

## PedsCases Podcast Scripts

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### **Pediatric Strokes**

Hi everyone! My name is Miriam Maes, I'm a Queen's Medical student just starting out my 4<sup>th</sup> and last year – jeez, time has flown by! In today's episode of Pedscases we're going to chat about pediatric strokes. I've been given lots of help and insight from Kingston's own pediatric neurologist, Dr. Morrison-Levy. If you're listening, thank you for all your guidance, Dr. Morrison-Levy!

I'll warn you that today's episode is quite dense, but I'm going to try to make it as simple as possible. First, let's talk about our learning objectives:

1. Define different categories of pediatric stroke
2. Discuss the presentation of strokes in pediatrics
3. Identify risk factors for strokes in pediatrics
4. Develop an approach to management of pediatric strokes
5. Discuss outcomes of pediatric strokes

To start off today's episode, I'm going to run through some definitions pertaining to stroke.

### **Stroke Definition and Classification**

In the pediatric world, stroke is separated into two age groups: perinatal strokes and childhood strokes. Perinatal strokes occur between 20 weeks gestation and 28 days of life, while childhood strokes occur any time after this up to age 18. The main reason these categories are used is because their mechanisms and presentation are typically quite different, so it's clinically pertinent to separate these in your mind. I'm going to dive deeper into perinatal strokes towards the end of this episode, so just hang tight.

Before we get any further, let's talk about the basics... as many of you know, strokes are neurological injuries and they're caused by either an occlusion of a blood vessel, leading to an *ischemic* stroke, or a rupture of a vessel causing a *hemorrhagic* stroke.

### **Ischemic Strokes**

Ischemic strokes often cause focal damage in the territory of a blood vessel, because all the tissue downstream of the occlusion is damaged. In adults, this is a major cause of stroke, causing up to 80% of adult strokes. In the pediatric world it causes only 55% - the first of many differences between the two groups that we'll remark on in today's episode. Broadly, ischemic strokes can be caused by issues in venous flow or arterial flow (in other words, arterial ischemic stroke, AIS).

Let's start with the first category of ischemic strokes - arterial issues. Arterial issues can either be localized (occurring in situ) or thromboembolisms. Localized issues either form within the brain's vasculature, due to things like vasculopathies, hypercoagulable states, or inflammation.

Thromboembolism occurs when a clot forms elsewhere and travels into the brain's vasculature. Keep in mind that a venous clot can travel through venous-arterial shunts and cause arterial ischemia, but clots can also originate in the heart or dissected arteries. And that's arterial strokes.

The second category of ischemic strokes are issues in the venous system, typically it's an issue with drainage. A common cause of pediatric stroke that falls into this category are CSVTs: cerebral sinovenous thrombosis, the obstruction of a major venous sinus by a clot. These can cause ischemic strokes due to the lack of blood flow, but CSVT can also result in rupture of the vessel and subsequently a hemorrhagic stroke.

### Hemorrhagic Strokes

That brings us to our other major category of stroke - hemorrhagic strokes. This category includes intraparenchymal bleeding as well as subarachnoid hemorrhages, which can be traumatic or spontaneous. As I mentioned earlier, one cause of hemorrhagic stroke is CSVT, which can also be caused by a multitude of things including trauma and ruptured vascular malformations.

So, to quickly summarize: strokes can be ischemic or hemorrhagic. If they're ischemic they can be further classified into arterial and venous. Arterial strokes can be localized, also called in situ, or from a thromboembolism. Venous strokes are typically a problem with drainage, including CSVT.

### **Prevalence**

Now that we have the terminology down – how common are pediatric strokes, and when are you most likely to see them?

Perinatal strokes are the most common, occurring between 1 in 1600 and 1 in 4000 births. Childhood strokes are much less common, effecting somewhere around 1 in 10,000 per year. There are many risk factors for pediatric strokes that we'll really dig into later, but keep in mind that children with Trisomy 21, Down Syndrome, as well as Sickle Cell Disease make up a large proportion of childhood strokes.

### **Presentation**

With that being said – how does a stroke in pediatrics present?

Classically, stroke will present with sudden-onset focal neurological deficits. Hemiplegia is actually *more* common in children than adults with stroke, occurring in about 85% of children. The presentation differs slightly, however, depending on the type of stroke – hemorrhagic or ischemic – as well as the area involved. Generally, ischemic strokes are more likely to present with hemiparesis or focal neurological deficits, while hemorrhagic strokes more often present as a change in mental status or a headache. Hemorrhagic strokes can also cause focal brain damage, typically due to mass effect and ischemia of adjacent tissues. Children often will have generalized signs and/or symptoms such as seizures or changes in mental status that are more difficult to localize to one vascular territory.

In perinatal strokes, respiratory distress, lethargy, hypotonia, focal seizures, and signs of encephalopathy are presentations you should be attuned to. Children this age obviously can't verbalize how they're feeling, so any signs of an acute change of mental status or deterioration should bring stroke onto the differential. This is similar in toddlers, where you may see a deterioration in their overall condition – lethargy, crying, irritability, difficulty feeding, and vomiting. For older children, they may be able to better describe their symptoms, or they may be more noticeable as they move and speak more effectively.

## Risk Factors

Okay, so now that we've discussed the classification of strokes and what they look like, let's chat about when stroke should be highest on your differential – as we go through these risk factors, I'll mention some relevant treatment options to some cases, but I'll be covering treatment in more detail later on.

Risk factors for stroke in our pediatric population are very different than in adults, who are more likely to have strokes caused by hypertension, diabetes, and atherosclerosis. Additionally, TIAs are more commonly missed in pediatrics as young patients may not be able to communicate symptoms of TIAs in the same way adults can. Because 13% of those with TIAs will go on to have a stroke, we are also more likely to miss an opportunity for prevention. So, let's get into risk factors that are important in pediatrics.

The first risk factor is sickle cell disease (SCD), it's one of the most common risk factors for pediatric stroke and in patients with SCD stroke should *always* be on your differential. SCD, as a very brief overview, has the S form of hemoglobin which causes polymerization and ultimately leads to the characteristic sickle shaped red blood cells. This in turn causes vaso-occlusion as the sickle shaped blood cells struggle to fit through the arterial and capillary beds, which you can predict causes an ischemic injury. Sickled cells also hemolyze and become sequester in the spleen, which causes anemia and decreased oxygen carrying capacity, which, again, contributes to ischemia. And finally, chronic inflammation and vascular damage which is common in sickle cell disease can also affect blood flow and make an ischemic stroke more likely.

How much more likely? 11% of patients with sickle cell disease will have an ischemic stroke by age 20, and of those who have a stroke the recurrence risk is 70%.

The good news is that there is screening we can offer these patients to reduce the likelihood of stroke. Patients with SCD should be offered annual screening with a transcranial doppler ultrasound from age 2 until 16 to assess for narrowed arteries. Positive ultrasounds can be treated with transfusions to decrease the risk of stroke to less than 1%, and a stem cell transplant can be considered as a curative treatment.

Moving onto our next risk factor: moyamoya disease, which is more common in patients with Down syndrome, SCD, neurofibromatosis, and patients who have previously had head and neck irradiation. Patients with moyamoya will experience progressive stenosis in the major arteries of their brain. Strokes in these patients are related to hyperventilation or dehydration. For these patients, treatment involves revascularization surgeries using their external carotid arteries.

Arterial dissection is another cause of stroke in patients – and can happen in healthy children. On history, you may hear about a recent injury, or any other sudden twisting of the neck like in chiropractic manipulation – it may be recent or occurring a couple weeks previously. Less commonly, it can occur spontaneously, especially in those with connective tissue disorders. In these cases, involving your local vascular and neurosurgeon colleagues is the next best step.

The next big category is cardiac disorders, the second most common risk factor for pediatric acute ischemic strokes. I have stated previously that Down syndrome is associated with stroke, and that's because of the link between Down syndrome and a number of risk factors, such as moyamoya, but also due to the cardiac conditions associated with Down syndrome. Congenital heart disease affects 50% of patients with Down syndrome. Typically, cardiac conditions cause embolic strokes, however if children are

being treated with anticoagulation for a cardiac disease they are also at risk of a hemorrhagic stroke. Acquired heart diseases such like those affecting the valves, endocarditis, and cardiomyopathies also increase the likelihood of stroke, as does surgical repair of cardiac conditions. The best approach in these cases is providing teaching to the parents and informing them of which symptoms and signs warrant a trip to the emergency room.

Moving from the heart to the blood, I'm sure none of you are surprised that Sickle Cell disease is not the only hematological condition that is linked to stroke. Other prothrombotic conditions, anything that causes clotting, such as hereditary thrombophilia is a risk factor for stroke – specifically venous strokes, but they can cause arterial strokes as well. In these cases, you may elicit a family history of strokes or heart attacks under age 50, DVT or pulmonary embolisms, or recurrent pregnancy loss. Liver and kidney diseases causing deficiencies in proteins C and S can also cause a prothrombotic environment. Patients with nephrotic syndrome lose factors which prevent coagulation in their urine, and therefore are at higher risk of stroke, as are patients with Von Willebrand disease.

Our final big category is cerebrovascular abnormalities, which cause 45% of nontraumatic hemorrhagic strokes. Arterial-Venous Malformations, or AVMs, are abnormal arteries which connect directly to veins. When AVMs rupture, they cause hemorrhagic strokes. AVMs can be associated with certain genetic conditions, like hereditary hemorrhagic telangiectasia. In these patients, serial imaging and involvement of pediatric neurosurgery who can discuss the risks and benefits of surgical interventions more precisely based on the size and symptoms.

So, as a quick recap: the major risk factors for stroke are sickle cell disease, Down syndrome, moyamoya, arterial dissection, cardiac and hematological disorders, and cerebrovascular abnormalities. However, there are other situations in which stroke should be higher on your differential.

In patients with polycythemia, hyper viscosity syndrome increases the risk of stroke. Conversely, those with anemia can also have an increased risk of thromboembolism. Patients with cancer are at increased risk, as both the malignancy and its treatment increase the stroke risk. Some infections can also increase the risk of stroke; for example, varicella causes vasculopathy which can contribute to an ischemic stroke. HIV can induce a vasculitis, and infections around the head and neck, like meningitis and even otitis media or sinusitis, can increase stroke risks. This is why asking about recent illnesses and a vaccine history is always important!

Childhood strokes include strokes in our adolescent population, who share many of the risk factors that adults possess. Those who have migraines with aura, users of estrogen containing birth control or who are pregnant are all at an increased risk of stroke. Drugs such as amphetamines, ecstasy, and cocaine can also increase the likelihood of stroke.

We love our genetics and the zebras in peds – and some of these contribute to pediatric stroke as well. Marfan syndrome, for instance, is one connective tissue disorder than increases the likelihood of dissection. Tuberous sclerosis, homocysteinuria, mitochondrial dysfunction, and familial lipoprotein disorders are some other conditions that can increase stroke risk.

Finally, nutrition and metabolic conditions, especially when untreated, can lead to stroke. This includes deficiencies in folic acid or vitamin B12, as well as enzymatic conditions like isovaleric acidemia.

I know that was a lot of information – but the big take away is there are a lot of risk factors for pediatric stroke! Recognize which patients have significant risk factors, such as children with sickle cell or AVMs, but keep in mind there are many other risk factors and try to keep stroke on the differential for any patient presenting with a generalized deterioration, altered mental status or focal neurological deficits.

### **Differential**

Speaking of differentials, what else should also be on the differential if you are worried about stroke? Depending on the presentation, focal seizures, intracranial neoplasms or infections, metabolic abnormalities such as MELAS, or hypoglycemia should be on your differential (which, by the way, is why you always have to follow through on your ABCs and your DEFG – don't ever forget glucose!). Consider other causes of raised intracranial pressure as well. Complicated migraines and Todd's paresis are diagnoses to consider, but these are diagnoses of exclusion and can't be diagnosed until stroke is effectively ruled out.

### **Investigations**

So – you have a patient who you think may be having a stroke. What next?

You may be familiar with the NIH Stroke Scale from your adult neurology rotations. There is, in fact, a pediatric version that assesses the same 11 domains, and has been adapted for each age group. Because strokes are an emergency, it's important to continue your diagnostic workup while administering supportive therapy.

If possible, the first step is the most sensitive form of imaging: an urgent MRI. If this confirms a stroke, you can go on to focusing on your support. If it doesn't but you have a very high suspicion, you can consider using further imaging. If you don't have access to an MRI from the get-go, the next best option is a CT brain and a CTA head and neck, although these will not show an acute ischemic stroke for up to 12 hours.

If the imaging shows an ischemic stroke, further imaging of the arteries and veins is necessary to assess their patency and the vascular anatomy.

For a hemorrhagic stroke, a non-contrast head CT is best, but if the imaging doesn't show anything and your suspicion remains high, a lumbar puncture is the next step to rule out a subarachnoid hemorrhage. If, on the other hand, your head CT is positive for a hemorrhagic stroke, further imaging including magnetic resonance venography is necessary to look for a CVST which will be present in 10% of children.

Catheter angiography is another imaging options that will give the most detail and has the benefit of being diagnostic as well as therapeutic, with the major caveat being that few physicians are trained in performing this in children and, depending on the extent of the stroke, the risks may outweigh the benefits. As you'll see in just a moment when we discuss treatment, assessing the effectiveness of this treatment is challenging due to the relatively low prevalence of pediatric stroke.

While imaging is the backbone of the diagnosis, don't forget, in fact don't EVER forget glucose – DEFG! You also may want to do a toxin screen if the history suggests its relevance, as well as specific blood tests for hematological or vascular disorders. While determining if a stroke is present is the most important, finding out the underlying cause by assessing the risk factors and ordering screening tests are the next steps.

## Management

And now, as promised, we'll chat about management. We've discussed a couple specific treatments for specific risk factors already, and we need to acknowledge that it's difficult to study stroke treatment in this population due to its relative infrequency. Just recently, the TIPS trial which was assessing tPA use in the pediatric population failed to move forward due to low enrollment rates. Some centers are creating their own guidelines for the treatment, and offer tPA, for example, but always give the parents the warning that these treatments have yet to be proven in children. This is true for many stroke treatments, and by and large our approach to stroke is informed by the adult literature.

With that being said, while your workup is being completed you should start with neuroprotective therapies to maximize their cerebral perfusion. These interventions are as easy as lying the head of the bed flat, or at 30 degrees in the case of raised intracranial pressure, keeping their temperature in the normal range, controlling any seizures that occur, and correct their oxygen and sodium if necessary. Assess, and if necessary correct, any abnormalities in their volume status, anemia, or hypoxemia. Aim to maintain the blood pressure between the 50<sup>th</sup> and 95<sup>th</sup> percentile but make any reductions very slowly to avoid further ischemia. Anything more specific depends on the etiology of the stroke, but these neuroprotective strategies should be done for all patients while the diagnostic process is ongoing.

We'll start by chatting about more specific details on the hemorrhagic stroke. For these patients, you want to prevent another bleed which you may do by correcting issues with coagulation or other hematological conditions. Improve their platelet counts, and provide the coagulation factors they're deficient in. Keep in mind, adults have some amount of cerebral atrophy while children do not, meaning that there is minimal space for blood to pool in their heads – surgical intervention may need to be considered and may need to be more aggressive.

For ischemic strokes, your patients should be transferred to the PICU, have an echocardiogram with a bubble study done, and continue with the neuroprotective strategies and diagnostic workup that you've already started. You'll want to specifically look for any thrombophilia going on in this child. Recurrence rates are typically quite low, between 1 and 2%, in this population, so most children will not need chronic anticoagulation, unless they have cardiac abnormalities or systemic thrombi.

Thrombolytics, like tPA, and mechanical thrombectomy, as mentioned, have no evidence for their use. Neonates are especially bad candidates for mechanical thrombectomy because devices haven't yet been made for the tiny neonatal arteries.

Longer term, rehabilitation like baby constraint-induced movement therapy has been shown to be helpful for mobility issues resulting from strokes.

The one pediatric subpopulation which has been studied in stroke is sickle cell disease. As we mentioned previously, this population should be offered screening, transfusions to avoid hyper-viscosity, and if possible, a stem cell transplant.

## Perinatal Strokes

Before we move on to outcomes, I wanted to spend a moment discussing perinatal strokes in more detail as they are distinct from other pediatric strokes. While they can happen any time between 20 weeks gestation and 28 days after birth, most will occur in the hours to days after delivery. Like many other neonatal issues, perinatal strokes are more common in premature infants, or in infants with other risk



factors like inherited thrombophilia, cardiac issues, coagulation disorders, trauma, and infection. Eighty percent of these strokes will be ischemic. The focality of the symptoms will typically be the feature that differentiates it from a global hypoxic-ischemic injury. While this focality differentiates it, don't expect to see unilateral motor deficits in this age group. Strokes are much more likely to present as focal or generalized seizures. Many will also have encephalopathy and demonstrate irritability, hyper or hypotonicity, lethargy and poor feeding.

MRI is still the most effective form of imaging for diagnosis, but a thorough workup of the risk factors needs to be done. Risk factors at this age include maternal and placental risk factors in addition to fetal risk factors. Maternal risk factors include maternal infection, thrombophilia, pre-eclampsia, cocaine use, or smoking. The placenta should be assessed for infarction, abruption, insufficiency, and chorioamnionitis. And the fetus should be assessed for infection, thrombophilia and congenital heart disease.

### **Outcomes**

Finally, let's discuss outcomes of pediatric strokes which are unfortunately quite poor. Pediatric patients have a 10-25% mortality, and 25% will have a recurrent stroke, although this differs based on the subtype. Two thirds of patients with a pediatric stroke will go on to develop seizures, learning or developmental disorders which sometimes don't present for many years.

In the perinatal population, hemorrhagic strokes have worse outcomes in the short term, but better outcomes in the longterm as compared with ischemic strokes. Most neonates will survive ischemic strokes, but up to 90% will have significant neurological morbidity which may not be fully manifested for years.

We know that early recognition and treatment are important for improved outcomes – which is why stroke should always be on your differential. You're much more likely to correctly diagnose a stroke, and diagnose it earlier, if you're considering that your patient may be having a stroke!

With that being said – I know this has been a whole lot of information, so what are the few points you should be taking away?

- 1) There are many risk factors that increase the likelihood of strokes in the pediatric population, you should know some of the big, can't miss ones in mind such as: Sickle Cell disease, coagulation disorders (inherited and acquired), congenital heart disease, Down syndrome, birth control and street drugs.
- 2) When you're assessing a patient, obtain a comprehensive history – consider their age, presentation, recent illnesses, past medical history, and family history as part of assessment.
- 3) Keep a broad differential that includes stroke as a possibility – because the best way to diagnose it is to suspect it at the earliest juncture possible!

Thanks so much for joining me for this episode, I hope it helps in your rotations and practice, and thank you to all those working with pedscases for all you do! Until next time...

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