Pediatric Manifestations of Neurofibromatosis Type 1-Pediatric Grand Rounds-Meeting 11-15-24

November 15, 2024, 1:29PM

1h 2m 46s

Kamat, Deepak M started transcription

Kamat, Deepak M 0:05
I turn it off.
Did it go off your screen?

Calderon, Delia 0:09
No, I still see the box on this on the screen.

Kamat, Deepak M 0:10
OK, OK. So you have to do it, I think individually, yeah.

Calderon, Delia 0:13
Yeah, I think we each have to do that because it's a little notice to everyone letting them know.

Kamat, Deepak M 0:20
Yeah, that we are recording, yeah.

Calderon, Delia 0:23
So I clicked it off of mine and Doctor Shaw. If you wanna do if it's distracting for you, click off.

Shah, Shafqat 0:29
Done.
Alright.

Kamat, Deepak M 0:37
Good morning and welcome to pediatric grand rounds.
It's my pleasure to introduce multiple speakers today.

Doctor Sharpat Kashya is going to lead the discussion, then joining her will be doctor Ujabala Saboo doctor Brian Fox, Dr. Sinekat McCormick and Doctor Julie Fisher.
I'm going to introduce Doctor Shah, who is a clinical professor in pediatric hematology oncology.
Doctor Shah graduated from the Johns Hopkins University in 1987.
With honors in molecular biology, and subsequently she joined Duke University School of Medicine in 1991 and completed her pediatric residency at Emory University in 1994. She joined UT as her to complete her pediatric hematology oncology Fellowship between 1994 and 1997.
Doctor Shah's career has focused on childhood cancer survivorship.
And neuro oncology.
She's a leader of Neurofibromatosis program in the Department of Pediatrics.
She has been working to expand resources at UT Health and University Hospital for Children and young people with neurofibromatosis.
She also supports local and statewide organizations that support families affected by Neurofibromatosis.
Doctor Schaf, thank you very much for organizing this presentation with multiple speakers.
We are looking forward to your presentation.
The floor is yours.

Shah, Shafqat 2:04
Thank you for your kind words.
We are ready to go.
I know that we have quite a bit of ground to cover here, so I'll go ahead and get started.
The objectives today are listed here.
I will describe the genetic basis of neurofibromatosis and then in turn my Co speakers will go ahead and discuss the common ocular neurologic, orthopaedic conditions that are seen commonly in norfibromatosis type 1.
At the end, Doctor Fisher will discuss the risks for malignancy in neurofibromatosis type one patients and at the end I will then have just a few slides describing our clinic and a multidisciplinary assessments that we.
Are performing for the children here in South Texas and there are no disclosures or conflict of interests for any of our speakers.

So as you may know, as I recall, in medical school, neurofibromatosis type one is a neurocutaneous disorder and it was first described in over 100 years ago by a German pathologist, Dr. Ravan Reklenhausen. And you know back in the day we used to call it Von Re.
'S disease.
But now that we know that the gene has been identified in 1990.
We know that the understand the genetic basis of this condition.
We know that it is actually a fairly common condition affecting one in 2000 to 3000 births and in many situations about half the patients it is inherited from a parent and about half the patients is it's a new mutation.
It's interesting because the NF1 gene, which is located on chromosome 17, it's a very large gene, so it is prone to mutation.
It the gene product is actually a tumor suppressor.
Called neurofibromin and mutations in this gene lead to proliferation of nervous tissue and additional mutations can lead to development of cancer. Now, in the last 20-30 years, there has been quite a bit of work trying to describe the clinical criteria for this condition, but we do know.
That genetic testing also can be performed in the modern era to help families understand the basis of the condition and.
For counseling for other members of the family.
So you can see this is the cascade and the cell membrane where neurofibromin works to control the Ras pathway and the rasp pathway is very important in cell proliferation and so you can see that there's lots of molecules that interact with neurofibromin and these are all molecules down.
As you see, coming down the right side and that potentially are targets to try to control the proliferation of these tumors and I think a molecular basis of nerve fibromatosis 1.
Something that's very fascinating and is being studied more and more in the laboratory.
But the clinical criteria for neurofibromatosis type one actually has been updated to include now the genetic diagnosis as part of the criteria in order to make the diagnosis, you need to have at least two of the cardinal diagnosis, and you can see that the others are listed here.
And they include cafe Ole spots neurofibromas or plexiform neurofibromas.
Axillary freckling optic gliomas, lich nodules, Bony changes, having a first degree

relative with NF1.
So when we see patients in our clinic, the genetic counselors will go through this checklist with the patients to explain how the criteria are useful in making a diagnosis. Sometimes in children, you know, you may not have as many caffeole spots or they may be small.
And so in that situation, family history would be very important. And then offering genetic testing if the patient.
Been diagnosed with mass or a tumor of some kind.
It would be helpful prognostically and for treatment purposes to have a genetic diagnosis.
So the bulk of the discussion today will be, you know, really from my partners in crime and I'm going to set up the discussions by having presentations of different clinical scenarios that we've seen over the years. And these are based on some of the patients I followed in.
In the last 10 years or so with neurofibromatosis type one and we will go through conditions that present in the young children and then all the way to adolescents. So the first case that I will talk to you about is one of a newborn. And so doctor S.
Will lead the discussion of this situation.
I just want to mention a few things about Doctor Saboo.
She's associate professor in ophthalmology.
She's fellowship, trained in pediatric ophthalmology and has done a residency in Hyderabad, India.
She has completed a research fellowship in Massachusetts and a cornea fellowship at Harvard Medical School, as well as a two year fellowship in clinical Pediatrics sister business in the UT Southwestern.
So she's very well train.
We are lucky that she came to UT health in 2018 and she has been very helpful to the nurfi rheumatosis type one population as being the point person to get them into the eye clinic to help them screen for ocular conditions and to help establish diagnosis of.
NF1, So she might be consulted early on in the first year of life by pediatricians that are seeing patients with skin findings.
As I said before and F1 is a neurocutaneous disorder and so one of the.
Most common presentations will be just the cafe Orleigh, the brown spots, and so sometimes you know again at time of birth there may be just one or two.

They may not be very large and then usually you know, over time the families will ask about these lesions. And I think one thing pediatricians can do very readily is to call someone that has expertise in fibromatosis.
So that might be a genetic counselor. That might be somebody.
In here might be Doctor Fox in neurology.
And you can start to doing the appropriate assessment and it's very important to do this assessment early on because some of the ophthalmologic findings.
Really do present early in very young children, so if you call Doctor Fox or Doctor Saboo, they will expedite evaluation of vision of the child even before a diagnosis.
Maybe you know, maybe possible on clinical grounds.
They will try to expedite those patients, so the appropriate evaluations can be done in a timely fashion. So I'm going to allow Doctor Sabu to go ahead and present her slides.
Doctor saboo.

Saboo, Ujwala S 8:54
Good morning, everyone, and I'm gonna talk to you all about the ocular findings in neurofibromatosis one patients. So most common things that we see in eyes in NF1 patients is leach nodules, lexiform, neurofibromas, korad, Hamar, Thomas Optic, pathway, gliomas and traptases. Because of these optic pathway, GL.
So what unleashed reduce?
These are basically melanocytic hamartomas of the iris.
They are usually difficult to see on penlight examination and require a slight lamp examination.
They are seen as little tiny, less than 1mm, sharply demarcated exclusions on the iris on the dark color iris. They can be seen as light colored excenses and on light colour irises they can be seen as dark colour XP senses as seen in this picture.
They are usually asymptomatic.
They do not affect vision and the prevalence increases with age. So less than 5% in less than three years of age.
The increase and up to 100% of adults over 21 years of age may present with Alice nodule.
They are one of the diagnostic criteria as Doctor Shaw mentioned.
So the other thing that we come across is like we found neurofibromas.
These are benign peripheral nerve sheath tumors, as everywhere else in the body.

They are soft, painless nodules that arise underneath the skin.
They can feel like bag of worms when palpated in the eyes.
They will involve the eyelid, eyebrow orbit or temple and plexiform neurofibromas of the eyelid can present with P posis proptosis trabismus.
They can cause I'm live PR due to vision.
Obstruction can also be associated with congenital glaucoma and skull deformities.
This is one of our patient in which in whose left eye we can see like the form neurofibroma of the left upper eyelid, and it was obstructing her visual access.
It was also causing astigmatism because of the pressure from the neurofibroma on the eyeball, and so we gave her glasses. She underwent treatment with the NEK inhibitor and eventually she underwent a surgical debulking.
Complete exhibition of these tumors is usually not possible because these are very diffuse.
And sometimes surgical debulking is combined with otosis surgery, such as a frontalis suspension to lift up the upper eyelid.
Another thing that we notice in these patients and which is commonly seen nowadays because of the availability of multimodal imaging, is the coroll abnormalities. These can be seen in 82% of the adults with NF1 and has been recently introduced as a diagnostic criteria along with.
The leash nodules.
These are basically oh, white bodies, consisting of proliferating Schwann cells.
Arranging concentric rings around the exons.
These are flat.
I'll defined corridor hamatoma.
As we see in this picture on the left hand side of the screen, the fundus picture these are look like tan, yellowish, whitish or black in color.
They're flat. They're difficult to be exam on fundus examination, but they're very well seen on the infrared photography or the Oct imaging. These whitish patches that we're seeing on this black and white picture.
These are the coroll abnormalities, and again they do not affect vision.
So the next thing that we gonna talk about is the optic pathway, glioma. These are most common intracranial tumors in NF1 patients.
They are who Grade 1 pylocytic astrocytomas arising within the optic pathway and the hypothalamus.
They can be in.

They can involve any part of the optic nerve from the arbiter portion to the chiasm to the optic tract and optic radiation.
Their prevalence is ranging from 15 to 20% of.
These of NF patients.
Optic pathway tumor progression is uncommon in children with NF1 and.
The patients who have chiasma and hypothalamic glioma have higher probability of visual loss and also they can cause hydrocephalus and precautious puberty. Optic nerve optic radiation. Involvement of these optic pathway gliomas are a little more aggressive optic pathway gliomas in patients with NF1.
So what do they do on vision?
So optic pathology in the eyes.
Optic pathway glaucoma is rarely grow after 10 years of age.
In symptomatic optic pathway glioma, you could see visual acuity decrease.
They can affect visual fields.
They can also present as optic disk swelling or PALAR. They can cause proptosis, trabismus, or nystagmus.
So as we see in this slide, proptosis can occur most commonly in orbital portion of the optic pathway glioma and sometimes proptosis is pulsatile because if the spinalod wing is absent or dysplastic as this can happen in NF1 patients.
Only the dura separates the brain and the orbit and the pulse.
This can be pulsatile now on the right height nerve and suspected small focus of contrast enhancement may present an optic pathway glioma.
The central side shows Proptosis on the left eye due to orbital glioma and on the left side you can see a picture of the MRI showing a left sided fractas due to retro bulbar or vital neurofibroma.
So because these optic pathway gliomas can occur early on in children and they can affect vision, there are recommended screening criterias for eye screening in NF1 patients. So at the time of diagnosis or even suspicion of NF1, all these kids should get an eye exam and.
Then an annual eye exam, so thereafter, until eight years of age after eight years of age.
They at least should get every two yearly exams until 18 years of age.
The eye exam includes reliable age appropriate visual acuity assessment, color vision testing, assessment of pupils, eyelids, occulomotability and your segment examination with slit lamp, optic nerve assessment and ocular frontus examination

with indirect ophthalmoscopy and visual field testing in older children.
Diagnostic imaging modalities such as optical coherence tomography, which is a non invasive technique in.
To measure the nerve fibre layers.
Thickness we can.
We can measure the thickness of the optic nerve fibers in this patients where we are suspecting an optic pathway glioma is performed.
So these are basically different charts that we use for visual activity testing in children, very young children.
Cannot, who are nonverbal or do not understand matching, yet we use these tellers visual acuity chart which is on the left side of the slide.
The slightly older children are around two to three years of age.
They can match pictures.
We use island pictures, symbols and older children who can understand letters.
Use hotm charts or the normal E Charter.
Television testing is done with Ishihara chart and HRR charts.
Fundoscopic examination example showing of Piller of the optic nerve. We can see significant color difference in the temporal portion of the optic nerve and the second pictures were showing a lot of swelling in the optic nerve.
The other testing we do is the visual field testing the different methods based on age and cooperation, we can use confrontation visual field which is very basic test, more sophisticated test such as automated visual field which is a second picture on the slide.
In cooperative kids, they should be able to do these testing, which will tell us visual field deficits in these patients.
The 3rd is a Goldman visual field which is a manual visual field.
Very useful instrumental.
Patients who have attention span, lack or have ADHD, which is not uncommon in patients with NS. We can do these testings to measure visual field in these patients.
Now this is the oculular coherence tomography.
As I said before, there's a noninvasive imaging technique that measures the thickness of the Arctic nerve or the retinal nerve fiber layer, and this is useful in diagnosing and monitoring progression of optic pathway glioma.
So this will give us a thickness on the nerve fibre layer and we can see over the years we can see changes in.

The thickness and optic pathway gliomaza affected by the glioma in the optic nerves.
So do all optic pathway gliomas need treatment?
No. So not all optic pathway gliomas need to be treated.
Treatment is indicated only when there's decline in vision. The first line treatment is standard chemotherapy with vincristine, or carboplatin. Molecularly targeted therapies, such as any K inhibitors and wedge of inhibitors such as bevasizumab, are promising new treatment modalities, radiotherapy and radical surgical resection of these tumors have very.
High morbidity.
And they are reserved as the last resort. Debulking surgery with lateral orbitatomy is rarely performed in these patients. If there is a very large orbital component which is causing disfigurement and pain in non seeing answer.
So this is the from my side.
I would emphasize that all these patients where the suspicion of NF are being diagnosed with NF needs eye exams and regular screening so we can detect optic pathway gliomas early on and reduce the.
Possibility of permanent visual damage. Thank you.

Shah, Shafqat 19:25
Yes, I think I'd like to emphasize that as well because once the visual damage has occurred, it's very rare for things to improve. Even with therapy. Usually when you are seeing visual loss, especially in a young child, it may be at late stages and so you know our.
Goals for treatment is to preserve the vision that the child still has and hopefully decrease the risk of a progression to the chiasm or to the other optic nerve.
Thank you, doctor Saboo.
Now I'm going to go on and present.
Another scenario that's fairly common as we follow these children and they enter school age range, some of them as doctor Saboo mentioned, will have learning issues.
ADHD is seen at a higher rate in this population and so I'm presenting now the case of a six year old who's about to start school.
He's, you know, he maybe went to kindergarten and then.
Seemed to be doing well.
Was transitioned to 1st grade and a few months into school.

You know, it seems that something has changed and is coming home complaining that his head is hurting. You know, his family does take him to the pediatrician. That has been following him regularly. And you know, they don't find any common reason for the headaches.
No sign of infection or anything.
A headache diary is recommended and at the next follow up visit it seems that the headache frequency is increasing and the patient is, you know, needing Tylenol every now and then to treat the headaches coming home early from school.
And so a consultation to Doctor Fox and the pediatric neurology clinic is expedited as this is a child with NF1 that is at risk of a neurological problems. And so doctor Fox, if you can unmute yourself and put your camera on, we'll go ahead and have you.
Discuss NF1 patients and headaches.

Faux, Brian Michael 21:27
Thank you. This feels like a relay today.
Hopefully won't drop the baton.
So when we see a child at this age or any age with headaches, our first goal in neurology is always to evaluate for secondary causes.
Those would be things that be extrinsic to the brain proper, causing the abnormalities, tumors, vascular malformations, infections, clots, those kinds of things.
So that's always first in our mind with any child with headache. But.
In NF1 in particular, there are some facts that guide us.
So we do know that children with NF1 have higher prevalence rates of headaches, and there you can see the data anywhere from 20 to 80%.
Experience a headache of some sort.
Most of them are going to be tension type, just like a child without NF1 and some of them are going to be migraine type which tends to be a little less common which we see mirrored in our non NF1 patients.
We're always mindful and more mindful.
One for a younger child, as the history can be a little bit more difficult to get. And we're also mindful that we won't don't want to miss secondary causes of headaches and we'll go through those in a bit and how we differentiate just based upon history and Phys.
And then also 4%, we know that could be possibly due to a glioma and so anywhere

throughout the central nervous system and peripheral.
So we do know also that patients with NF1 have higher impact scores. And if you think about headache in general, we do know that often times it is the most obvious problem masking things like anxiety, depression, insomnia, social stressors, etcetera.
We also see some children that can have referred pain, just as Doctor Saboo mentioned because of.
Lesions were anywhere in the head.
And neuropathic pain is also something that might cause a different kind of headache. Secondary cause.
But burning, tingling, numbness and itching.
And this can be seen up to 46% of children with NF1.
As far as the Physiology of why NF1 has more pain.

Shah, Shafqat 23:20
H.

Faux, Brian Michael 23:24
It's really has to go back to another cartoon of where NF1IS firing and from Doctor Shah's earlier cartoon about neurofibromin and where it leads.
This this pathway wasn't even listed, but it's the pain pathway through this crmp 2 collapse in related mediator protein two and what this lack of phosphorylation does, it leaves it in an active state. And this in turn leads to down regulation of or upregulation rather of casetone and.
Gene related peptide which?
For us in Pediatrics, we have not seen much of calcitonin gene related peptide but within the next decade or so.
Trials are coming through how we treat this molecule.
In short, CGRP.
Is identified like substance P as being a pain perception molecule primarily so this lack of control over crmp leads to sensitization of small painful neurons, and that's where the pain comes from. Secondary headaches in NF1 can happen again. A primary headaches like migraine and tension are much.
More common, but we're always mindful not wanting to miss things like optic gliomas and so. But these gliomas can happen throughout the.
Nervous system. So much so that if you have a low grade glioma in the brain, always

think about NF1 going backwards because they might not have a lot of other symptomatology depending upon their age, they can happen subcortical brain stem, but again, the optic gliomas are usually.
Asymptomatic in the majority of children, hydrocephalus can happen based upon where an optic glioma is located, and you do have a 50 fold increase risk of a higher grade glioma developing, which is.
A possibility.
Other things that can cause headache, pain in children and this six year old would be things like Moya, Moya, a stenosis of some sort, and eurisimal alterating the endothelium because of the NF1 and as mentioned norovibromas and then a painful peripheral sensor neuropathy which tends to be.
Very rare in children.
As with all children with headache features of worse than secondary headaches or what we go through in the history, we want to know if it's a severe incapacitating and if it's increasing in frequency and severity. So beyond the timing of the headache, how long has it been going?
On the frequency.
Severity of it, if it's changing really bothers me.
New headaches bother me.
They're a little bit difficult as opposed to one that's been there for a while.
I'm not as worried vomiting that's persistent, increasing a lot of times.
GI doctors will see children first with vomiting and then find out that it's due to something secondary cause of the headache. If it's exclusively occipital or frontal location if it awakens them from sleep. Worth with Valsalvo a negative family history and it's one of our typical questions is.
There anyone in the family?
If it's negative, it makes me a little bit more worried and then obviously the strongest two are the last two neurological finding of any sort plus a headache. And then any change in behavior personality because a lot of children can't report eloquent problems.
But they will have a change in behavior, personality in particular.
And going back and where are all of this data came from?
Is is pretty old 1982, but looking at a cohort of children abnormal findings on the initial neurological examination are particularly compelling evidence of the diagnosis of a secondary cause of a headache. 85% of children will exhibit papilledema,

strabismus, weakness, or ataxia within eight weeks.
Of headache, onset and virtually all children will have one of these findings by 6 months, and I do rely upon that time frame.
So if I have a well established headache even in a patient with.
I'm not as worried.
And I also know if I can get them into a diagnostic criteria of either a migraine or tension as per the international classification of Headache disorders.
I do know with a normal neurological exam, they're on the left side of the chart.
You'll have a 0.4% chance of missing something significant now if they have a non specific headache type that rises to 2.4%, but it really speaks to the importance of doing a thorough neurological and fundoscopic exam.
And this comes into the help supervision statement that was put out.
In 2019 by the AAP and it, I often get questions about, well, who would you image? I would think if they would violate any of the previous mentioned red flags, strongest of which would be focal neurological phenomena, you would image them. But the routine imaging is.
A controversial question in NF1.
And typically it's not done.
And very Privy to the risks of anesthesia or sedation in the young child where it's not going to change things.
And if I can get a good exam, they really.
Would be going through one of these criteria first to get imaging.
As far as what we find on imaging, it's not uncommon to have these ubos unidentified bright objects in the brain. Typically the younger you are, the more common they are.
They're also, you might see, is focal areas of enhancement might be mentioned and there are nothing to typically be worried about.
We think they may be due to changes in the way the myelin sheath is laid down.
But these are not tumors and they will change the next time. If you would reimage that person.
As far as headache treatment for patients with NF1, it's no different than anybody else with headache. In our clinic, we have the benefit of having some very experienced providers and you will soon have a grand rounds here on 1st of December with Doctor Azar Akbar who is.
Certified in headache management, but our headache management is no different

for NF1 or any secondary cause.
We treat the whole person and what that means is we engage with all aspects of their care from sleep, hydration, exercise, dietary, etcetera.
We do use baseline foundational lifestyle modifications and we go through this diagram with the families as they come through our care and there you see a lot of things are not really hinging upon pharmacological care, but I'll go through those briefly.
The non pharmacologicals would be mental health counseling for various reasons.
Cognitive behavioural biofeedback relaxation.
Coping guide 8 imagery hypnosis, physical therapy, acupuncture and their yoga, etcetera.
And there you can see some of the nerve stimulation devices which are starting to trickle through from either cranial nerve stimulation.
To remote nerve stimulation to alpha stimulation.
Nutraceuticals are the one of our key baselines I'd have to say. Everybody gets magnesium at some point.
Has to have a good trial of it.
Coenzyme Q10, riboflavin these medications, or nutraceuticals rather have all outperformed placebo, which is saying something.
And pediatric headache trials. Given the 50% placebo response rate as far as other treatments, Botox is applicable as well.
And again, that's kind of up the pyramid. We're going to try simple things first and there you'll see improvement in chronic migraine headaches and then even our own doctor Akbar was able to publish on this.
Just this past year, improvements in childhood etic our goals of care for using pharmacological agents are to.
I would say the biggest one is prevent medication overuse or you're starting to use too much.
Of acute abortions because we don't want to get into those type of headaches.
We don't want to use ineffective medications and the headache classes are highly varied and so there is no specific difference in the treatment of these headaches in NF1.
But given how the crmp leads to the CGRP upregulation, newer medications that fit into this, the calcitonin gene receptor.
Peptide blockers might have a greater role in NF1.

So what are these medications? Well.
To back up a step, they either work on serotonin or CGRP.
And they can be used in states of either acute treatments when you have a headache and need to get rid of it, or they can be used as a prophylactic agent so they're varied.
In general, these medications are not FDA approved for anyone over 18.
So we have some children under 18, either on trial for these medications or.
They're through special exception through their insurance provider in my experience.
You'll hear more from Doctor Akbar at the 1st of December Grand Rounds.
They're highly effective, particularly in the older children.
Working to down regulate the most sensitive mediator of pain that CGRP and so.
And if one specific treatments they're not studied and they are scarce, there has been some studies, particularly if you have pain associated with plexiform neurofibromas, either surgical, electrical, surgical techniques.
There's more that we'll talk about Inib and other MEC inhibitors anti CGRP inhibitors.
Anti crmp 2. All of these medications are now in trial for NF1, but there is a paucity of data, so it falls back on the typical pain treatments we use either for headaches or.
For neuropathic pain, and then we've also even seen some very good response rates too.
Acceptance and commitment therapy.
Well, with I didn't present the data here, but also for relaxation based therapy in children.
And again you can see there that our goals are trying to have them take less over the counter medicine.
Use mindfulness techniques or diffusion techniques to adapt to their pain.
And so with that, I will turn it back over to Doctor Shah, but hopefully our six year old will get some good care Karen for their headaches.

Shah, Shafqat 33:09
Yes, actually I got a phone call from a 10 year old mom yesterday.
So I think that they'll be coming to see you fairly soon for the similar kind of evaluation. But as you stated, there is definitely a lot of anxiety and other issues that come into play in the pain experience here.
And so it is really a whole person approach in trying to deal with these chronic issues in this patient population.

So I thank you, Doctor Fox.
I know you came to us.
Just a few years ago in 2021, but I certainly have enjoyed.
Being able to share the bulk of the NF patients with you and certainly you know trying to deliver comprehensive care can only benefit these families.
So I appreciate your support.
I'm going to move on now to talk a little bit about another case for Doctor McCormick to discuss.
Doctor McCormick is, as many of you know, she's board certified orthopedic surgeon with fellowship training in children and musculoskeletal conditions.
She is very involved here on campus with healthcare policy and community engagement.
She's the assistant Dean in the Office for Academic Opportunity and Education and Educational Excellence, and she engaged.
Regularly with learners across the medical continuum to optimize their clinical impact and educational experiences.
And so Doctor McCormick might be called by me to see a child with NF1, for a variety of reasons. But many times it will be for back pain.
So here we have a situation where an 11 year old who has been seen regularly in ophthalmology neurology by by the genetic counselors.
Starts to have, you know, regular back pain, especially when she's sitting down in school for a long period of time and after a long car ride.
Her family. She's really complaining quite a bit.
The pediatrician does evaluate her and notices something abnormal with the spine exam and calls to expedite a referral to pediatric orthopedics. And so now we will go on to have Doctor McCormick discuss these orthopedic manifestations in NF.

McCormick, Sekinat K 35:15
Good morning.
Thank you for having me 'cause. I have to be part of this panel, so we're gonna mostly just talk about scoliosis and congenital pseudarthosis of the tibia. And very briefly, we'll mention the metabolic bone disorders, OK.
So spinal deformity in NF almost 50% of NF1 patients will present with spinal deformity.
The exact mechanism of developing spinal deformity is not explicitly known.

It's suspected to be due to osteomalacia.
Just weakening of the bone.
Intraspinal neurofibromas, we generally are going to find some pretty specific.
Vertebral findings, such as rib penciling, which is the narrowing of the ribs when we see multiple of those in a row, those can lead to some to some severe development of scoliosis. We also see vertebral scalopin, which is not explicit to neurofibromatosis.
But when we see posterior ver.
Scalopin, which is the red arrow pointing to the.
Back half of the vertebra, that is. That is pretty specific for norfar dermatosis, because you can actually have scalloping in other parts of the vertebra.
So if you're evaluating.
So if you're evaluating.
A X-ray and you see the posterior aspect.
You wanna be concerned for NF and the reason why that's important is because you wanna be able to start monitoring those patients early, some other.
Some other findings include Dural Ectasia, which is again just this stack that the kiddos develop at the end of the spinal cord.
Down there we see red wedging rotation.
Dysplasia of the pedicles.
All these things combined will go on to cause curvature development.
We can go to the next slide.
So in scoliosis that patients with neurofibromatosis develop we we have two types.
We have nondystrophic and what dystrophic we're going to mostly focus on the dystrophic the non dystrophic.
They really present more like typical AIS patients, but they can go on to develop dystrophic scoliosis. And it's important to recognize when a scoliosis is dystrophic because those are the curves that are going to go on to really progress.
Rapidly.
Dystrophic scoliosis is defined defined by having some of those previously stated vertebral anomaly findings.
We also we also see a lot of significant kyphosis in these patients and it's important for us to recognize this because we can end up having very, very fast progression of the spinal deformity. While most of the time scoliosis is not something that's going to cause.
Any significant morbidity in the short period? That's not the case with scoliosis,

scoliosis seen in NF.
These curves can become so severe that they can actually lead on lead to cause paralysis as the deformity enters the spinal canal.
So it's very important to to recognize them.
We will follow these patients on.
Thank you for going to the next slide.
We will follow these patients on a pretty routine basis when we find.
Ions, particularly ones who are complaining about back pain or other things.
Well, I we recommend getting an early MRI just to see if there's any intraspinal lesions that need to be followed or looked after, and the patient that with our current patient that we were talking about here, this 10 year old, she actually does have neurological findings that were.
There preoperatively and postoperatively. When we see rapid progression, we will repeat the MRI.
So when it's nondy strophic, we observe we brace.
We may fuse them a little bit earlier than we fuse typical AIS patients, but the most important thing that we follow is to see if they're going to go on to become dystrophic patients. Next slide.
So in the case of our kiddo who was presented to us, I think.
Maybe, maybe like two years ago. I'm not quite sure. You can see on the slides. I don't know how well they.
Project for you all. But if if you look at that bottom right, you can see a good example of a cafe Ole spot. If you look at the.
If you look sorry about that ringing, if you look at that middle photo at the very bottom, you can see the cafe Olay spots as well.
But also you can notice it's very easy to miss a scoliosis in this case if it's not explicitly described, go into the next slide please.
So here are her preoperative radiographs.
So on the left here you can see this pretty significant curvature.
Here are you all seeing my arrows as well, or is that not projecting? Probably not.
What you see here on the left, this left.
Thank you.
Thank you.
Thank you.
OK. What you look on the left side of the rib cage, you can see how those ribs are

super teeny tiny those ribs that are closer up to like rib 1234, super tiny and you can compare that to the ribs on the other side on.
The right side.
Which are more normal on appearance.
That's a great example of rib penciling, and you can see the significant deformity that she has morbidity for these patients is increased when they have what we call kyphosis, which to describe would be something sort of like a hunchback almost.
That pretends significant morbidity.
She thankfully did not have that, which made her surgery significantly more doable.
Next slide please.
So we took this patient to the operating room after a course of about one month in what we call haloggravity traction, which allows us to pull her spine out to length a little bit. Some of the good comparative things that you guys can you can see of the.
Change is really looking at the rib cage, even if you're not looking at what the overall Bony curvature is, we can look at the rib cage, but even in this setting.
Our need to follow her doesn't go away because we know that patients with dystrophic scoliosis.
And still go on to have curve progression as they grow?
So this is something that will continue to follow on her next slide.
Going to congenital pseudarthrosis of the tibia.
So we only see it in 5% of NF patients.
However, and all the patients who present with.
A tibial bowing of the tibia, 75% of them.
Are actually NF patients.
So while it's not super common in NF where we see it the most are in NF patients.
It presents as anterior lateral bowing of the tibia within the first year of life.
It's important to sort of remember the direction of the bowing for the orthopedist, because we have been we have Boeing that we see in the tibia.
That's completely benign and doesn't require much except for maybe like one or two follow-ups. However, when we see anterior lateral bowing of the tibia, that is, that is generally going to trigger us to have a patient worked up for.
Neurofibromatosis opposite to other thing.
Opposite to what's typically seen with thinning of cortices, we see thickening of cortices in this case and our our biggest goal in these patients when we see them is to avoid developing a fracture because once they develop a fracture, it's actually

significantly harder to take care of next.
Slide and this is just a quick example of the difficulty.
It is when we have interlateral bowing of the tibia.
It requires significant amount of bone grafting.
Operations, repeat operations and so when we see it in that first year of life, that is something that we're going to monitor very, very closely, treat and embrace.
Do what we must to try to avoid developing a fracture because once a fracture develops it, the path forward for those kids is is very difficult. Next slide.
Alright, thank you.

Shah, Shafqat 43:49

Thank you, Doctor McCormick. So as you can tell the orthopedic manifestations in these children can be significant and can really take years of management. And fortunately, many of them will continue to have chronic pain and will need that managed as well.
And physical therapy certainly has a role to play in managing these kids before and after surgery, so I appreciate those comments from Doctor McCormick, and we're not going to move on to the last case.
You know, in an older child, and this is actually a true to life story.
In my own experience, I have followed a young girl that had optic glioma at three years of age and she was diagnosed with NF1 at that time she had had caffeiole spots at birth, but that had not really been evaluated.
And so she did have progressive vision loss, and we did treat her with chemotherapy.
She did well for some time.
She did have some headaches that were managed periodically, but as she got older she really got very busy.
She is very active in dance teams at school with taking horseback riding lessons. She seems to be doing very well and had less regular follow up in our clinic.
Fortunately, we did have her come back before she went off to college and she was able to get a comprehensive evaluation in the clinic.
She gave actually a history that was a bit concerning of ****** discharge.
And initially, she really didn't want to discuss it very much.
She you know, I think she's just focused, really, in moving on, graduating high school, moving out of town for college.
But we were able to have her come back to have that evaluated further.

I you know, I did talk to some other specialists about her case and we felt that she should be.
Image as soon as possible and so ultrasounded mammograms were ordered.
However, it took again some time for the child or the young adult to come in.
You know, pretty typical for what?
Young adults do, and I think our radiologist teams on the breast side were very suspicious with the imaging and really, you know, pursued a biopsy very rapidly. And the first biopsy that was performed actually did not have a diagnosis of cancer, but they really were very suspicious and.
Another biopsy was performed and breast cancer was diagnosed and we were able to refer her to the Mays Cancer Center for treatment. And she's.
Very close to finishing her treatment. She's on oral medications at this point and has been having a regular follow up. She did get a bilateral mastectomies performed as part of her treatment and because of hernorfibromatosis radiation was not part of the plan as we worry about radiation Exp.
Closure inducing new tumors in this patient population.
So with this experience, I had Doctor Fisher, our current third year fellow presenter and tumor board, and I thought it was a good opportunity to share that information here. Doctor Fisher is.
As I stated, a third year fellow and she is also in the Masters of Clinical Investigation program here at UT Health. She completed her medical school with a military at university Uniform Services University School of Medicine and did her Pediatrics at the San Antonio Uniform Service.
Health Education Consortium and Dell Medical School. She has an interest in neuro Oncology and her basic research during fellowship is in new agents for use in sarcomas nerve sheath tumors in patients with neurofibromatosis type 1.
So I will.
Allow Julie to go ahead and unmute herself.
Complete her part of the presentation.

FM **Fischer, Julie M** 47:49
Thank you.
So in patients with NF1, they have loss of neurofibromin and this leads to uncontrolled cell proliferation and tumor growth in the nervous system. And this can result in cancer for these patients, most tumors in NF1 patients are benign. However,

some malignancies are seen at an incre.
Rate and it's important to be aware of these.
These patients are predisposed to specific malignancies to include optic nerve, gliomas, malignant, peripheral nerve sheath tumors, GI stromal tumors.
Cytoma, Rhabdomyosarcoma and leukemias, among others.
Additionally, females with NF1 are increased risk of breast cancer compared to the general population, and interestingly, they found that somatics or not germline mutations like we see in these patients but just somatic mutations in NF1, gene have been reported in 27.7% of.
All breast carcinomas and this is thought to be a potential driver in the development of breast cancer.
In in these patients.
So this is an article by Suarez, Kelly et all. It was published in 2019.
It's a meta analysis and systematic review of the literature reporting this increased breast cancer risk in NF1 patients.
So this review, it looked at 16 cohort studies of 211 patients in addition to 75 case reports. And so the figure shown here, it's a descriptive analysis of these combined 286 reported cases of NF1 and female breast cancer the.
NF1 patients are shown in red.
See your data, which serves as a control for the general population, is shown in blue.
So figure A is looking at the age diagnosis and it shows that there was a median age of 46 years, a time of breast cancer diagnosis in the NF1 females. And this is compared to 62 years in the general population and it shows that the.
Peak age of breast cancer diagnosis in the NF1 females was between 34 and 44 years, which is considerably lower than the general population.
When you look at figure B, so this is looking at the stage at diagnosis and it shows that NF1 women younger than fifty were found to have more advanced disease at the time of diagnosis.
Of their breast cancer and compared to those 50 years of or older, and then looking at Figure C.
So this is showing the age of death among female breast cancer patients and it shows that the median survival for all cases of NF1 women with breast cancer was five years. And this is compared to the reported median breast cancer survival of over 20 years in the.
General population looking at the SERE database.

And additionally, the median age at time of breast cancer death was found to be 48.5 years in this group of NF1 breast cancer.
Compared to 68 years in the general population, so overall looking at this figure, we can conclude NF1 patients tend to get breast cancer younger, they have more aggressive.
Stages at diagnosis and they die younger due to their breast cancer compared to other patients.
So this figure just shows the Kaplan Meier curves looking at relative breast cancer survival.
So these curves estimate survival probabilities for the all the collected NF1 cases in red compared to the SERE data in blue.
So the general population control.
You can see in the top left panel it shows 76 females with NF1 at all ages.
The bottom left panel represents 29NF1 females page ages 15 and older.
On the right represents 43 female NF1 patients aged 50 years of age, less than 50 years of age, and so overall looking at these curves you can see patients with breast cancer that have NF1 have a significantly reduced survival compared to the control and it.
Even more noticeable in those younger patients under age 50.
So looking at this data overall, we can conclude that there's a high incidence of breast cancer and NF1 women younger than 50 years of age and these patients tend to present, as I mentioned, with more advanced disease and possibly experienced an increased breast cancer related mortality and.
Additionally, we can conclude that women with NF1 have a three fold increased risk of developing breast cancer compared to the general population and A5 fold increase risk of breast cancer.
In patients less than 50 years old compared to.
The general population, and additionally women over 50. They also do have a smaller but still increase risk of breast cancer.
One thing that's important to know about this study is.
The SERE database.
So it's looking just at the United States, whereas all of these other studies were conducted all over the world.
So it might not be a complete perfect comparison.
So just something to note, but it does give us good data to know to look at.

So this abbreviation stands for the European Reference Network on genetic tumor risk syndromes, and this is a comparative literature review published in 2023, which details guidelines developed by NF1, expert groups and patient representatives for how to appropriately perform surveillance on these patients to look for.
Tumor risk.
So this is an overview of the screening guidelines.
I won't go over all of the guidelines.
They're very long, but I'm just going to cover a few of the ones that relate to malignant neoplasms for these patients.
So on the right second to far right column, you can see the strengths of the recommendations and these are listed as strong, moderate or weak.
Strong recommendations refer to those that have expert consensus and consistent evidence.
Moderate refers to expert consensus with inconsistent evidence and or new evidence likely to support.
Of the recommendation, whereas week refers to export expert majority decision without consistent evidence. So for example you can see some of the strong recommendations include optic pathway, glioma surveillance at least annually with visual screening including visual assessment and fundoscopy from ages 0 to 8.
So this is the importance of our referral to Doctor Cebu Orbital and Periorbital Plexiform neurofibroma surveillance with clinical assessment.
Refraction error visual fields ocular motility at every.
Visit at all ages and then malignant peripheral nerve sheath tumor and atypical neurofibromatous neoposm surveillance with exam and history taking at every visit, among other recommendations listed here.
So additionally, there's a moderate strength recommendation to screen for breast cancer with an annual MRI or mammography if Mri's not available.
I'm starting at age 30 for these patients and then at 50, transitioning to the routine screening recommendations. And there's also moderate recommendations for blood pressure screening as a possible indicator for feochromocytoma and paragangliomas. In addition to surveillance for gastrointestinal stromal tumors with clinical exam and history starting in.
Adolescence.
Obtaining an abdominal MRI or CT of clinical suspicion arise arises.
So to go into a little more detail regarding Optic pathway glioma.

So these patients should have a baseline ophthalmology assessment at the initial clinical presentation. As we mentioned previously, in addition to age appropriate visual screenings. Additionally, the screening should be done by a trained pediatric or neuro ophthalmologist and it should include age appropriate assessments of visual acuity visual field.
Pupillary screening, eye movements and optic disc appearances.
Doctor Cebu discussed.
In addition, if the exam is subjective.
Pathway glioma, or if the provider's unable to perform a reliable exam in a patient over the age of two, the suggestion is to do screening with MRI if the patient is found to have a symptomatic optic pathway glioma, they should of course be urgently referred to a.
Center that has expertise in this area.

Shah, Shafqat 56:12
Thank you, Julie, for that presentation. I think fortunately those guidelines were published not too long ago and so we have been able to incorporate them and it's nice that sometimes as we're trying to take care of these patients, we're trying to get assessments, frequently Mris and insurance compan.
Often times don't understand why we're we're doing these things. And so having us something in the literature to justify our management is helpful.
But I think the big point that I wanted to make today and for the rest of.
Talk is really to emphasize the comprehensive care that these patients require. You know, from the beginning with making a diagnosis with the help of genetic counselors, and then with multiple medical specialists trying to assess all their developmental issues, neurological concerns, eye findings, and then from the psychosocial PERS.
You know, trying to help them in school and providing guidance as they age and become adults and how to make sure that they don't fall out of healthcare, which tends to happen with our young adults.
So as you can see, many many providers beginning from the general pediatrician, hopefully who can help initiate some of the consultations. I think that one of the patients I saw yesterday, she has nine consultations this year for a variety of different conditions.
So it is a lot of work from the pediatric perspective as well, but I think it's very

important that again this comprehensive approach is taken so that if things are developing.
You know, symptoms are addressed, inappropriate fashion.
And I definitely rely on people in all the different departments. Neurosurgery, dermatology, plastic surgery, pain medicine, and psychologists and genetic counselors in order to deliver much of this care.
And so I just wanted to emphasize that our program here has been up and running for about 5 years now.
And we can be reached by easily, by e-mail or on the PT mock phone.
And if there is a child with a potential neurocutaneous disorder, doctor Fox.
Certainly. What would like to be consulted soon, and if it's a young child where there is a possibility of NF, best thing to do is get doctor Saboo an e-mail or message on on the EMR.
And she's very good at getting these patients worked in.
And I just would like to thank everybody who helps take care of these patients.
You know, it's certainly more than one person job and you know, I think the families are getting the message that there are some local resources and they're not having to go.
Out of town, as much in order to see some of the specialists to take care.
I'm still working on trying to identify adult providers for many of these patients that are 18 or older.
That is a significant challenge as adult neurologists are so busy with a variety of other conditions.
So we're that's definitely a work in progress and I certainly welcome any discussion or emails.
About any patients, so we can help expedite their evaluation and I believe that's our last slide. If are there are any questions in the chat?
Doctor Kamat, I would like to make.

Kamat, Deepak M 59:24
Doctor Shah. Doctor McCormick. Doctor Fisher, Doctor Fox and doctor.
Presentation and educating us on how to manage patients with. NF1.
There are two questions in the chat bug.
One is from Doctor Gross.

Excellent presentation. Many of these patients have no serious complications.
How do you approach this with families?

Shah, Shafqat 59:46

So that is a very good question.
I think you know, they may not have any complications as children, but one of the reasons why they should still be seen regularly is that, you know, they may have some issues that come up later in childhood or as adolescence, or they may have family members that are.
Undiagnosed and so we certainly like them to meet with a genetic counselors as they get older and they can take some ownership.
You know of of their condition and understand the impact if they have their own children. What the risk of passing the N F1 gene is.
So there's quite a bit of.
You know, issues that can develop, you know, as I age out of the pediatric population and we'd like to continue to educate them and the families.

Kamat, Deepak M 1:00:30

The question from Doctor Perlman, our nfn patients especially susceptible to radiation.
Should we try to avoid cities in favor of other imaging modalities?

Shah, Shafqat 1:00:41

Yes. So that is actually a question that I'm having right now with Doctor Fox and a little boy who is having some headaches and it seems that his headaches are fairly acute.
So I think getting a head CT is probably the quickest thing that we're going to be able to do for him.
He does have autism and may not be able to sit still with an MRI. So I think in the acute setting, if you need to get a head CTI think that's fine, but.
Our choice would be MRI and you will definitely get much more detail.
From an MRI than you will with act, but you know to rule out hydrocephalus, for example, a head CT will be adequate.
You know, head trauma.
You know, if you have some other reason and you need to get a very quick expedited

study in the ER, our plan would be the recommendations really for planning regular screenings or a patient with a glioma that you're monitoring.
You know, the recommendation would be the MRI and not just CT.
And there is a consider.

Kamat, Deepak M 1:01:40
Thank you Doctor Lopez.
Doctor Lopez is asking is there a specific epic order for referral to your clinic?

Shah, Shafqat 1:01:48
That is an excellent question we have asked about that at this point for all our hemog specialist, there is really just one order and then the screening happens at the level of the lead physician in the clinic who does the the screening. And so if you put in.
The consult patient with NF1, then that will come to my inbox or Doctor Tomlinson's inbox.
But there is just one epic order for pediatric hemod.

Kamat, Deepak M 1:02:15
Any other questions, comments for our special?
Ists.

Shah, Shafqat 1:02:23
Thank you for your attention.

Kamat, Deepak M 1:02:25
Thank you all.
I'm gonna conclude then this morning's grand round.
Thank you all for attending.
Thank you panelists for wonderful discussion.
Wish you all a very happy Friday and happy weekend. Thank you.

McCormick, Sekinat K 1:02:37
Thanks for having us.

Kamat, Deepak M stopped transcription