Dr. Jason Barnes:

Hey, there, welcome to another episode of ENT in a Nutshell. My name is Jason Barnes and today we are joined by Professor Simon Lloyd from Manchester United Kingdom and we'll be discussing neurofibromatosis type 2. Professor Lloyd, thanks so much for being here.

Dr. Simon Lloyd:

Thank you very much for the invitation. It's really a pleasure to join you.

Dr. Jason Barnes:

When you see a patient with neurofibromatosis type 2, how would you say they typically present to your clinic?

Dr. Simon Lloyd:

So it's a condition that can present in many ways. I guess the important thing is to differentiate it from patients that present with sporadic vestibular schwannomas. In neurofibromatosis type 2, the typical presentation is with a vestibular schwannoma, but over time the patient often develops bilateral vestibular schwannomas. And that's said to be pathognomonic of NF2. I have to qualify that though, there are patients that present with a single vestibular schwannoma. And if you look at the criteria for NF2 actually, it's possible to present with NF2 without any vestibular schwannomas. So, I would say the most common presentation is in the same way as somebody with sporadic vestibular schwannoma would present with hearing loss, or tinnitus, or perhaps imbalance. In the same way somebody with NF2 might present with those same symptoms.

I would qualify that too by saying that the younger patients that present with NF2 often don't present with vestibular schwannoma type symptoms. They can present with neuropathies. Around 30% of patients can develop a peripheral neuropathy. Also, other non vestibular symptoms are common in the younger patients. So for example, ocular manifestations with NF2 with hamartomas, or cataract is a common way for younger patients to present. And similarly in the younger age group, actually the tumor that most commonly presents is a meningioma within the cerebellopontine angle or within the cranial cavity elsewhere rather than the vestibular schwannoma.

Dr. Jason Barnes:

And when we kind of hear the buzz words for NF2 on a learning side we hear bilateral vestibular schwannoma, do you find that when patients present with vestibular schwannoma they're presenting with bilateral vestibular schwannoma? Or is it typically staggered where you see one first and then identify one later?

Dr. Simon Lloyd:

It very much depends on the individual case. I think, a de novo NF2 patient usually would present with unilateral hearing loss, or tinnitus, or dizziness in the same way as any other vestibular schwannoma patient would. But they would then be found to have a vestibular schwannoma on the opposite side as well when they have their first MRI of the head.

Dr. Jason Barnes:

And can you speak a little bit to the epidemiology of this disease. How many people are affected by it and what are some risk factors for it?

Dr. Simon Lloyd:

So the prevalence in the UK is about one in 60,000, and the birth incidence is about one in 33,000. And what you'll see is that the incidence goes up with increasing age. So, below the age of five, is extremely rare to present. But by the time you reach 45, or 50, almost every patient with NF2 will have presented with symptoms of some sort. So the acquisition of a diagnosis of NF2 is usually complete by the time you get to the age of 45 or 50. The distribution between male and female is pretty similar. And in terms of risk factors, it's a genetic disease. So, a tumor predisposition syndrome. So around 50% of the patients that we see are de novo presentations. And then the other half are usually familial cases that have had other family members diagnosed with NF2.

It's a really interesting condition in terms of the underlying genetics, because around 30% of the patients that present de novo actually have a type of genetic condition called mosaicism, whereby the germline mutation doesn't occur in the zygote. It actually happens during early embryonal development. So you end up with two cell populations, you end up with a population that's normal and a population that has the genetic mutation. And that means as the fetus develops and they grow into an adult, they have some of their cells that have the mutation and some that don't. And that means that they can get segmental tumor development. So they might get tumors on the left hand side or the right hand side, or they might tend to just get tumors within the cranial cavity and not in the rest of the spine or the rest of the body.

And mosaicism also has an impact on inheritance as well, because neurofibromatosis type 2 is generally regarded as a autosomal dominant condition where the inheritance is 50/50. So if you've got full blown NF2, your children will have a 50% chance of developing the same disease. But with mosaicism, because there's only some of the cells in the body that have the genetic abnormality, the chances of passing on the NF2 to your child if you've got mosaic disease is lower than it would be if you had full blown NF2. And then the interesting thing about that is that when the children do inherit the NF2 gene, then the next generation has an autosomal dominant inheritance. So they have a 50/50 chance of developing the disease.

Dr. Jason Barnes:

And I want to get into pathophysiology a bit more in the genetics. But before we do, say I'm the resident who's about to walk in and evaluate a patient with NF2, what am I looking for in physical exam for these patients?

Dr. Simon Lloyd:

So from an ENT perspective, I think the important thing is to ask them what sort of symptoms they've had. Most often it's hearing loss, tinnitus, dizziness. And then with the physical examination, the key is to assess the hearing, assess their balance function, and then assess the cranial nerves. It's not uncommon particularly with large tumors for patients to have neuropathies of the trigeminal nerve, so they might have facial numbness. They might even in rare cases, develop trigeminal neuralgia, and they might lose their corneal reflex, which is a fairly early sign of trigeminal nerve involvement. Those are the usual signs that go along with vestibular schwannomas. For the larger tumors, and those that have got significant brainstem compression, you might also see some nystagmus. Typically in the early phases, you'll get the peripheral types of misdiagnosis. But with larger tumors, when you've got large brainstem compression, you'll get more central nystagmus as well and some patients even present with bruns nystagmus, which is a bi directional type of nystagmus.

And then with patients that have other types of tumor, if they've got lower cranial nerve tumors that kind of thing, then they may also present with defects in those cranial nerve. So tongue weakness

and swallowing defects. The other area that is quite often affected is the orbit. So meningiomas around the optic nerve can also affect vision as well as the other ocular manifestations. So, visual acuity assessments and that kind of thing play an important role. And then going on to investigations, obviously the key investigation with vestibular schwannomas in particular is to carry out an audiogram, a pure tone audiogram and the speech assessment.

Dr. Jason Barnes:

And do you find that there are many skin manifestations for these patients?

Dr. Simon Lloyd:

So certainly, you can see skin manifestations. It's less common in NF2 than it is in NF1. But about 70% of patients with NF2 do have some kind of skin manifestation when you look carefully. So they can get intracutaneous phlox, which are often associated with excess hair formation. They can get fusiform schwannomas of peripheral nerve so they present as subcutaneous lumps. And they can also get some café-au-lait spots, but usually significantly less than you see in NF1. So, it's only about 1% of patients that get more than six café-au-lait spots lesions.

Dr. Jason Barnes:

And moving on to pathophysiology. You started to talk about the genetics of this disease. Could you tell us more about the actual genetic insult that is involved in this disease process?

Dr. Simon Lloyd:

Yeah, so the primary gene abnormality is in the neurofibromatosis type 2 gene. And there are obviously two copies of that gene in the genome. And the patients that have neurofibromatosis type 2 have a mutation of one of those alleles. And then they develop a tumor when they have the second hit. And the gene product is a protein called merlin. And that's a 595 amino acid protein that is produced throughout the whole body, but it's particularly prevalent within schwann cells, which is why schwann cells have a predisposition to developing tumors.

And I guess this is a good time to mention other kind of syndromes that look like NF2, but aren't NF2. And there are two other genes that can actually mimic NF2. And that's the LZTR1 mutation and the SMARC-B1 mutation. And those two conditions can look like NF2 but are very slightly different. So they don't usually present with vestibular schwannomas. They often present with schwannomas elsewhere. And they can also develop meningiomas in the same way as you can with NF2. So when we genetically screen patients we always look for those two genetic abnormalities as well.

And the fact that we now know that there's a number of different syndromes that can look like NF2 has actually made us reevaluate the way that we classify NF2. And we've been looking at a different ways of doing that. And it may well be that going forward over the next few years that we'll try and change the nomenclature. We may change it to say for example, a schwannoma predisposition syndrome linked with a particular gene. So NF2 might become schwannoma predisposition syndrome merlin, and LZTR1 mutations might become schwannoma predisposition syndrome LZTR1 for example.

Dr. Jason Barnes:

And can you tell us which chromosome this is located on. And are the other predisposing genetic insults on the same chromosome?

Dr. Simon Lloyd:

Yeah, all of those three types of mutation are on chromosome 22. And the mutation for merlin is on the long arm of chromosome 22.

Dr. Jason Barnes:

And when we talk about the different types of presentations of this disease, are there different characterizations or manifestations depending on the type of mutation and how a patient might present with this?

Dr. Simon Lloyd:

Yeah, definitely. Historically we've divided NF2 into two main groups, depending on the severity of the disease. There's the so called Wishart type, and the Gardner type, and they're really phenotypic descriptions. The Wishart type is named after the surgeon that first described NF2, he was the president of the Royal College of Surgeons of Edinburgh at the time. And in those patients, they get very much more aggressive disease in the Gardener type. In recent years, we've kind of moved away from the phenotypic descriptions and we now look more at the genotypes. And there's a very clear link between the type of gene mutation that we see and the severity of the disease.

So, for example, the types of mutation you might see include truncating mutations, splice site mutations, deletions, missense mutations. And the truncating mutations which result in a protein product that's quite considerably abnormal tend to result in a more severe disease. Whereas the missense mutations, which is usually just a single point mutation, you tend to get a more normal protein product. And that usually results in less severe disease. And there's a really clear link between those genotypes and phenotypes. So for example, if you've got a truncating mutation, you tend to have faster growing tumors, you tend to get more meningiomas, you might develop more spinal tumors meningiomas or ependymomas for example. And there's a link between genotype and mortality as well. So, if you've got a missense mutation, then your overall survival is significantly better, for example, than if you look at those that have got truncating mutations or large deletions.

Dr. Jason Barnes:

And what is the natural history of this disease? What happens if this disease goes untreated?

Dr. Simon Lloyd:

So again, it very much depends on the genotype and the associated phenotype. If you've got mosaic disease, there are many patients that develop bilateral vestibular schwannomas, some of which don't grow, and many of those patients were able to manage conservatively without needing to intervene in any way. But if you take a typical patient with full blown neurofibromatosis type 2, what tends to happen is their vestibular schwannomas grow over time, they tend to develop deafness as a result of that, which in NF2 and bilateral vestibular schwannomas can obviously be bilateral. And it's actually the hearing loss that can cause the greatest change in their quality of life in the largest proportion of patients, which is very different from the sporadic vestibular schwannomas. Because those patients have good hearing in one ear, so the hearing loss doesn't really have much impact.

And then over time they can develop other symptoms because of the growing vestibular schwannomas. So they might start to get balance disturbance and symptoms of brainstem compression. And if you look historically, patients with NF2 was really the very significant brainstem compression that can develop in these patients that end up resulting in the patient's death in the long run through

respiratory depression and typical features of brainstem compression that result from vestibular schwannomas.

So that's the vestibular schwannoma side of things. But it's not just a vestibular schwannoma condition. So it's not uncommon for patients with NF2 to develop spinal problems. It's actually fairly unusual for us to end up needing to intervene with spinal tumors, but certainly not unheard of. And if you leave tumors within the spine unchecked, then there's the possibility of developing peripheral neurological deficits because of that. And similarly you can develop schwannomas on other peripheral nerves. So brachial plexus and other peripheral nerves that can also result in neurological deficits.

And then you've got the other manifestations, the ocular manifestations. So, it's common for people to develop cataracts in the long run. They're not always clinically manifesting but if you look in everybody's eyes, around 80% of patients will have some form of cataract formation and with full blown NF2. And then you can get poor visual acuity because of the effects of meningiomas affecting the optic nerve, and also from ocular hamartomas as well. So those are the predominant symptoms that can develop if you leave NF2 unchecked.

Dr. Jason Barnes:

And moving on to differential diagnosis. I wanted to talk about what else is on your differential and most specifically talk about NF1. Could you spend some time maybe contrasting NF2 to NF1 and maybe explain why NF2 is called what it's called?

Dr. Simon Lloyd:

Yeah, so there's a lot of confusion between NF1 and NF2. And I think for many years the diagnostic criteria were not particularly clear. But I think now we have a much better understanding of the genetics of the two conditions and the two have become very clearly differentiated syndrome. So with NF1, vestibular schwannomas are not a feature. And I think that's one of the key things to be aware of. With NF1 you tend to get more skin manifestations, so you get more café-au-lait spots, and the café-au-lait spots that you get are usually larger.

The histo pathology of the tumors is also different. So in NF2 you don't tend to get neurofibromas. So really, NF2 is a misnomer. Whereas in NF1 it's common to get two or more neurofibromas. And you can get plexiform neurofibromas, as well, which can affect any part of the body. And you also get these typical leashed nodules within the eye in NF1 which you don't get in NF2. And obviously, there'll be a family history in many patients of NF1. In patients that present with NF1, whereas that's not the case in NF2.

Dr. Jason Barnes:

And it seems like NF2 is kind of its own specific diagnosis, but is there anything else you keep on the differential diagnosis in considering this disease presentation?

Dr. Simon Lloyd:

I guess, just the other tumor predisposition syndromes, the LZTR1, and this might be one type conditions. Like, I think it's probably a good time just to say that actually not everybody with a bilateral vestibular schwannoma has NF2. If you look at the proportion of patients with bilateral vestibular schwannomas, if you present very young, then almost certainly you will have NF2. But if you present over the age of 70 with bilateral vestibular schwannomas, then there's probably only a 50% chance that that individual has NF2. And the two tumors are probably actually just too sporadic vestibular schwannomas.

Dr. Jason Barnes:

Next I wanted to move on to the workup. You mentioned audio logic testing. But when you see a patient who you suspect has NF2, what is your full workup for these patients?

Dr. Simon Lloyd:

So they get a full ENT and neurological examination, which we've talked about already. And then in terms of investigations, the audiological assessment consists of a pure tone audiogram and speech discrimination testing. And we use word scores, the Arthur Boothroyd word scores when we're carrying out the assessment. And that's important to do both because people with vestibular schwannomas not just in NF2 but sporadic tend to get some distortion of the sound. So the pure tone audiogram sometimes doesn't give a really good representation of their actual functional hearing, whereas the word scores tend to give you a much better functional assessment of the hearing.

I guess after the pure tone audiogram and the speech assessment, the next line of investigation is imaging. And the mainstay of imaging is magnetic resonance imaging. And we have very specific protocols for ensuring that we get the best pictures in terms of imaging both the head and the spine. And we will carry out contrast enhanced imaging with gadolinium, both axial and coronal cuts. And we'll carry out T1 and T2 sequences with high resolution fine cut imaging through the head and spine. And that gives us the best possible modality for identifying tumors. We also image the chest and the abdomen which often is covered by the spinal scan, and if there are other specific tumors that are giving signs or symptoms.

Dr. Jason Barnes:

So say you get the MRI and you identify the bilateral vestibular schwannoma, what does that lead you on to for additional testing?

Dr. Simon Lloyd:

So, obviously the other manifestations of NF2 are very important. And the care of patients with NF2 is multidisciplinary. And one of the key things to do is assess the eye. So we always involve ophthalmology colleagues, and they can assess the patient for the ocular hamartomas and the cataracts and any visual acuity abnormalities. And then the other element of assessment presentation is the genetic assessment. And the genetics team plays a key role in the management of any patient with NF2.

What we tend to do initially is to carry out genetic testing in blood. And if you've got full blown NF2 then there's a 95% chance that we'll be able to identify the gene abnormality within blood. But patients that have mosaicism can sometimes be a real challenge to diagnose the genetic abnormality because blood doesn't carry the mutation in quite a significant proportion of patients that have mosaicism. So in those patients, if we need to know what the genetic abnormality is, we'll try and biopsy a tumor or ideally two tumors, so that we can make sure that we've got the same genetic mutation identified in two separate tumors. And that doesn't have to be vestibular schwannomas. If you've got peripheral tumors, then biopsying those tumors sometimes can be quite helpful. We don't do that routinely for every patient. Because sometimes biopsying these tumors can lead to consequences that we would rather avoid. But it's certainly something that we do do from time to time.

Dr. Jason Barnes:

And with all of this information together, how do you make the official diagnosis of NF2? Is there a diagnostic criteria that you follow or is it only genetic?

Dr. Simon Lloyd:

No. So, the genetics is important, but there are diagnostic criteria that are widely used. The most commonly used is the revised Manchester NF2 criteria, and that basically has five different arms. One is the presence of bilateral vestibular schwannomas. And then the second is a family history of NF2 and a unilateral vestibular schwannoma. The third criteria is a family history of NF2 or unilateral vestibular schwannoma or one of two types of other manifestations, so meningioma, cataracts, glaucoma, neurofibroma, schwannoma, or cerebral calcification.

And then the other criteria are multiple meningiomas and two of those conditions that I've just mentioned. Or, finally, an actual mutation that's identified in blood or in two distinct tumors have been biopsied. But you'll probably know from that description that actually the idea of the pathology that's present in NF2 has changed. So I mentioned that gliomas and neurofibromas fall into that revised Manchester NF2 criteria, whereas in actual fact gliomas and neurofibromas aren't actually a feature of NF2. And we've only really become aware of that over the last 20 years since the revised Manchester criteria were developed. So the gliomas are now generally speaking, found to be ependymomas. And the neurofibromas pathology isn't really something that we see in NF2. So I think what we'll see in the next few years is a change of the classification system that we use for diagnosing NF2.

Dr. Jason Barnes:

And when we move on to treatment, we do have another podcast episode specifically about vestibular schwannoma. And in that episode, we talk about observation, stereotactic radiosurgery and microsurgical removal. And we've kind of outline the different indications for each of these. I imagine NF2 poses a more difficult challenge. How do you approach the treatment of NF2? And what are your treatment options?

Dr. Simon Lloyd:

So I guess fundamentally, in terms of vestibular schwannoma, the treatment options are very similar to those for sporadic tumors. There is however, one other treatment option that has become available over the last 10 years probably now. And that's medical therapies. So forms of chemotherapy, and in particular, the use of a drug called bevacizumab, or Avastin, which is its trade name. And that really has revolutionized the way we manage many of our patients with NF2. But I'll go back to that later on.

So if we go back to the tumors when they first present, it's certainly very common for us to manage tumors conservatively. And I think historically we've tended to manage tumors much more conservatively in NF2 than we have in sporadic disease. Because we know that they've got bilateral tumors. And if you treat both tumors, then you can end up causing quite significant disability to the patients through your own interventions. So if you go back 30 years, we would have been watching vestibular schwannomas until they get really very large in order to preserve their hearing and to preserve them functionally. And then we would end up being faced with having to remove a four centimeter tumor with the potential greater risk of undertaking that type of tumor.

Now, I think we have a much more proactive approach to taking out vestibular schwannomas or treating vestibular schwannomas with radiotherapy or with medical therapies. We'll tend to get involved much earlier on. Because we know that removing a tumor when it's smaller is associated with much lower morbidity. And there are much more effective rehabilitation modalities now that we can use. So for example, with vestibular schwannoma if we take it out, we can place a auditory brainstem implant to rehabilitate the hearing. In some cases we're able to take the tumor out and use a cochlear implant. And we're certainly able to use cochlear implants in patients that have got conservatively managed tumors or tumors that have had radiotherapy or Avastin treatment. So now, we tend to deal with one vestibular

schwannoma relatively early on, and then we're able to rehabilitate the patient and then we can deal with the second vestibular schwannoma if we need to at some point in the future knowing that we've given some degree of rehabilitation already for the other ear.

Dr. Jason Barnes:

And what's the role for radiosurgery here?

Dr. Simon Lloyd:

So there certainly is a role for radiosurgery in NF2, but the condition is a tumor predisposition syndrome. And there is a germline mutation throughout the body that makes it much more likely that somebody will develop a tumor. So when you use radiotherapy, you're much more likely to cause that second hit and induce a new tumor. And that means that we tend to use radiotherapy in a more limited number of cases. And certainly we're reluctant in the younger cohort to use radiotherapy. We tend to use stereotactic radiosurgery, and certainly in our department, we use gamma knife and there are other centers around the world that use other forms of stereotactic radiosurgery. And if you look at the literature, the success rates of radio surgery in NF2 are not as great as they are in sporadic vestibular schwannomas. So with the sporadic vestibular schwannoma we'd expect somebody to get a 95% control rate with stereotactic radiosurgery. But for neurofibromatosis type 2 patients, the control rate is probably more like 50% over a five or 10 year period.

Dr. Jason Barnes:

And you started to talk about bevacizumab, could you tell us a little bit more about how that's used and how effective it is?

Dr. Simon Lloyd:

Yeah, sure. So, bevacizumab is a VEGF receptor antibody. So, vascular endothelial growth factor antibody. And what that does is it binds to the VEGF receptor. And because VEGF is one of the cytokines that results in angiogenesis within tumors, having the VEGF antibody bound to the receptor, reduces the angiogenic tendencies of the tumor. And there's very good evidence. Now, certainly in NF2, that by blocking that VEGF receptor, you can significantly slow down the rate of growth of vestibular schwannomas. We've also seen similar results with other forms of schwannoma around the body. So particularly spinal schwannomas, we've had some really fantastic results with reversal of neurological deficits with treatment of peripheral schwannomas with bevacizumab. And in vestibular schwannomas bevacizumab has also been shown to slow down the loss of hearing and in some cases even improve the hearing in some cases.

Dr. Jason Barnes:

So in the specific case of NF2, is bevacizumab always used or are there certain indications for it?

Dr. Simon Lloyd:

No, there are certain indications for it. It's a drug that up until recently has been very expensive. So certainly in the UK its use has been rationalized to some degree. And currently we have quite strict criteria. So the tumor has to be growing at least four millimeters per annum. And there has to be some kind of threat to function. So in the case of vestibular schwannoma, that would be hearing, those criteria will be very different from one country to another, and certainly in the UK with Avastin now coming off

license, the cost of the drug has come down and we may well relax our criteria for the use of bevacizumab.

We currently use around five milligrams per kilogram for nightly for bevacizumab. And it's a parenteral treatment so it's an injection. So it's not easy to deliver the treatment, which is another reason why we don't use it for every patient with a growing vestibular schwannoma. And you can reduce the dose that you give over time to try and reduce side effects of the drug. And most patients tolerate it really, really well. There are some problems with it in terms of nephrotoxicity. There are some problems with affecting patients fertility, and it can affect blood clotting. So in some cases, it can make you more prothrombotic. And in some cases, it can make you more prone to bleeding. And so it's not a drug without problems, but most of the time patients tolerate it very well.

Dr. Jason Barnes:

And I understand that when we talk about outcomes and expectations. There are other types of tumors that are being resected by maybe our neurosurgical partners, but how do you counsel patients on both expectations for surgery, and also outcomes regarding their vestibular schwannomas?

Dr. Simon Lloyd:

So I guess the patient's pretty up to speed with the options for treatment from the outset. We're very clear with them at the beginning that we are able to manage the patient's tumors conservatively in many cases, but in the long run it's likely that they will come to some kind of treatment. And we go into some detail explaining what the potential benefits and risks of each of those treatment options are over time. But with surgery, we obviously explain that there's a significant risk of damaging the facial nerve very much dependent on the size of the tumor when we're operating. So smaller tumors have a much lower risk of damaging the facial nerve than larger tumors. We counsel them with regards to the potential for recurrence, which is more common in NF2 than it would be in a sporadic tumor. And we counsel them with regards to the other complications that can develop with vestibular schwannoma. Surgery such as CSF leak, stroke, intracranial hemorrhage, meningitis, damage to the other cranial nerves in the area and the risk of dying as a result of the surgery.

Dr. Jason Barnes:

And what's your approach in terms of gross total resection versus subtotal resection?

Dr. Simon Lloyd:

That varies a lot between units. Our own personal philosophy is that we try and remove all the tumor in every case, if we can, but if there looks like there's going to be significant damage to the facial nerve, it's not that unusual for us to leave a very small amount of tumor on the facial nerve. And that little bit of residual tumor is de vascularized. And it's pretty unusual for it to regrow, although there is a greater risk of regrowth in NF2 than there is in sporadic tumors. But often, in NF2 we're not just dealing with an isolated vestibular schwannoma, you can often get facial schwannomas in association with the vestibular schwannoma, you can get lower cranial nerve schwannomas associated with it. So you might be dealing with a conglomerate of tumors. And in that situation, we try and take out the vestibular schwannoma but leave any other non vestibular tumors in place so that we don't give them too many cranial nerve deficits following surgery.

Dr. Jason Barnes:

And how do you follow up with these patients?

Dr. Simon Lloyd:

So they get followed up in outpatients around six weeks postoperatively, and we see them again at three months. If they have facial weakness, we'll be able to counsel them about whether that's likely to recover depending on whether the nerve was functioning well intraoperatively. And we can also get an idea of whether it's going to recover from whether or not they still got a little bit of residual function if they do have facial weakness at all. And then the follow up after that really is with the same imaging modalities that we've already discussed with cross sectional MRI imaging of the head.

Dr. Jason Barnes:

Well, Professor Lloyd, thank you so much for this discussion. I was going to move on to our summary next, but is there anything else you wanted to add before we close our time together?

Dr. Simon Lloyd:

I think one of the things we touched on briefly is hearing rehabilitation in NF2. And as I mentioned earlier on, the thing that affects the quality of life of patients with NF2 the most is bilateral hearing loss. And over the last 20 or 30 years, we've been fortunate to be able to develop a number of different modalities for hearing rehabilitation in NF2. For the last 10 years we've been using cochlear implantation in various different groups of patients in NF2. So we can use it in patients that have got conservatively managed tumors. We can use it in patients that have had stereotactic radiosurgery and we can sometimes use it in patients that have had cochlear nerve preserving surgery.

And those patients that have had cochlear implants can do very well. Not everybody does. I have to say those patients that have conservatively managed tumors tend to do better than those that have had other types of treatment to their tumor. But we can expect patients with conservatively managed tumors to achieve up to 60% in their sentence scores with their cochlear implant. Those that have had surgery or radiotherapy, they tend to score on average around 35% or 40%. And so they don't do quite so well with their cochlear implant.

And for those patients that have had their vestibular schwannomas removed and the cochlear nerve isn't intact, the use of auditory brainstem implantation has been extremely important for these patients. And although auditory brainstem implantation doesn't offer the same degree of hearing rehabilitation that a cochlear implant might, they certainly allow patients to be able to appreciate environmental sounds and they act as an aid for lip reading so that patients can function much more easily on a day to day basis.

One more thing I'd like to add is that the management of NF2 is very much multidisciplinary. And certainly our team here in Manchester and many of the larger teams across the world consist of ENT in neurosurgery, audiology, oncology, genetics, pediatrics and radiology. And without that team approach, I don't think the outcomes of management of NF2 can be optimized.

Dr. Jason Barnes:

Well, Professor Lloyd, thank you so much. I'll now move into our summary. NF2 is a genetic disease that includes a clinical presentation of bilateral vestibular schwannoma or vestibular schwannoma with other tumors such as a meningioma. The pathophysiology is related to genetic insult to chromosome 22 related to the Merlin gene. Although 50% of patients are de novo mutations and do not have a family history. Workup is extensive to include MRI audiologic evaluation, ophthalmology evaluation and genetic consultation, and patient is diagnosed once they meet specific NF2 diagnostic criteria.

Treatment requires a multidisciplinary approach considering quality of life, location of tumors and hearing status, and treatment often include surgical resection as well as medical therapies such as bevacizumab, and sometimes radiation therapy. Outcomes are dependent on the extent of disease and their options for hearing rehabilitation such as cochlear implantation, and auditory brainstem implantation.

Professor Lloyd, anything else you'd like to add?

Dr. Simon Lloyd:

No, it sounds great.

Dr. Jason Barnes:

Wonderful. I'll now move into the question asking portion of our time together. As a reminder, I'll ask a question, pause for a few seconds and then give the answer. So the first question is, what is the most common genetic mutation we find in patients with NF2 and how many patients present with new mutations?

The most common alteration is a chromosome 22 affecting the Merlin gene. This is an autosomal dominant inheritance pattern, but about 50% of patients present with a new mutation and no family history.

The next question is, what are the diagnostic criteria for NF2?

There's a list of diagnostic criteria for NF2 and it's as follows; a patient could one, have bilateral vestibular schwannoma. Two, have a first degree relative with NF2 and a unilateral vestibular schwannoma or any of the two following meningioma schwannoma, glioma, neurofibroma or cataract. They could also have a unilateral vestibular schwannoma and any two of the following, again the meningioma, schwannoma, glioma, neurofibroma and cataract. They could have multiple meningiomas and unilateral vestibular schwannoma or any of those other tumors. And finally, this can be genetically diagnosed. And as Professor Lloyd said, this can be from a blood sample or from two separately biopsied tumors.

And for our last question, what are the treatment options in patients with NF2?

There's a broad answer to this question and it's dependent on patient presentation. But in terms of vestibular schwannoma, tumors can be observed. They can undergo microsurgical resection. There is a role for stereotactic radiosurgery, and there's also more convincing evidence that Bevacizumab can be helpful in the management of these tumors. And finally, hearing restoration is always a consideration with either cochlear implantation or ABI.

Thanks so much, and we'll see you next time.