, nonpeptide, oral somatostatin receptor agonist.

So let's review first the data on the injectable octreotide. So this is octreotide long-acting in a prefilled pen. The data show—and this is the CAM and this is the placebo—the dose was 20 mg subcu at every 4 weeks, and the patients were controlled in 70% versus less than

40% on placebo. All of these patients were controlled on either lanreotide or octreotide. It's not approved yet. Patients can self-inject with a pen, and they did this in a published trial. Has similar efficacy and safety to currently approved first-generation SRLs, octreotide and lanreotide, and comes in 1 dose.

How about pasireotide? Pasireotide is a nonpeptide, small molecule selectively targeting highly potent somatostatin receptor Type 2 agonist. It's in late-stage development, also not approved. There are several studies. I'm going to show you one. Patients, again, were controlled on either octreotide or lanreotide long term, and they were switched to this medication. Very strict criteria, and they were controlled after switching to pasireotide in 83.3% versus 3.6 on placebo at 34 to 36 weeks. So this is what we have presented to the symposium at ENDO. Before both of these trials, there were several other posters presentations and even oral presentations regarding the new data of the extension. So I'm very excited about these new therapies, also, and how we can improve the treatment of our patients, individualizing with what they prefer, also, to take.

Key points for pasireotide, as I said not approved yet. Once per day early in the morning, and symptoms reported per patients were stable over time and, remember, relatively similar with the SRLs also.

So I wanted to end with the importance of the disease control value. The disease timeline, we have to do a better job in controlling the patients more. We have to look at all the comorbidities, as I mentioned earlier, to decrease comorbidities and also to decrease cost, if we can. And we have to look, and we tried for several of these outcomes, to look also at years gained and cost savings. And it will be very important not forget to increase the quality-adjusted life years.

And with that, thank you so much for joining me, and this has been CME on ReachMD.

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