Transcript Details
This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/optimizing-patient-outcomes-in-acromegaly/12456/

Released: 05/14/2021
Valid until: 06/30/2022
Time needed to complete: 30 minutes

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Optimizing Patient Outcomes in Acromegaly

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Optimizing Patient Outcomes in Acromegaly” is provided by Prova Education.

Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Samson:
The quality of life and overall survival of individuals with acromegaly are negatively affected by delays in diagnosis and treatment and by the provision of suboptimal therapy.

Hi, I’m Susan Samson from the Mayo Clinic in Florida, and I’m joined today by my friend and colleague, Dr. Kevin Yuen from the Barrow Pituitary Center at the University of Arizona College of Medicine and Creighton School of Medicine in Phoenix. Welcome, Dr. Yuen.

Dr. Yuen:
Thank you, Dr. Samson. I’m excited to be here today to discuss how we can design personalized approaches to treatment for our patients with acromegaly.

Dr. Samson:
Well, we have a lot to cover today, so let’s dive in. To start things off, Dr. Yuen, can you describe, please, the importance of prompt diagnosis for our patients with acromegaly?

Dr. Yuen:
Certainly. The importance of prompt diagnosis is crucial because we know that patients with acromegaly have multiple comorbid conditions and also impaired quality of life, and so it really isn’t surprising that when you diagnose these patients early, you can promptly treat them and minimize these comorbidities and improve their quality of life. The common signs and symptoms of acromegaly certainly can be divided into different categories: tumor mass effects, frequently causing headaches, visual disturbances, and also the systemic effects of chronic growth hormone and IGF access, such as acral growth, facial feature changes, skin changes, joint pains, and also organ enlargements. And all these things can actually impact and cause increased comorbidities in these patients. And therefore, in relation to all these symptoms, the diagnosis and testing of these patients needs to be thought of by the doctor or the provider who sees these patients. So you really must know about this condition in order to think about it, in order to set the process of testing for this condition.

So in order to test patients that you suspect with acromegaly, the first thing to do is to perform a blood test for IGF-1. And together with the signs and symptoms, and if there is an elevation in IGF-1 – occasionally the IGF-1 is very, very high – often, that confirms the diagnosis. But in the situation where the testing of IGF-1 levels is moderately high, one can also proceed to go on to perform an oral glucose tolerance test to confirm the diagnosis and see if the patient has appropriate growth hormone suppression, because if the patient does not have appropriate growth hormone suppression, usually growth hormone levels less than 1 nanogram per mL, then the diagnosis of acromegaly is often confirmed on these 2 parameters.

Dr. Samson:
I like that you brought that up. Often, I'll see patients referred to me that may have had a growth hormone test done but have not had an IGF-1, and it's such a great test for looking at integrated growth hormone levels and understanding the diagnosis. But of course, we can see false positives and false negatives, and I think it's very important that should a primary care physician or provider see an elevated IGF-1, that that patient is promptly referred to endocrinology for more specialized testing. We certainly know that complications are lowered when a patient is controlled biochemically, as you brought up. And so the earlier we could meet that patient and work toward therapies is really important. And over the years, we've come to realize how important the multidisciplinary team is in caring for our patients with acromegaly. The endocrinologist is at the helm, but there are certainly other specialists that are key to improving our patients' health and quality of life, and that can include everyone from a cardiologist who is optimizing their cardiovascular health to pulmonology, looking at issues of sleep apnea, orthopedic surgery for osteoarthritis, gastroenterology for colon health – and we really try to incorporate all of these specialists into our practice. And certainly, there's data showing that as you control IGF-1 and growth hormone in our patients, their quality of life does improve. So this is not just about longevity and mortality and morbidity, but also about everyday function for our patients.

And I think you might agree with me that for most patients, surgery is still the first line in the majority of patients, and we should be sending our patients to very high-volume pituitary surgeons. And unfortunately, some patients will have large tumors or they could be invasive into the cavernous sinus or elsewhere, and that can make achieving a surgical cure – not just debulking, but a surgical cure can be very challenging. And so sometimes we have to turn to additional therapies. I don't know if you have any other thoughts about that, Dr. Yuen.

Dr. Yuen:
Certainly, yes. I think surgery is still the first-line treatment, especially in the setting where the patient is able to see an experienced surgeon in high-volume centers, pituitary centers. But occasionally, there are occasions where patients may not be amenable to surgery for a variety of reasons. Their general health may not permit surgery or if patients simply are not keen to go in surgery, especially during the COVID pandemic that we are going through now. So during this situation, there are other choices that we can discuss with the patients about how we can approach and treat them, at least medically first, to control the disease and reduce the potential comorbidities that are associated with the disease, at least until surgery can be considered.

And so in terms of the therapeutic options aside from surgery, the patient can be considered for medical therapy and there are several types of medical therapy that are available currently. You have the somatostatin receptor ligands, which work directly on the pituitary gland to reduce growth hormone secretion. You also have a medication called cabergoline which, although is commonly used for hyperprolactinemia cases, but certainly can be considered for patients with acromegaly to reduce growth hormone secretion. There's also another medication which is a growth hormone receptor antagonist, pegvisomant, and that is also an option, too. And then also, you can also consider radiation, but that is usually the last option, at least after medical therapy is considered first.

And in terms of medical therapy, most of them are injectables, except recently there is also an oral preparation that has been made available, a somatostatin receptor ligand. So currently, there is a lot of activity going on, but certainly patients have a lot of choices to be considered for therapy if surgery is not appropriate at the time, or certainly if the patient, after having had surgery, remission is not achieved.

Dr. Samson:
Thank you for detailing those medications, and I do think sometimes we have patients where they might be on one of the very good medical therapies and they still are not controlled, and many of us will try combination therapies in order to reduce the IGF-1 into the normal range or control growth hormone, depending on which medications. For example, you might combine a somatostatin receptor ligand targeting the tumor with pegvisomant that's targeting IGF-1 production from the liver, and together those drugs can bring the IGF-1 levels under control. So we certainly do, in our own practice, have to consider combination therapy in some patients that have more challenging tumors to deal with.

For those just joining us, this is CME on ReachMD. I'm Dr. Susan Samson. I'm here today with Dr. Kevin Yuen. We're discussing the role of second-generation somatostatin receptor ligands in the management of patients with acromegaly.

Keeping this great overview you did of current therapies in mind, Dr. Yuen, can you please take us through the algorithms from the most recent guidelines and consensus statement from the Pituitary Society?

Dr. Yuen:
Certainly, Dr. Samson. There has been a recent publication that came out from the Pituitary Society giving us guidelines on how to manage patients with acromegaly, specifically a growth hormone-secreting pituitary tumor. And certainly, the recommendation is still advocating surgery being the first-line treatment, and occasionally if surgery is not amenable for some patients, primary somatostatin

receptor ligand therapy may be considered in some patients. In those patients who have had surgery, if those patients are well controlled following surgery and the disease is in remission, then monitoring periodic IGF-1 levels is recommended. For those patients who are not controlled, there is a potential to either consider further medical therapy or, in the sense that if the patient still has tumor that is still visible on MRI, consideration for reoperation is also a possibility. The combination therapy or certainly therapies that are used can be in the form of either somatostatin receptor ligand, after the remission is not achieved, or pegvisomant. And if disease continues to be a problem, then one can either consider increasing the somatostatin receptor ligand dose or even adding pegvisomant as a combination therapy. There's also some suggestion to consider using second-line somatostatin receptor ligand, like pasireotide, in situations where further control is required.

So that is really some further guidelines that has been published that really just helps us to fit into some sort of a paradigm as to how we deal with patients with acromegaly, especially those who have difficulty in controlling the disease.

Dr. Samson:
Thank you. I'm kind of interested also in how pasireotide fits into the algorithm in terms of even combination therapies. You know, we know from the PAOLA study that patients were not fully controlled on octreotide or lanreotide, that a proportion of patients would be further controlled when switched to pasireotide. So that's an important option for lack of control, and there certainly is a lot of interest in how we can combine therapies for the most effective therapy, but also cost-effectiveness. For example, recently there was a study published on using lower-dose somatostatin receptor ligands with weekly pasireotide instead of daily, and that actually was cost saving and yet achieved IGF-1 control in a good proportion of patients.

We also know from data from the PAPE study, which had a couple of articles come out in around 2018, that if patients were on a combination of octreotide or lanreotide with pegvisomant, that some could be switched to pasireotide and have full control, or for those that didn't achieve full control, that the pasireotide plus pegvisomant would control a large proportion, but there was a 50% dose-sparing effect with pegvisomant. So those combinations are also an option for our patients to control the IGF-1.

Well, it's fantastic to see the updates in therapeutics and to know that they're recommended for use in clinical practice. It certainly has broadened our armamentarium against this disease. But there are always side effects, and we always have to think about our patients' safety. Could you talk about the potential side effects that we could expect to see from pasireotide, Dr. Yuen?

Dr. Yuen:
Certainly, Dr. Samson. The side effects that are commonly reported associated with pasireotide include hyperglycemia and glucose intolerance, and this has often been reported that it's much higher in terms of the incidence compared to the first-generation somatostatin receptor ligands. In addition, there are also other common side effects associated with the somatostatin receptor ligands, such as the GI side effects, namely diarrhea, abdominal discomfort, abdominal pains, nausea, and also vomiting. The reason for the higher rates of glucose intolerance associated with pasireotide is the fact that is has an affinity on somatostatin receptor 1, 2, 3, and 5. And by doing so, it can actually reduce or have an effect on the insulin secretion as well as a reduction in glucagon and incretin effects.

Dr. Samson:
So that's really interesting, you know, with those 2 receptors. You know, the GI side effects are so common between all of the receptor ligands, but then we're seeing more hyperglycemia with pasireotide. But what you bring up are 2 important points. So one of the things we know about patients with acromegaly is they have more gluconeogenesis because growth hormone is that counter-regulatory hormone that promotes liver glucose production. So if I'm managing a patient with mild hyperglycemia on pasireotide, I still have metformin as my first line, wanting to decrease that gluconeogenesis, as it is one of the most important roles of metformin in the treatment of diabetes. But also, you know, knowing that mechanism where incretin secretion, such as with GLP-1, is decreased by pasireotide, it is rational to think that using an incretin-based therapy could be really helpful here, and I'm thinking back to a study that we presented at the Endocrine Society in 2019, where we looked at patients on pasireotide with hyperglycemia and treated first with metformin. And if they needed additional therapy, they could be randomized to insulin or a DPP-4 inhibitor, which moved forward into a GLP-1 receptor agonist and certainly showed that incretin-based therapies are an excellent alternative to treat hyperglycemia caused by pasireotide.

Are there any patient characteristics you look for prior to starting pasireotide, with regard to baseline glucose status?

Dr. Yuen:
Indeed. What was learned from the PAOLA study was that patients with normal glucose tolerance at baseline were found to be less likely to develop hyperglycemia or diabetes. So in this situation, you can kind of tailor your management with patients, and especially even patients who already have glucose intolerance and diabetes. You might have to pay more close attention to their diabetic medications in anticipation that can potentially worsen over time with this medication. But certainly, those who are in good control or

who are normal glycemic at baseline, certainly does not appear to have that much as high risk compared to those who have impaired glucose tolerance at baseline.

Dr. Samson:
Right, and one of the things I've discovered over time as well is, you know, some of our patients with acromegaly unfortunately already have diabetes and are on insulin. And when we treat the growth hormone, when we are able to get control of the disease, I have found that their insulin requirements can actually decrease because you have taken away the growth hormone-induced insulin resistance in those patients. So I've actually had to make adjustments of their insulin therapy downward to avoid hypoglycemia because of the improvement in the control of their growth hormone levels. So that's a little bit of a caveat. Sometimes we don't think about that in patients already on insulin, there may be actually an improvement in terms of their therapy or be therapy sparing.

Dr. Yuen:
And indeed, I've seen that, too, in several of my patients with diabetes, where their insulin requirements do decrease after successful treatment with pasireotide, in lowering their – in normalizing their IGF-1. So that's certainly a true phenomenon that I've seen in my clinical practice as well.

Dr. Samson:
Well, I wondered if we could go through a case from my practice and just discuss how what we've discussed earlier here applies in this particular patient's case. I have a patient who's a 56-year-old female, and she was referred for assessment of an elevated IGF-1. And she came with a very interesting history. Three years prior, she was told to stop her estrogen-containing oral contraceptive pills because she was now over 50, and it was to see if she was in menopause. And after stopping her oral contraceptive pills, she started to manifest a lot of symptoms when she had felt like she was previously healthy, and that included debilitating joint pains that prompted a primary care referral to rheumatology, an autoimmune workup that was negative. She had new onset of paresthesias and saw a neurologist in order to be assessed for nerve conduction and electromyography. She started having premature ventricular contractions and saw a cardiologist who did a Holter monitor on her and started a calcium channel blocker. She saw gastroenterology, who found several polyps in colonoscopy, and an IGF-1 was performed at that time but was not followed up, and no imaging was performed.

So that was 3 years prior to seeing me. She really attributed all of her symptoms to the fact that she went off of estrogen and requested that her doctor restart it. And it wasn't until 3 years later that she continued to have ongoing issues, including new-onset and worsening snoring. She noticed her shoe size had increased over the past 2 years. Changes in her bite – she had sought her dentist out because of this. And so when she made it to our pituitary center, now she really did have very clear symptoms of acromegaly, but really over the last 3 years, they had gone unrecognized as a constellation. When I examined her, I didn't find a lot of physical facial features that you could attribute to acromegaly. She didn't have frontal bossing or have increased soft tissue padding of her hands. She had mild palmar sweating. She didn't really have other thickening of her features that you would say are acromegalic per se, but she did have a very large macroadenoma on the MRI we performed at the time of her visit. And, you know, she really made me think about what are the factors that lead to delay in our patients' diagnoses, and what happened in her case?

Dr. Yuen:
Indeed, Dr. Samson, your patient has certainly gone through the run of the mill, seeing so many different specialties, and indeed the diagnosis is delayed. And it is actually known that – in fact, several studies are actually showing that there are gender-specific differences in the presentation and the diagnosis of acromegaly. Specifically, delays are actually more commonly seen – slightly more commonly seen, in fact, in women more so than men, despite the fact that it is commonly understood that women tend to see doctors more frequently. Now, it could all well be that many of the symptoms that are associated with acromegaly, such as headaches or sweating or joint pains, are also very commonly seen in the general population, which does not resonate so much that the patient may have acromegaly because these are very common symptoms seen in primary care practice. So that may be a reason why delays in diagnosis occur. And I guess also, given the presentation of your patient, where she has seen different specialties for specific different problems – again, common problems in this patient's age group – is also not uncommon as well, and that has also contributed to the delay in diagnosing this condition. We also know that women tend to also have a poorer quality of life, and they tend to have lower IGF-1 levels at presentation, maybe a result of the fact that the estradiol effects it has in somewhat lowering the IGF-1 levels compared to men. So all these factors, perhaps, also may contribute and play into the delay in the diagnosis of women compared to men.

So, Dr. Samson, can you take us through some of the medical therapy that you would consider using in your patient who has presented to you that you just described?

Dr. Samson:
I did send her to surgery for consideration of postoperative IGF-1 assessment and possible medical therapy, should she require it. You know, when we think about the patients that might fail surgery, it's usually those with a much higher growth hormone level,

macroadenomas, especially when we see invasion into the cavernous sinus. So we can often have a pretty good idea, preoperatively, of where that patient will land post-op. In her case, I would want to attack the tumor using a somatostatin receptor ligand, and if you know about the characteristics that can lead to first-generation resistance – I'm talking about T2 hyperintensity on MRI or your pathologist reports that this was a sparsely granulated tumor – always very helpful to have that information because those things can predict that we're going to see less of a response to the first-generation somatostatin receptor ligands, and pasireotide would be a consideration in this patient.

Well, Dr. Yuen, it has been a pleasure having this fascinating conversation with you, and before we conclude, is there anything you'd like to add to make sure that the audience really heard today?

Dr. Yuen:
Indeed. Certainly, this is a field that is very exciting for us involved in treating these patients. There's new drugs that are being developed, there's also combination therapy for medications, so it's a very exciting field. But I think the important thing is that we must, as providers and physicians, do a better job of diagnosing these patients earlier, because even with the best medications that we have, if these patients are not diagnosed early enough, certainly we won't be able to at least address the comorbidities early, and maybe even prevent them from happening. So I think we must do a better job in recognizing this condition and diagnosing these patients earlier. And maybe might be able to help increase the awareness of this condition to the non-endocrinology colleagues, to think about this condition, because you really must know about it to think about it, in order to set the diagnostic process to properly diagnose these patients.

Dr. Samson:
I agree with you. Spreading the word about the presentations and the symptoms and hopefully that we can catch patients so much earlier in their course is a key, and I think the other thing that I took away from this discussion today is how many options we do have, and we can really take a personalized approach to medical therapy in our patients if we think about their lifestyle, their needs, and also what we know about their particular tumor and situation. So I think we have a lot of opportunities as physicians to personalize our therapies for them.

Well, that's it. We're out of time. I want to thank our audience for listening in and offer a special thank you to my colleague, Dr. Kevin Yuen, for sharing his thoughts with us today. It was really great speaking with you, Dr. Yuen.

Dr. Yuen:
Thank you, Dr. Samson. It was a pleasure being here today, and certainly I thoroughly enjoyed our discussion on this topic here today.

Announcer:
You have been listening to CME on ReachMD. This activity is provided by Prova Education.

To receive your free CME credit, or to download this activity, go to ReachMD.com/Prova. Thank you for listening.