ANNETTE GREFE: For most of us, we at some point get sort of used to the idea, for better or worse, that older people might have strokes. At least people older than you or I.

But for a teenager to suffer a stroke or maybe even a toddler, that's a whole different ball game. But as a pediatric neurologist, I do see this happen quite a bit. Really, way too much.

And it's different. It's different in children. Little folks have different strokes. Ah, OK. All right.

So I'm going to talk about the impact of stroke in childhood. I'm going to talk about some of the major challenges that we have, namely, delays in recognition. I'm going to talk about why those delays happen. I'm going to spend a little extra time on the question, why do children have strokes in the first place? And then I will address some of the treatment options and controversies.

So as you might imagine, stroke in children is pretty rare. The incidence is about two to three per 100,000. But if you think about that, that's about five children per year in a city the size of Winston-Salem. So not insignificant. And there are some indications that that incidence may be increasing.

Most children survive a stroke, but there is about a 5% mortality. In fact, it's one of the 10 leading causes of death in children. And the recurrence risk is pretty high. So for somebody who's had a first-time stroke as a child, there's about a 19% risk of recurrence within the first five years.

Of those children who do survive, about 68% to 85% have long-term disability. They may have speech problems. They may have a mild or a severe hemiparesis. And in addition, they often have seizures, learning, and behavior problems.

Now think about it. If somebody who's 95 years old and has a stroke, they may live with that stroke for another three or four years. Children who have a stroke will live with a disability for maybe 70 or 80 more years. So there's tremendous amount of social impact as well as financial impact.

To illustrate that, a study at Kaiser Permanente by Gardner and others calculated the cost of stroke in about 266 children compared to controls. And they figured out, in 2003 dollars, that the adjusted five-year cost for a single child with stroke was about $135,000. That does not include lost productivity by the parents who are probably having to take care of that child.

So stroke in childhood is a pretty serious issue. But unfortunately, most children often don't get recognized early enough that they're having a stroke. In 2002, a study here by Gabis and others determined that the median time to an initial medical review was about 28 hours. I apologize for the mistake. It's actually 35.5 hours is the time to MRI. So 28 hours to see a doctor, 34 hours to get an MRI.

A similar study about six years later in the UK, where they analyzed 50 children with stroke or TIA, showed that in about 2/3 of kids it took more than a day to see a neurologist. In almost a third, it took more than 24 hours to get a clinical diagnosis of stroke. And in almost all of them, it took more than 24 hours to get an MRI.

A study in Australia looking at 88 children, they did a little better. But the median time to diagnosis was still about 25 hours. A little more for outpatients, a little less for inpatients. In this study, 75% of kids did see a physician within three hours. But it still took about 4 and 1/2 hours to get to any kind of imaging, and that includes CT. The study didn't specify whether it was looking at CT scan or MRI. So that certainly would not get the child within the time frame for any kind of tPA.

Often the priority just is not very high. In that same institution in Australia, they looked at children who had a, quote, "brain attack." And they defined that pretty loosely as some kind of sudden onset of neurologic dysfunction. They found that, of those kids, only about 35% were transported by ambulance. The rest were brought in by their parents, by private vehicle. Only 25% were given a pretty high triage score.

Most were seen pretty quickly, within about 22 minutes. But again, the time to neuroimaging was about 4 and 1/2 hours.

So why do these delays happen? Well, a big part of it is just a low index of suspicion, especially by the parents. I mean, which parents expect their seven-year-old to have a stroke? Not very many. Also, small children might have a very hard time telling you about their symptoms, especially numbness or vision loss. And even medical providers often are not particularly aware of children having the possibility of having a stroke.

In addition, children often have different and sometimes more subtle presentations. Well, seizures aren't exactly subtle, but it's not typically what you think about for a stroke. But children often present with seizures as a first sign of a stroke.

Often the strokes are stuttering or fluctuating more so than in adults. A lot of times they have headaches, or maybe they have neck, shoulder, or occipital pain, even if there's no hemorrhage. But, for example, with a dissection, which may overshadow the neurologic symptoms.

Or they may have spells triggered by hyperventilation, as in one particular kind of stroke, which I'll talk about. And so it might be mistaken for a panic attack.

They also have different risk factors. We basically don't see atherosclerosis in children. We do see some hypertension and hyperlipidemia, but that's really quite rare. Of course, many teenagers smoke, and there's plenty of diabetes. But those are generally not present long enough to cause any severe arteriopathy in childhood or adolescence.

So if you don't have hypertension, high cholesterol, smoking, or diabetes, you shouldn't have a stroke, right? Well, that's wrong, because children do have a lot of different other kinds of and often age-dependent risk factors.

Also, there's a wider differential. A lot of mimics, a lot of mimics in children that can fool you into suspecting and thinking about a stroke but thinking that, oh, it's got to be something else.

In that same study in Australia, Mackay and others looked at close to 300 patients with some kind of brain attack, again, that was sort of a sudden onset of neurologic dysfunction. And they found that 28% had hemiplegic migraine, 15% had either seizure or Todd's paralysis or combination, 10% had Bell's palsy, and only 7% had stroke.

Now in adults, if they presented with sudden symptoms of neurologic dysfunction, probably 73% or so would be found to have had a stroke. Conversion disorder was 6%. But still, so it's pretty rare. But that means that basically for every four children with a hemiplegic migraine, of which we see a ton, one will have a stroke. For every four children with hemiplegic migraine, there's a fifth one who will have a stroke.

We also have trouble getting imaging, the right kind of imaging, quickly. As you know, CAT scan is relatively insensitive to early changes of ischemia. And we don't like to get CT scans, and especially CTA, in children, especially young children because of the high radiation dose, especially to get a good picture. There's pretty good evidence that this can cause subsequent cancers. So we try to avoid those.

But because of all those mimics, we do need to get some kind of confirmation. And that's why we need the MRI. Now the trouble is that most children under age 10 are not going to lie still for the 20 to 45 minutes that it's going to take to get a decent MRI. Especially when they're already panicked because they can't talk or they can't move a limb that they're used to being able to move. So those kids are going to need sedation. And trying to get a sedated MRI, especially at night, urgently or at a Friday afternoon, is not a piece of cake, even at our institution.

And then on top of that, there's kind of a perception sometimes that really doesn't matter how quickly we assess these kids, because we can't give them thrombolysis anyway, right? Well, I'll address that in a little bit.

But now I'm going to focus on why children do have strokes. The International Pediatric Stroke Study registry groups the etiologies for childhood stroke into these major causes. Cardioembolic; arteriopathies, which include dissection, Moyamoya, and other arteriopathies; sickle cell disease; thrombophilia; and others.

So I'm going to give you a few examples. So here was a 10-month-old boy who wakes up from a nap. He's a little fussy. And as he sits up, his grandmother notices that he's leaning to the left. And he's not using his left arm. And maybe he's not using that left leg quite as much either.

So she takes him to the Brenner ED from Walnut Cove in her private vehicle. When he gets there, the resident finds the child pretty alert and playful, but he has decreased tone on the left side, about 3 out of 5 weakness in his left arm.

Now he has a very significant previous medical history in that he was born with coarctation of the aorta and a double-outlet right ventricle. About a month ago, he had a repair of that coarctation and had a Glenn shunt placed. He had no immediate complications and was placed on aspirin prophylaxis.

Nonetheless, this is what his MRI showed. So big old right MCA stroke. The MRA was normal. But when we took another look at his heart, we found a small thrombus near the pulmonic valve. So cardioembolic stroke is one of the most common, it's probably the most common, cause of stroke in childhood. Usually due to some kind of structural cardiac defect, especially complex congenital heart disease. Especially with the right to left shunting.

Valve disease. Sometimes cardiomyopathies, especially acquired viral cardiomyopathies. Arrhythmias. Cardiac surgery. Catheterization also a big risk factor. And ECMO is a huge risk factor.

Another category is dissection, dissection of the internal carotid or vertebral arteries. That's a fairly common cause for stroke with trauma, especially any kind of neck trauma. Head and neck manipulation, which is one reason we don't like children to have chiropractic manipulation of the neck. Kids who have any kind of connective tissue disease, such as Marfan's or Ehlers-Dahnlos, are particularly vulnerable to this. And then a fairly high percentage are idiopathic.

So here's another case. This was an eight-year-old boy with prior history of headaches who has very sudden onset of right facial and arm numbness. He also had a little trouble answering questions and seemed a little confused. He was seen by his pediatrician, who noted a right facial droop. So she very astutely sent the child to the Brenner ED.

He got there within about two hours of onset of the symptoms. And by that time he was actually back to normal. He'd had bad headaches in the past, some of them with nausea and vomiting, but didn't really complain of a headache this time. He did say that his head was feeling better. We weren't quite sure what that meant. And there is a history of migraines in the mother.

So we sent him home with a presumptive diagnosis of complicated migraine but planned to have an outpatient MRI and MRA done. So that was done two days later. And this is what we found on the MRI.

So some little ditzels of white matter changes. We see those quite a bit, so in and of themselves, they didn't really worry us so much, although there were maybe a few more than we usually would expect. Here's a few more on the posterior regions.

But what we did see were some changes on the MRA in the area of the internal carotid artery distally. There were some motion artifacts. We were hoping that that was basically just all it was. But to be sure, we got a catheter angiogram. And this is what we found.

I hope you can see the narrowing and the distal ICA there on both sides. So this kid had Moyamoya. And he was found to have a genetic mutation that predisposes to Moyamoya, or is associated with it. He is now on aspirin and has undergone a pial synangiosis to bypass the stenosis and help supply collateral blood supply.

Nonetheless, he keeps having daily TIAs, especially with hyperventilation, which is a common trigger. He's kind of an anxious kid, so he tends to hyperventilate. And he's had several additional infarcts, as you can see here.

Moyamoya is a pretty significant cause of stroke in childhood. As you probably know, it's a progressive stenosis of the ICA, proximal MCA, and ACA. Usually it's associated with formation of extensive collaterals, small collaterals. And when they do an angiogram, you will see all those collaterals forming kind of the picture of a cloud of smoke. Moyamoya is the Japanese term for cloud of smoke.

We call it Moyamoya syndrome if it's secondary to entities such as sickle cell disease, neurofibromatosis, trisomy 21, or cranial radiation. We call it Moyamoya disease if it's primary, as in this child, and also common in the Japanese population.

OK, next case. So this was a previously healthy 13-year-old. Mom heard a noise from the kitchen and finds him lying on the floor. He's talking incoherently with slurred speech, is agitated, not moving his left side. In the emergency room he's sleepy but arousable. Has normal language but is very dysarthric.

He has a left lower facial droop and, again, about 3 out of 5 weakness on the left in the upper and lower extremities. And an upgoing toe on the left.

You don't really need the arrow sign here to see that big stroke in the pons. We did an MRI. And that's a little bit more subtle, so I hope you can see that little stenosis right in the middle of the basilar artery right there. We saw it high and low but could not find a specific cause for the stenosis.

So this is an example of a focal arteriopathy. Again, about 20% of kids have that as the cause for their stroke. Most often it's in some way post-infectious or inflammatory. Chicken pox is particularly well known for this. But it could be any other virus, especially enterovirus. Could be Lyme disease as the inciting factor, or Bartonella. A lot of times, again, it's idiopathic.

It's usually transient, resolving after three to six months. But a small percentage, about 6%, progress to Moyamoya.

OK, my final case. Here's a five-year-old boy who develops a headache in the evening and eventually cries himself to sleep. He wakes up several hours later, again, complains of headache. The father takes him to the bathroom and notes that he's kind of limping with the left leg. So he takes him to the emergency room.

There the child is pretty sleepy, uncooperative, so we don't get a good exam. But we notice that he definitely is moving his right side much better than the left. His history is significant for sickle cell disease. And for that reason, the emergency room checks his fraction of hemoglobin, sickle cell hemoglobin, and they find that it's pretty high, 71%. It's recommended that it be kept under 50%, but the father had refused transfusion.

So this is what we found with him. On the left side, kind of posterior, MCA stroke and also changes in the corpus callosum. And you might notice a few small ones over on the right anterior region. And then a higher cut. Pretty large stroke in the anterior area in the ACA distribution.

So sickle cell disease is another big bad actor. It used to be even worse. And in the past, the incidence of stroke was about 280 to 285 per 100,000. With the STOP trial that you may have heard of, which was done in the '90s, we found that most strokes in children with sickle cell can be prevented by chronic transfusions.

What we do is we screen these kids with transcranial Dopplers on a yearly basis. And if they have high velocities that suggest stenosis, then they get put on a chronic transfusions program. But again, this father had refused the transfusions.

Thrombophilia is the other big group and that's the individual entities are similar to what we see in adults. Interestingly, we find some kind of coagulopathy in somewhere between 30% and 50% of pediatric stroke patients. But it's often in combination with other risk factors. It's not usually the sole cause.

We might find deficiency of protein C, protein S, antithrombin, genetic abnormalities in Factor V of Leiden, prothrombin gene, or MTHFT. And lipoprotein A deficiency as well as the lupus anticoagulant or antiphospholipid antibody.

Other causes include sympathomimetic drugs, especially taking an overdose such as stimulants or decongestants or other kinds of substance abuse, cocaine, et cetera. Very rarely, we do see some genetic or metabolic disorders that can predispose to stroke, such as Fabry disease, which we see in young adults as well that's X linked and distinguished by a particular kind of rash that you usually see in the groin or around the hips.

Menke's disease is not easily missed. Those are kids who are profoundly delayed and have very odd, fragile, brittle kind of kinky hairs, we call it. It's a copper transport disease that predisposes to strokes. As well as homocystinuria. These are kids or adults with kind of a Marfan phenotype who tend to have high levels of homocysteine.

In addition, other problems, systemic problems, can cause strokes, especially coagulation problems. Severe iron deficiency; thrombocytosis; polycythemia; and other kinds of systemic diseases, especially cancer, of course, can give you coagulation problems in a child.

Because there's such an extensive differential, such a wide variety of causes, our workup tends to be quite extensive. It's not just carotid Dopplers and an echo. We usually start with an MRA and make sure to include the neck and the aortic arch. We do carotid Dopplers if we suspect a dissection. And if it looks suspicious for that, we'll usually go on to catheter angiogram if we suspect that, or a vasculitis.

We'll do a cardiac echo with bubble study. And then, if we don't find anything there, we'll do extensive lab work for the functional and genetic thrombophilia disorders that I mentioned. We'll generally take an iron profile, look at inflammatory markers, including the van Willebrand antigen for vasculitis. And we may do an LP, looking for any infectious etiologies, especially the focal arteriopathies, opening pressures, cell count protein cultures, et cetera.

So now let me talk a little bit about treatment options and controversies. The trouble with acute treatment is that we really don't know that much. Most of the treatment recommendations have been extrapolated from adult studies. Over the past decade, several groups have gotten together to try to come up with recommendations, including the Royal College of Physicians, the American Heart Association, and the American College of Chest Physicians.

Unfortunately, they differ in a few very specific details and important details. And when you look at it, again, because a lot of this is just extrapolated from adult studies, for example, the AHA document of 93 recommendations, only two actually are based on level A evidence. The rest are level B or C.

There is consensus, to some extent, for anticoagulation. There's consensus that it is indicated for cardioembolic disease and dissection, at least at this point, despite recent data that in adults that aspirin might be just as good. The guidelines differ as to whether we should start anticoagulation until cardioembolic disease and dissection have been ruled out or wait.

The chest physicians say yes. The Royal College says no. And the American Heart Association is basically on the fence.

Now what about tPA? So current guidelines recommend not using tPA in children outside of a clinical trial. That did not have consensus regarding older adolescents, and that kind of makes sense.

Why would you give tPA to an 18-year-old but not to a 17-year-old who meets all the criteria except for age? So it's a tough one. But on the other hand, you do want to have good clinical and scientific data. And for that you need a randomized controlled trial.

That's why my friend Cate Amlie in Seattle actually managed to get together a study that was funded, the TIPS trial, Thrombolysis in Pediatric Stroke. That was a 17-center phase I trial funded in 2010. A lot of groundwork went into preparing that trial. Unfortunately, that was halted this year due to low enrollment. And part of that, as I kind of mentioned earlier, is that kids just don't get to diagnosis on time.

In practice, quite a few children have received thrombolysis. There's an article just hot off the press, just published in the *Journal of Pediatric Neurology* this month by Nasr where they reviewed a national database of something like 7,000 children who had had arterial ischemic stroke over the past 12 years or so.

99% of those children received tPA, so that's about-- I said 14%. That's 0.14%, I apologize. I'm sorry, 1.4%. 1.4%.

They found that, of those who did not get tPA, there was a death rate of 4.7%. Those children who did get thrombolysis did have a higher rate of intracranial hemorrhage, but none with fatalities. Interestingly, there was also a higher rate of discharge to short- and long-term care facilities.

The reasons for this are unclear, but the authors speculate that possibly it's because only children with pretty large strokes would even be considered for getting tPA. Now in contrast to the controls, where there was a 4.7 death rate, there were no deaths from stroke in tPA patients. So definitely, it looks like tPA can save lives in children. But it's definitely not ready for prime time.

So what else can we do? Well, as you heard probably previously, we definitely can help by trying to protect the penumbra, the brain tissue surrounding the core of the stroke, and try to avoid malignant edema. And this is pretty much the same thing as we do with adults. And it should be done in a carefully monitored setting such as a pediatric ICU or intermediate care unit. We need to avoid fever, hypoxia, hypo- and hyperglycemia, treat seizures aggressively, and avoid hypotension and excessive hypertension.

Now in kids, normal blood pressure ranges vary quite a bit as they grow older. And so you can't just establish one number that you need to stay with. A good rule of thumb would be to keep the systolic to about 15% above 95th percentile for a sustained period of time. And you can maybe allow it to go 20% above the 95th percentile for just brief periods.

As far as surgical options, we definitely will think about decompressive craniectomy for any child in those first critical 48 to 72 hours who develop severe edema and show signs of herniating, especially with a big, unilateral MCA stroke. There really aren't any data on other interventional procedures, just a few case reports.

If you suspect vasculitis or some kind of transient focal arteriopathy that might be inflammatory in nature, we would consider steroids, usually a short course of IV steroids. And of course, we need to have early access to physical, occupational, and speech therapy.

Back to those delays. How can we minimize that? Well, as I said, the TIPS trial was halted. But there was a lot of preparation going on to get ready for this trial, to make sure that the 17 centers that were selected were ready to actually give the tPA. When they looked at this initially, they found that there was a lot of variation in readiness. So before hospitals were declared ready to give tPA, the organizers of the study did a lot of work to get them to that point.

And they established certain criteria for readiness. And this may sound familiar for those of you who are familiar with adult stroke centers. There should be a pediatric stroke team available 24/7. There should be a strict orders set for the emergency room as well as the PICU. And sedated MRI should be available 24/7.

Not all the centers have met all of those criteria. But we think that having these criteria should lead to formation of both primary and very comprehensive pediatric stroke centers. And it's our expectation that this will lead to significant improvement in outcomes, as it did for adults.

Here at Wake Forest, we haven't quite met all of those criteria, but we're in the process of working on that. We have a new faculty member join us in January, Dr. Farooq. He has a particular interest in pediatric stroke. And so my first priority for him when he gets here is to help us establish such a pediatric stroke center here at Brenner.

So in conclusion, I want to remind you that strokes in children are rare but debilitating. Currently, there are long delays to definite diagnosis and treatment. In part, this is due to many stroke mimics and the very different and varied etiologies.

Nonetheless, urgent treatment is critical. If you're going to live with a stroke for 70 or 80 years, even a 5% or 10% improvement makes a huge difference. But it all starts with awareness, awareness that kids have stroke too.

We need to educate the parents, especially parents of children with heart disease or sickle cell. And we all need to keep stroke in mind, even in the youngest patients. So if you see a child that you suspect might have a stroke, call 911 or call our PAL line at 1-800-277-7654. Thank you.